

The Outcome of Retinopathy of Prematurity

Screening for Retinopathy of Prematurity Using an Outcome Predictive Program

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Purpose: The purpose of this study was to compare the calculated risk of progression to threshold retinopathy of prematurity (ROP) and risk of an unfavorable structural outcome using the computer program, RM-ROP, with the observed incidence for infants born at Jackson Memorial Hospital (JMH) and to determine how many children would have been treated unnecessarily if the threshold criteria for treatment were lowered on the basis of the clinical findings and RM-ROP risk calculations.

Design: Noncomparative interventional case series.

Participants: All 292 surviving premature infants weighing 1250 g or less at birth and born at JMH between January 1, 1997, and December 31, 1998, were included in the study.

Methods: Baseline demographic factors and data from sequential ophthalmic examinations were entered into the RM-ROP program for risk calculation. Infants reaching threshold disease received diode laser indirect photocoagulation of the avascular retina. Three-month follow-up was obtained for infants receiving laser treatment.

Main Outcome Measures: The development of threshold ROP and an unfavorable structural outcome, defined as a posterior retinal fold or posterior retinal detachment occurring within 3 months of threshold disease.

Results: Thirty-eight eyes were diagnosed with threshold ROP, with 18 of 20 subjects having bilateral disease. Three-month posttreatment follow-up was obtained on all 20 children, with 19 having good structural outcomes. Thirty-two percent of eyes (12 of 38) reaching threshold never had a risk estimate greater than 0.10. However, only 6% of eyes (35 of 546) that did not reach threshold ever had a model predicted risk greater than 0.15. All right eyes with zone 1 prethreshold disease, 60% of those with zone 2 stage 2+ disease, and 23% with zone 2 stage 3 disease progressed to threshold ROP.

Conclusions: The similarity between the risk distributions for the Miami and the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity study indicates the similarity in the populations with respect to risk factors identified as important by the model. The Miami data validated the model, with eyes reaching threshold having higher risks than eyes that did not. Actual risk estimates for eyes reaching threshold can be small. Changing the threshold criteria for treatment on the basis of various clinical and computer-generated prethreshold risk levels in our population would have resulted in the unnecessary treatment of many infants who never progressed to threshold disease. In the Miami population, if the model were used to manage an individual subject, close attention would have to be paid to small differences in risk. Although the RM-ROP software program may be a useful tool for following premature infants with ROP, the clinical examination remains the "gold standard." *Ophthalmology* 2001;108:27-35 © 2001 by the American Academy of Ophthalmology.

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The computer program, RM-ROP, designed by Dr. R. J. Hardy and colleagues, tracks the onset and progression of retinopathy of prematurity (ROP) at sequential eye examinations and calculates the risk at each examination that an eye will progress to threshold ROP. After threshold is reached, RM-ROP provides an estimate of the risk that an eye will have an unfavorable 3-month outcome with or without laser treatment. The system was developed using data from the examinations performed on the 4099 infants at 23 centers in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP).¹

Estimated risks were obtained by using logistic regression to model separately the influence of clinical variables

on both the incidence of threshold disease and the incidence of unfavorable structural outcome. Individual models were constructed for subject and ocular data that would be available at the first examination, the examination demonstrating the onset of ROP, and the examination demonstrating pre-threshold ROP. For example, variables found to affect significantly the incidence of threshold ROP at the first examination were birth weight, gestational age, ethnicity, birth in study hospital, multiple birth status, and vessels extending into zone I. Further details may be found in Hardy et al.¹

We used RM-ROP to generate risk estimates of developing threshold ROP for the premature infants born at Jackson Memorial Hospital (JMH). Each infant was entered into the program at the time of first examination for ROP, and the information was updated at subsequent examinations when ROP, prethreshold ROP, and threshold ROP occurred. On the basis of the subject's demographic and examination data, RM-ROP calculated the risk of progressing to threshold ROP at each examination. When threshold disease developed, the risk of an unfavorable structural outcome with or without treatment was determined.

At the Bascom Palmer Eye Institute, we currently treat eyes once they have reached threshold ROP as defined by the Cryotherapy for Retinopathy of Prematurity Cooperative Group (eight cumulative or five contiguous clock hours of stage 3+ in zone I or II).² However, across the country, physicians are beginning to treat at earlier stages. Knowing the outcomes of our infants over the past 2 years, we retrospectively analyzed this population at various clinical and computer-generated prethreshold risk levels to determine the number of excess eyes treated were we to adopt new treatment criteria.

The purpose of this study was to compare the calculated risk of progression to threshold ROP and the risk of an unfavorable structural outcome with the observed incidence for infants born at JMH using the previously described program. In addition, we wanted to determine how many children would have been treated unnecessarily if the threshold criteria for treatment were changed on the basis of the clinical findings and the RM-ROP relative risk calculations.

Methods

Population

All surviving premature infants weighing 1250 g or less at birth and born at JMH between January 1, 1997, and December 31, 1998, were included in the study. Baseline demographic factors such as birth weight, gestational age (based on postmenstrual age or Ballard scores),³ black versus nonblack race, and single versus multiple birth were recorded for each infant.

Examination

Sequential ophthalmic examinations were performed by Bascom Palmer Pediatric Ophthalmologists beginning at 32 to 34 weeks' postconceptional age. Follow-up examinations were performed at 1- to 2-week intervals, depending on the findings of each examination. Fundus findings were classified as (1) any ROP, (2) pre-threshold ROP—any zone I ROP or zone II stage 2+ or 3 ROP, or

(3) threshold ROP—eight cumulative or five contiguous clock hours of stage 3+ in zone I or II.² Ocular characteristics such as the presence or absence of vessels ending in zone I at first examination, time of onset of ROP, and presence or absence of ROP in zone I at first ROP examination were noted. The time for ROP to reach prethreshold and the presence or absence of plus disease at first prethreshold examination were also recorded.

The study received institutional review board approval, and informed consent was obtained from the parents of each infant. Data were entered into the RM-ROP program for risk calculation. Infants reaching threshold disease received diode laser indirect photocoagulation of the avascular retina under topical anesthesia with sedation. Spots were placed one half burn width apart with a dull white laser photocoagulation mark as an end point. The technique has been well described elsewhere.^{4,5} Infants receiving laser therapy were examined at frequent intervals during their hospitalization and at 3 months for a final follow-up examination for the purposes of this study. Inclusion in the study did not depend on a required length of follow-up.

The total number of clock hours of stage 3 disease and the presence of threshold disease in zone I or II were noted at the threshold examination and used to calculate the risk of an unfavorable outcome in 3 months with or without treatment. An unfavorable structural outcome was defined as a posterior retinal fold or posterior retinal detachment 3 months after the diagnosis of threshold disease.

Results

There were 292 infants (584 eyes) in our study. The baseline characteristics are listed in Table 1. Some form of ROP was noted in 144 (49%) of our subjects, prethreshold was noted in 50 (17%) subjects, and threshold disease in 20 (7%) subjects. Thirty-eight eyes were diagnosed with threshold ROP, with 18 of 20 subjects having bilateral disease. Of significance, one subject had bilateral Rush disease.⁶ Thirty-seven eyes were treated with indirect diode laser treatment to the avascular retina. None of the subjects required more than one laser session. The average gestational age at the time of treatment was 38.5 weeks (\pm 2.8 weeks). The average time from birth to treatment was 13.8 weeks (\pm 2.7 weeks).

Three-month posttreatment follow-up was obtained on all 20 children. Nineteen children, including the one with bilateral Rush disease, had a good structural outcome. However, one child, who was diagnosed with unilateral threshold disease, had bilateral stage 5, total, closed-funnel retinal detachments develop. In this subject, only one eye was treated. The untreated eye was considered stable at the time of discharge and not in need of laser. The ROP was regressing and the child was discharged from the hospital. The child missed a scheduled follow-up appointment, the disease progressed in the untreated eye between examinations, and any opportunity to laser the eye before detachment was missed.

In our study group, subject characteristics such as birth weight and gestational age were significant risk factors for the development of ROP (Table 1). The average birth weight (\pm standard deviation) for all 94 subjects with ROP not reaching threshold in either eye was 837 \pm 192 g compared with 688 \pm 151 g for those reaching threshold disease in at least one eye ($P < 0.001$). The average gestational age was 27 \pm 3 weeks for infants with ROP not reaching threshold compared with 26 \pm 2 weeks for those who had threshold ROP develop ($P < 0.001$). In addition, infants with prethreshold disease were smaller and younger than infants with ROP who did not reach prethreshold. Race and number of births were not significant factors for threshold disease developing in our subject population.

Table 2 summarizes the subjects' ocular characteristics. All eyes with vessels ending in zone I at first examination or ROP in zone I at first ROP examination had threshold disease develop.

Table 1. Patient Characteristics

Patient Characteristics	All Infants (n = 292)	All Infants with Retinopathy of Prematurity in Either Eye (n = 144)	All Infants with Prethreshold Disease in Either Eye (n = 50)	All Infants with Threshold Disease in Either Eye (n = 20)
Birth weight (g) (mean ± SD)	910 ± 212	785 ± 192 <0.001*	688 ± 151 0.001†	675 ± 131 0.6‡
Gestational age (wks) (mean ± SD)	27.7 ± 2.4	26.6 ± 2.4 <0.001*	25.5 ± 1.6 <0.001†	24.8 ± 1.2 0.016‡
Black race n (%)	174 (60)	79 (55) 0.12*	26 (52) 0.7†	9 (45) 0.6‡
Single birth n (%)	247 (85)	122 (85) >0.9*	41 (82) 0.6†	18 (90) 0.3‡

* P value compares infants with any retinopathy of prematurity (ROP) with those without any ROP.
† P value compares infants with prethreshold ROP with infants with ROP but not reaching prethreshold.
‡ P value compares infants with threshold ROP with infants with prethreshold disease but not reaching threshold.
SD = standard deviation.

Seventeen (68%) of 25 eyes with plus disease at the first prethreshold examination had threshold disease develop.

Figures 1A, B compare the distributions of model predicted risks for the Miami infants with the 4099 infants of the CRYO-ROP study,¹ after accounting for subject and eye level risk factors identified by the model. Also displayed are the observed incidence of threshold disease and unfavorable outcome in the Miami data.

In Table 3, the model predicted risks for the individual 20 infants (left eyes) that had threshold disease develop ranged from 0.03 to 0.51 at first examination, 0.04 to 0.77 at the onset of ROP, and 0.05 to 0.67 at prethreshold ROP.

Table 4 compares the average model predicted risks at each examination of eyes reaching threshold with eyes that did not. The average risk was significantly higher for the eyes that reached threshold. For the 37 treated eyes, the average model predicted risk of an unfavorable structural outcome was 0.24 (standard deviation, 0.29; median, 0.39), a decrease of 43% from the average model-predicted risk of 0.41 if these eyes had been untreated. Thirty-six

of the 37 treated eyes (20 subjects) had good outcomes, whereas the single untreated eye had a poor structural outcome.

Table 5 compares the distributions for eyes (subjects) not achieving threshold with the distributions of those that did achieve threshold at each examination. Evaluating information from all examinations for each eye, 32% (12 of 38) reaching threshold never had a risk estimate greater than 0.10. However, only 6% of eyes (35 of 546) that did not reach threshold ever had a model predicted risk greater than 0.15.

Of the 50 subjects with prethreshold disease in our study, 46 subjects had an examination documenting their prethreshold level of disease. Nine eyes of five subjects progressed from ROP to threshold disease without a documented prethreshold examination. Table 6 shows the distribution of right and left eyes at prethreshold disease divided into zone 1, zone 2 stage 2+, or zone 2 stage 3 disease. Zone 2 stage 3 disease was the most common form of prethreshold disease, present in 73% of right eyes. All right eyes with zone 1 prethreshold disease, 60% of those with zone 2 stage

Table 2. Eye Characteristics

Eye Characteristics	All Eyes (n = 584)	All Eyes with Retinopathy of Prematurity (n = 274)	All Eyes with Prethreshold Disease (n = 92)	All Eyes with Threshold Disease (n = 38)
Vessels ending in zone 1 at first examination, n (%)	2 (0.3)	2 (0.7)	2 (2.2) 0.3*	2 (5) 0.4†
Onset age of ROP (wks) mean ± SD		35.2 ± 2.0	35.2 ± 2.0 0.8*	35.1 ± 2.0 0.4†
ROP in zone 1 at first ROP examination, n (%)		4 (1.5)	4 (4.3) 0.11*	4 (11) 0.16†
Plus disease at first prethreshold examination, n (%)			25 (27)	17 (52) 0.035†
Days from ROP to reach prethreshold examination mean ± SD			16.6 ± 13.8	11.5 ± 9.4 0.11†

Note: statistical significance is assessed in right eyes only.
* P value compares right eyes with prethreshold disease to right eyes with ROP that did not reach prethreshold.
† P value compares right eyes with threshold disease to right eyes with prethreshold disease that did not reach threshold.
ROP = retinopathy of prematurity; SD = standard deviation.

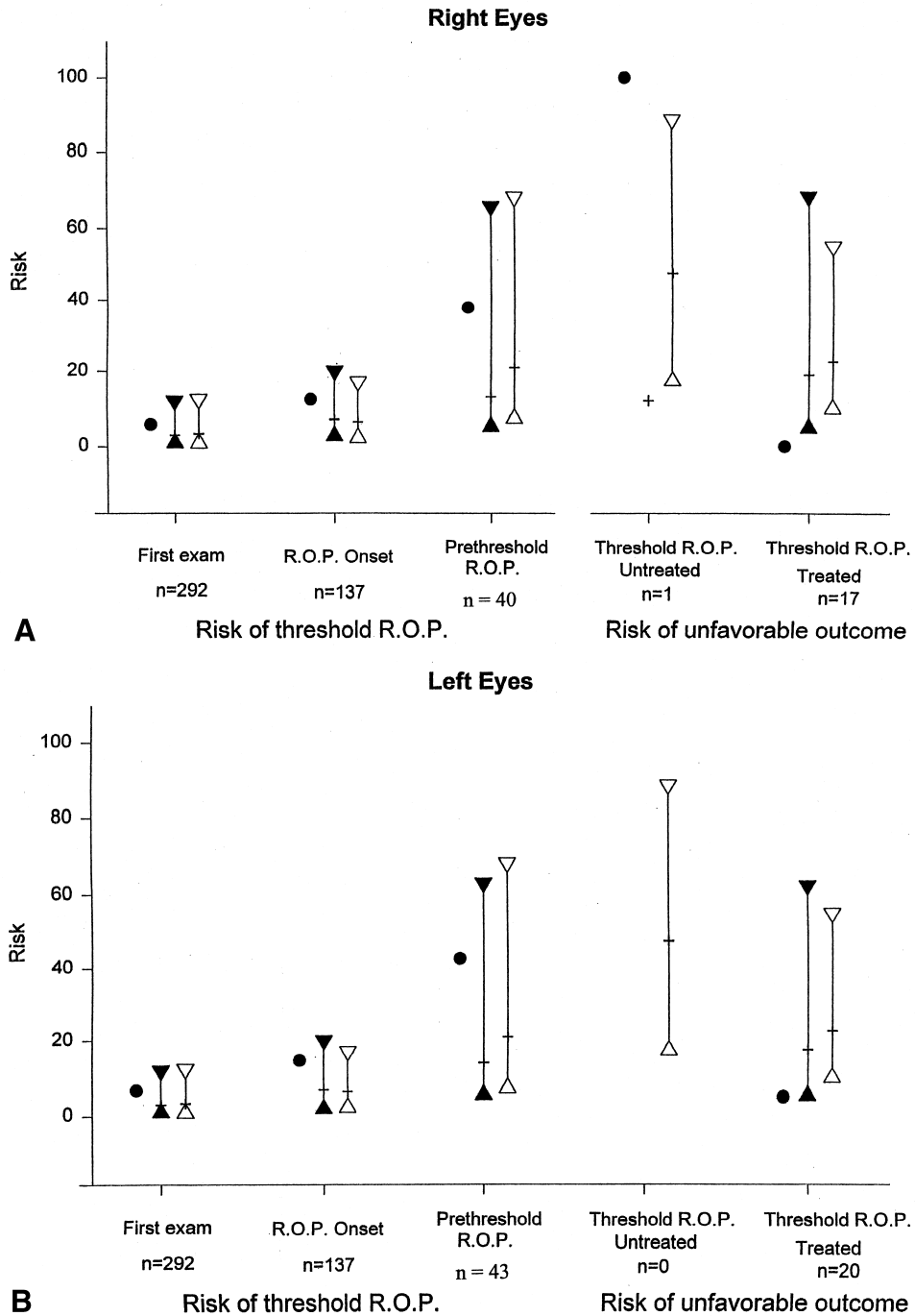


Figure 1. A and B, distributions of model predicted risks and observed incidence of threshold disease and unfavorable outcome for Miami infants (right and left eyes). ●, Miami incidence; ▲, 10th, 50th, and 90th percentile model predicted risk of threshold disease for Miami infants; △, 10th, 50th, and 90th percentile model predicted risk of threshold disease for Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) infants; (+) 50th percentile model predicted risk of threshold disease for Miami and CRYO-ROP infants.

2+ disease, and 21% with zone 2 stage 3 disease progressed to threshold disease.

If we had treated all eyes at any prethreshold level (any zone I ROP or zone II stage 2+ or 3 ROP), 83 eyes would have been treated, 54 of which never progressed to threshold disease (Table 7). Because we know from evaluation of our own data which eyes are most likely to have threshold disease develop, it is possible to tailor the treatment strategy to various levels of risk. Narrowing

our treatment to eyes with zone 2 stage 2+ or zone 1 disease, we would have treated 20 eyes, 5 of which never had threshold ROP develop.

Table 8 demonstrates the prethreshold disease risk for right and left eyes that progressed to threshold disease. Four of 20 right eyes (20%) with a prethreshold disease risk between 0 and 0.15 progressed to threshold disease compared with 9 of 20 (45%) with a risk greater than 0.15. Eight of 30 right eyes (27%) with a pre-

Table 3. Model-predicted Risks for Threshold Disease Developing at Each Examination for the 20 Infants (Left Eyes) Who had Threshold Disease Develop

Infant	Examination		
	First Examination	Onset of Retinopathy Prematurity	Prethreshold
1	0.03	0.04	0.51
2	0.12	0.14	0.17
3	0.06	0.07	0.10
4	0.16	0.18	0.61
5	0.19	0.72	0.46
6	0.04	0.05	0.05
7	0.09	0.13	0.18
8	0.04	0.05	0.09
9	0.51	0.77	*
10	0.13	0.16	0.19
11	0.15	0.18	0.66
12	0.13	0.16	0.59
13	0.21	0.25	*
14	0.18	0.18	0.47
15	0.03	0.04	*
16	0.20	0.22	0.67
17	0.11	0.15	0.17
18	0.09	0.09	0.08
19	0.05	0.06	0.51
20	0.10	0.10	*

*Infants progressed from retinopathy of prematurity to threshold disease without an examination diagnosing prethreshold disease.

threshold risk between 0 and 0.50 progressed to threshold disease compared with 5 of 10 (50%) with a risk greater than 0.50.

If we devised a treatment plan on the basis of the calculated risk estimate of threshold disease developing from RM-ROP and treated those with a risk greater than 0.50 at prethreshold, we would have treated 18 eyes, 7 unnecessarily. By lowering the level

of risk at prethreshold to 0.15, 41 eyes would have been treated, 20 of which never went on to threshold disease (Table 7).

Discussion

Our subject population was similar to the CRYO-ROP study (Table 9) except that we had a larger percentage of black subjects (60% vs. 39%). The incidence of ROP was higher in the CRYO-ROP study; however, similar numbers of infants had prethreshold and threshold disease develop.⁷ Any differences in our population would have been taken into account and adjusted for with the RM-ROP program when calculating the risk of threshold disease and unfavorable structural outcome.

Subject characteristics that statistically increased the risk of threshold disease were low birth weight and low gestational age. Unlike the CRYO-ROP study, race and multiple births were not significant risk factors in our population.^{8,9} However, previous studies of this subject population at JMH revealed similar findings, with no significant difference in the stage of ROP between infants of single-gestation pregnancies compared with those of multiple-gestation pregnancies.¹⁰

Vessels ending in zone I at the first examination, ROP in zone I at the first ROP examination, and plus disease at the first prethreshold examination were clinically significant ocular characteristics for the progression to threshold disease (Table 2). The mean onset age of ROP and the mean time for ROP to reach prethreshold were similar throughout the retinopathy groups. It is the combination of ocular and subject characteristics that were used to calculate a model-predicted risk of threshold disease.

The similarity between the risk distributions for the Miami and the CRYO-ROP study shown in Figures 1 A, B

Table 4. Model-predicted Risks of Eye Reaching Threshold—Summary Statistics

Examination	Right Eyes		P Value*	Left Eyes		P Value*
	Threshold Not Reached	Threshold Reached		Threshold Not Reached	Threshold Reached	
First examination						
Mean ± SD	0.04 ± 0.05	0.13 ± 0.11	<0.001	0.04 ± 0.05	0.13 ± 0.11	<0.001
Median	0.05	0.12		0.02	0.11	
Range	0.005–0.4	0.03–0.51		0.005–0.41	0.03–0.51	
n	274	18		272	20	
ROP onset						
Mean ± SD	0.09 ± 0.07	0.19 ± 0.21	0.003	0.09 ± 0.07	0.19 ± 0.20	0.001
Median	0.07	0.15		0.07	0.15	
Range	0.01–0.39	0.04–0.77		0.01–0.39	0.04–0.77	
n	119	18		117	20	
Prethreshold						
Mean ± SD	0.20 ± 0.20	0.35 ± 0.24	0.075	0.15 ± 0.15	0.34 ± 0.23	0.004
Median	0.12	0.46		0.11	0.33	
Range	0.03–0.68	0.05–0.67		0.02–0.67	0.05–0.67	
n	27	13*†		27	16**	

*By Wilcoxon two sample test.

†Five eyes were not observed at prethreshold.

**Four eyes were not observed at prethreshold.

ROP = retinopathy of prematurity; SD = standard deviation.

Table 5. Model-predicted Probability of Reaching Threshold Retinopathy of Prematurity for Eyes and Patients

Examination	Model-predicted Probability of Reaching Threshold Retinopathy of Prematurity	Eyes				Subjects			
		Threshold Disease Reached		Threshold Disease Reached		Threshold Disease Reached		Threshold Disease Reached	
		No	Yes	No	Yes	No	Yes	No	Yes
		n	%	n	%	n	%	n	%
First	0.005–0.05	412	75	10	26	206	76	5	25
	>0.05–0.10	83	15	7	18	41	15	4	20
	>0.10–0.25	45	8	19	50	22	8	10	50
	>0.25–0.50	6	1	0	0	3	1	0	0
	>0.50	0	0	2	5	0	0	1	5
	Total		546		38		272		20
ROP Onset	0.005–0.05	104	44	8	21	57	46	4	20
	>0.05–0.10	60	25	8	21	32	26	4	20
	>0.10–0.25	66	28	18	47	32	26	10	50
	>0.25–0.50	6	3	0	0	3	2	0	0
	>0.50	0	0	4	11	0	0	2	10
	Total		237		38		124		20
Prethreshold ROP	0.005–0.05	6	11	2	7	4	13	1	6
	>0.05–0.10	18	33	6	21	10	33	3	19
	>0.10–0.25	22	41	6	21	11	37	4	25
	>0.25–0.50	4	7	4	14	3	10	2	13
	>0.50	4	7	11	38	2	7	6	38
	Total		54		29		30		16

ROP = retinopathy of prematurity.

indicates the similarity in the populations with respect to risk factors identified as important by the model. At the first, onset, and prethreshold examinations, the observed incidence of threshold ROP was bracketed by the 50th and 90th percentiles of predicted risk. However, on an individual basis, surprises did occur.

Our only subject to have bilateral retinal detachments develop (baby 1) had a calculated risk of threshold disease developing of 0.03 at first examination and 0.04 at the onset of ROP. Although the initial calculated risks may not have been impressive, the model-predicted risk at the prethreshold examination (0.51) in both eyes was an indicator of problems to come.

The subject with bilateral Rush disease (baby 9) had calculated risks of threshold disease developing above the 90th percentile in both eyes throughout the examinations (0.51, 0.77). Once the subject did have threshold disease

develop, the risk of an unfavorable outcome with or without treatment continued to be well above the 90th percentile. However, although the model-predicted risk was high, the 3-month outcome was favorable bilaterally.

At the opposite end of the spectrum, baby 6 had a risk at the 10th percentile level of threshold disease developing at the first examination, onset of ROP, and prethreshold examination in both eyes (0.04, 0.05, 0.05) and went on to have bilateral threshold disease develop. These cases help to emphasize the importance of thorough follow-up examinations despite the model predicted risks.

It is informative to examine our one treatment failure from the standpoint of prethreshold risk. The infant that had bilateral detachments had a calculated risk estimate for both eyes of 0.03 at first examination, 0.04 at the onset of ROP, and 0.51 at the prethreshold examination of threshold disease developing. Clinically, at the prethreshold examination, the infant had 8 hours of zone 2 stage 2+ and 4 hours of zone 2 stage 3 ROP in both eyes. If we had treated this infant at a prethreshold level clinically or at a risk estimate greater than 0.15 or 0.50, could we have prevented the bilateral retinal detachments? Clearly, treating at the threshold level in one eye did not prevent further progression of disease.

Our subjects had favorable 3-month structural outcomes with only 1 child of 20 having bilateral retinal detachments. The incidence of a poor structural outcome in the CRYO-ROP study was 31.1% with treatment compared with 51.4% for control eyes, resulting in an overall reduction in the occurrence of unfavorable outcome of 39.5%.¹¹ Hunter and Repka¹² compared diode laser photocoagulation with cryo-

Table 6. Prethreshold Disease in Right and Left Eyes, Divided by Clinical Definition of Prethreshold Disease and Number Progressing to Threshold

	Right Eyes		Left Eyes	
	Prethreshold Disease n (%)	Threshold Reached n (%)	Prethreshold Disease n (%)	Threshold Reached n (%)
Zone 1	1 (3)	1/1 (100)	1 (2)	1/1 (100)
Zone 2/stage 2+	10 (25)	6/10 (60)	8 (19)	7/8 (88)
Zone 2/stage 3	29 (73)	6/29 (21)	34 (79)	8/34 (24)
Total	40	13/40 (33)	43	16/43 (37)

Table 7. Outcome of Eyes Divided by Clinical Criteria and Calculated Risk Estimates

Disease Classification	Eyes		
	(+) Prethreshold Disease	Threshold Reached	Threshold Not Reached (%)
All prethreshold disease	83	29	54 (65)
Zone 2 stage 2+ and Zone 1 disease	20	15	5 (25)
Risk \geq 0.50	18	11	7 (39)
Risk \geq 0.15	41	21	20 (51)

therapy for threshold ROP in a randomized study. Eighteen of the 19 subjects were followed for 3 to 15 months after treatment. One of 15 cryotherapy-treated eyes and 1 of 17 diode laser-treated eyes progressed to stage 5 retinal detachment. Both had zone 1 threshold disease. At 3 years follow-up, all 12 of their surviving infants receiving laser treatment had a good structural outcome, and 2 subjects of the 10 receiving cryotherapy had a poor structural outcome.¹³ Although our 3-month outcomes were similar to Hunter and Repka's,¹² our small sample size makes comparison with the CRYO-ROP study difficult.

At present, at the Bascom Palmer Eye Institute, we only treat eyes with ROP that have progressed to the threshold level of disease. However, across the country, physicians are beginning to treat at earlier stages. Because we know the computer-generated risk estimates of threshold disease developing, the clinical findings at the prethreshold examination, and the outcomes of our infants over the past 2 years, new treatment strategies for these eyes could be developed and tested before being applied to subjects.

On the basis of the excellent structural outcome of our subjects after treatment for threshold disease, it is difficult to argue that treatment at an earlier stage would be more effective. In our subject population, one would have to treat only those prethreshold infants with zone 2 stage 2+ or zone 1 disease to minimize the overtreatment of children who would not necessarily progress. Likewise, a calculated risk greater than or equal to 0.50 would minimize unnecessary treatments but not to the same extent as a strategy based on the clinical examination findings. And although our subjects have generally done well with diode laser indirect photocoagulation of the avascular retina, laser treatment is not without complications. Corneal and iris burns, corneal edema, hyphema, tran-

Table 8. Proportion of Prethreshold Eyes Progressing to Threshold Disease Divided by RM-ROP Calculated Risk of Threshold Disease

Prethreshold Disease Risk	Right Eyes n = 40 (%)	Left Eyes n = 43 (%)
0-0.15	4/20 (20)	4/22 (18)
\geq 0.15-1.0	9/20 (45)	12/21 (57)
0-0.50	8/30 (27)	10/35 (29)
\geq 0.50-1.0	5/10 (50)	6/8 (75)

Table 9. Baseline Characteristics and the Incidence of Retinopathy of Prematurity at Jackson Memorial Hospital Compared with the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity

	Jackson Memorial Hospital, n (%)	Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, n (%)
Total	292	4099
ROP	144 (49.3)	2699 (65.8)
Prethreshold	50 (17.1)	731 (17.8)
Threshold	20 (6.8)	245 (6.0)
Black race	174 (59.6)	1582 (38.6)
Single birth	247 (84.6)	3337 (81.4)
Birth weight (g) (mean \pm SD)	910 \pm 212	954 \pm 185
Gestational age (wks) (mean \pm SD)	28 \pm 2	28 \pm 2

ROP = retinopathy of prematurity; SD = standard deviation.

sient lens opacification, and cataract formation have been reported after laser treatment.¹⁴⁻²¹

Extrapolating to the country as a whole, an estimated 18,220 infants weighing 500 to 1249 g are expected to survive beyond 28 days from birth and become eligible for screening for ROP in the United States annually.²² On the basis of the CRYO-ROP studies, 17.8% of these infants are expected to reach prethreshold disease and 6.0% to have threshold disease develop.⁷ Therefore, treating these infants at threshold disease results in 1093 babies being treated with lasers; if these children were treated at prethreshold level, 3243 infants would be affected. Treating at a clinical prethreshold level in our subject population would have overtreated many who resolved uneventfully. A randomized clinical trial of treatment at prethreshold levels versus the accepted standard of treatment would be useful in answering these difficult questions with long-term follow-up to assess outcomes such as visual acuity and refractive error.

The RM-ROP program can be used to track the progression of disease and predict which children are most at risk for threshold ROP developing. Although the Miami data validated the model to the extent that eyes reaching threshold had higher risks than those that did not, the actual risk estimates for eyes that eventually reached threshold can be quite small (<0.1 or 10%). Thus, in the Miami population, if the model were used for managing an individual subject, close attention would have to be paid to small differences in risk, for example between 0.025 and 0.05. Another validation study with a different subject population might produce risk estimates for threshold eyes that were similar to the CRYO study data from which the model was derived, somewhat lower, as in the Miami population, or perhaps even higher. The significance of the model-predicted risk should be evaluated for each subject population. Although the RM-ROP software may be a useful tool for following premature infants with ROP, the clinical examination remains the "gold standard."

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Discussion

by

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The risk management program for retinopathy of prematurity (ROP) outcome (RM-ROP) is a useful multiple logistic risk model available to clinicians to assist in defining the risk of threshold ROP developing in an eye at three different points in time: at the first eye examination, at the onset of any ROP, and at the time when prethreshold disease is documented.¹ The second portion of the program, designed to give the risk of an unfavorable outcome when threshold is reached, depending on treatment or no treatment, was not used by Dr. Onofrey and colleagues, because all patients who had threshold disease develop were treated. This statistical model was derived from the examinations of 4099 premature infants in the CRYO-ROP study. Dr. Onofrey and colleagues used this model in studying the risk for 292 infants of similar birth weight at their institution. They confirmed the importance of certain risk factors for development of threshold ROP included in the RM-ROP models: lower birth weight, younger

gestational age, vessels ending in zone 1 at the first examination, and plus disease being present at the first examination showing prethreshold ROP. Although race and multiplicity of birth were not significant factors for threshold disease developing in their group of patients, data from the much larger group of patients in the CRYO-ROP study showed an increased risk for threshold ROP developing for white race and multiple births.^{2,3}

Individual case presentations by Dr. Onofrey indicate the need for conscientious surveillance and meticulous examinations and the importance of having a system in place for tracking all infants. However, looking at change in probability of an eye reaching threshold over time is not the purpose of RM-ROP. These are not continuous points in time, because RM-ROP probability rates are meant to be used at the single point in time when they are calculated. What is important is the probability of threshold disease developing *when* prethreshold is determined. This will alter the interval between examinations and change physician counseling of the family. The study by Dr. Onofrey and colleagues indicates that the mean probability for prethreshold eyes was significantly greater for those who had threshold disease develop compared with those that did not have threshold ROP develop. However, some prethreshold eyes with a low probability for

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