

A Tiered Approach to Retinopathy of Prematurity Screening (TARP) Using a Weight Gain Predictive Model and a Telemedicine System

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IMPORTANCE The Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) Study telemedicine system of remote fundus image grading and The Children's Hospital of Philadelphia Retinopathy of Prematurity (CHOP-ROP) postnatal weight gain predictive model are 2 approaches for improving ROP screening efficiency. Current screening has low specificity for severe ROP.

OBJECTIVE To describe a tiered approach to ROP screening (TARP) for identifying children who develop severe ROP using telemedicine and a predictive model synergistically.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a post hoc analysis of a cohort in the e-ROP Study (a multicenter prospective telemedicine study) and the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study (a multicenter retrospective cohort study). The setting was neonatal intensive care units at The Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania. Participants in the e-ROP Study were premature infants with a birth weight less than 1251 g and a known ROP outcome enrolled between May 25, 2011, and October 31, 2013. The G-ROP Study enrolled all infants undergoing ROP examinations with a known ROP outcome who were born between January 1, 2006, and December 31, 2011.

MAIN OUTCOMES AND MEASURES The mean outcomes were the sensitivity for type 1 ROP, reductions in infants requiring imaging or examinations, numbers of imaging sessions and examinations, and total clinical encounters (imaging sessions and examinations combined). The following 4 screening approaches were evaluated: ROUTINE (only diagnostic examinations by an ophthalmologist), CHOP-ROP (birth weight and gestational age, with weekly weight gain initiating examinations when the risk cut point is surpassed), e-ROP IMAGING (trained reader grading of type 1 or 2 ROP initiates diagnostic examinations), and TARP (CHOP-ROP alarm initiates imaging, and imaging finding of severe ROP initiates diagnostic examinations).

RESULTS A total of 242 infants were included in the study, with a median birth weight of 858 g (range, 690-1035 g). The median gestational age was 27 weeks (range, 25-29 weeks). Fifty-one percent (124 of 242) were female, and 49% (118 of 242) were male. The race/ethnicity was 27.3% (66 of 242) white, 56.2% (136 of 242) black, 2.1% (5 of 242) Native American, 1.7% (4 of 242) Asian, and 12.8% (31 of 242) other. The sensitivity for detecting type 1 ROP (32 infants) was 100% (95% CI, 89.3%-100%) with each approach. With ROUTINE, 242 infants had 877 examinations; with CHOP-ROP, 184 infants had 730 examinations; with e-ROP IMAGING, 242 infants had 532 imaging sessions, and 94 infants had 345 examinations (877 patient encounters); and with TARP, 182 infants had 412 imaging sessions, and 87 infants had 322 examinations (734 patient encounters).

CONCLUSIONS AND RELEVANCE The tiered approach to ROP screening was associated with a reduced number of examinations and imaging sessions compared with the other approaches. Applying a postnatal growth model and telemedicine system in a tiered approach may reduce the number of clinical ROP interventions more than either approach alone.

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2016.5203
Published online January 5, 2017.

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Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature occurring in premature infants. The management of ROP involves serial eye examinations by ophthalmologists of infants deemed to be at risk that is generally based on birth weight (BW) and gestational age (GA) guidelines.¹ For example, in the United States, these criteria are a BW less than 1501 g or a GA of 30 weeks or less.¹ In addition, larger infants (1501-2000 g) with a complex postnatal course may be examined at the request of the treating neonatologist. This approach to determining which infants to examine has high sensitivity but low specificity for predicting children who may develop ROP severe enough to require treatment. Of the infants meeting BW and GA criteria, less than 10% will require treatment to decrease the likelihood of progression to retinal detachment,²⁻¹⁰ and many larger BW and older GA infants never develop ROP. Alternative screening modalities have been studied to improve the efficiency of ROP screening, including postnatal growth-based predictive models and telemedicine approaches.¹¹⁻¹⁹

Multiple studies²⁰⁻²² have demonstrated that slow postnatal weight gain is predictive of the subsequent development of ROP. Slow postnatal weight gain is thought to be a biomarker for low serum insulinlike growth factor 1 (IGF-1),²³⁻²⁵ which has a permissive role in vascular endothelial growth factor (VEGF) activity, a hypoxia-induced vasoproliferative factor. Therefore, low IGF-1 levels result in poor retinal vascular growth, retinal hypoxia, and increased retinal VEGF production. Subsequently, when IGF-1 levels rise, VEGF is activated, and ROP develops.^{20,21} Multiple predictive models using weight gain, BW, and GA have been developed,^{11,26} including the following: weight, insulinlike growth factor, and neonatal ROP (WINROP)^{14,15}; The Children's Hospital of Philadelphia ROP (CHOP-ROP)¹³; ROPScore¹⁸; Colorado-retinopathy of prematurity model (CO-ROP)¹⁹; and Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP).¹⁶ These models have high sensitivity for predicting severe ROP (97%-100% in some populations), while potentially reducing the number of infants requiring examinations by 25% to 75%.^{13,14,19} The CHOP-ROP model is a logistic regression-based equation that had 100% (95% CI, 84%-100%) sensitivity for predicting type 1 ROP among 524 infants meeting current screening criteria and would have reduced the number of infants receiving examinations by 49% in its retrospective development cohort.¹³

Telemedicine approaches may use ophthalmologists or trained nonphysician readers to review retinal photographs to identify infants with ROP who require an examination by an ophthalmologist with expertise in ROP to determine the need for treatment.^{17,27} Photographs can be obtained by trained nonphysician imagers using a digital fundus camera (eg, RetCam; Clarity Medical Systems). The National Institutes of Health-sponsored multicenter e-ROP Study enrolled 1257 infants who had serial retinal photographs graded by trained nonphysician readers in a central reading center to identify referral-warranted ROP (RW-ROP²⁸), which was defined as the presence of any stage ROP in zone 1, any stage 3 ROP, or the presence of plus disease.^{17,27} Eyes with RW-ROP have ROP findings consistent with type 1 plus type 2 ROP.^{4,28,29} The e-ROP system

Key Points

Question Does a tiered approach to retinopathy of prematurity screening (TARP), combining a postnatal weight gain model with telemedicine fundus image grading, provide advantages compared with either approach alone?

Findings In this post hoc analysis of 242 infants from the Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) Study and the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study, all screening approaches had 100% sensitivity for severe retinopathy of prematurity. However, the tiered approach was associated with a reduction in the number of retinal imaging sessions and examinations.

Meaning These results suggest that applying a postnatal growth model and telemedicine system in a synergistic tiered approach can reduce the number of clinical retinopathy of prematurity interventions more than either approach alone.

correctly identified 97% (95% CI, 94%-98.6%) of the infants diagnosed as having RW-ROP on an ophthalmologist's examination.¹⁷

We sought to create and evaluate a tiered approach for identifying children who develop severe ROP (hereafter tiered approach to ROP screening [TARP]) by combining the use of a postnatal weight gain model (the CHOP-ROP model) with the e-ROP telemedicine system of retinal image grading by trained readers to detect the need for an ophthalmologist's examination. We hypothesized that using the 2 methods together would have a synergistic effect with regard to the reductions in the number of infants requiring examinations and the number of infants requiring retinal imaging.

Methods

We performed a post hoc analysis of prospective ophthalmological and image grading data from the e-ROP Study and retrospective weight data from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study. The designs of the e-ROP Study and the G-ROP Study have been published in detail.^{9,27}

The e-ROP Study infants were enrolled between May 25, 2011, and October 31, 2013, at 13 clinical centers in the United States and Canada. All infants had a BW less than 1251 g and had not been previously treated at the time of first examination at a study hospital. Gratings of retinal images by trained nonphysicians were compared with results of diagnostic eye examinations by study-certified ophthalmologists. The follow-up schedule for examinations was determined by the examining ophthalmologists according to commonly used clinical guidelines, typically 2 weeks for immature vasculature, stage 1, or regressing disease and 1 week for zone 1, stage 2, or stage 3 ROP. Imaging was available for each clinical examination.

The G-ROP Study was a multicenter retrospective cohort investigation conducted at 30 hospitals in the United States and Canada to enable the development of ROP prediction models with highly precise estimates of the sensitivity for severe

ROP.⁹ The study enrolled all infants undergoing ROP examinations with a known ROP outcome. The data collection period included infants born between January 1, 2006, and December 31, 2011, on whom extensive data, including daily weight measurements, were retrospectively collected by certified data abstractors.

This post hoc analysis, approved by the institutional review boards at The Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania, used data from these 2 Philadelphia, Pennsylvania, hospitals, which participated in both the e-ROP Study and the G-ROP Study. Written informed consent was obtained for infants in the e-ROP Study. Waiver of informed consent was permitted for the G-ROP Study. For infants who were enrolled in both studies, weight data from the G-ROP Study were used. For infants enrolled in the e-ROP Study only, weight data were abstracted from medical records between May 25, 2011, and October 31, 2013, after institutional review board approval.

Four alternative ROP screening approaches were evaluated. The first approach (ROUTINE) used current ROP screening criteria. Because the e-ROP Study only enrolled infants with a BW less than 1251g, all infants in the study received diagnostic examinations in the ROUTINE approach. The second approach (CHOP-ROP) used the CHOP-ROP model to determine whether infants received examinations. The CHOP-ROP model consists of a logistic regression-based equation with terms for BW, GA, and daily weight gain rate (calculated using the difference between the mean of the immediately preceding week's daily weights and the mean of the penultimate week's daily weights).¹³ This model is recalculated on a weekly basis to predict the risk of developing Early Treatment for Retinopathy of Prematurity (ETROP) type 1 or type 2 ROP, and diagnostic examinations are initiated if the predicted risk is greater than 0.014, which is referred to as a CHOP-ROP alarm. In the third approach (e-ROP IMAGING), trained nonphysician reader grading of findings consistent with RW-ROP on retinal imaging initiates examinations. Finally, the fourth approach (TARP) uses the 2 modalities serially; the CHOP-ROP model is repeatedly calculated. If the CHOP-ROP model predicts risk above the alarm threshold level, retinal imaging sessions are begun with grading of retinal images until RW-ROP characteristics are noted, which in turn initiates a diagnostic examination by an ophthalmologist.

For each screening approach, the sensitivity for type 1 (treatment requiring) ROP was calculated as the proportion of infants with type 1 ROP who, as a result of the screening method, begin to receive ophthalmologist examinations before or simultaneous with the development of type 1 ROP. The 95% CI for the sensitivity was calculated with the Clopper-Pearson exact method.³⁰ Additional outcomes for each screening method included the number of infants receiving examinations, the number of infants undergoing imaging, the total number of examinations, and the total number of imaging sessions. The total number of encounters was also calculated as the total number of imaging sessions plus the total number of eye examinations. The reductions in infants requiring examinations or imaging, imaging sessions, examinations, and overall clinical encounters are a more clinically intuitive and mean-

ingful representation of the specificity of each screening approach and are presented instead of the specificity.

The sequence of events was accounted for in the analysis of these outcomes when determining which imaging and examination data would be considered. Therefore, in an approach using the CHOP-ROP model, examinations were only considered if they predicted the risk to be above the alarm threshold level, and in an approach using e-ROP Study telemedicine, eye examination data were only considered if the examinations occurred after trained readers identified RW-ROP. To illustrate this concept using the TARP approach, if a hypothetical infant was born at 26 weeks' postmenstrual age (PMA), the CHOP-ROP model would be applied on a weekly basis until the risk was above the threshold alarm level; imaging session and diagnostic examination data would not be considered during this time. If the model alarmed at 34 weeks' PMA, then imaging and image grading would be instituted. At this point, the CHOP-ROP model would stop being recalculated, and the eye examination results would not yet be considered. If image grading indicated the presence of RW-ROP at 37 weeks' PMA, then eye examination data would begin to be considered, and image grading results would no longer be included. In this manner, the simulated sequence of events was realistically treated. All analyses were performed using statistical software (SAS, version 9.3; SAS Institute Inc).

Results

Altogether, 242 infants were included in the study. The median BW was 858 g (range, 690-1035 g), and the median GA was 27 weeks (range, 25-29 weeks). Fifty-one percent (124 of 242) were female, and 49% (118 of 242) were male. The race/ethnicity was 27.3% (66 of 242) white, 56.2% (136 of 242) black, 2.1% (5 of 242) Native American, 1.7% (4 of 242) Asian, and 12.8% (31 of 242) other. Sixty-one infants (25.2%) developed RW-ROP, of whom 32 infants (13.2%) eventually developed type 1 ROP. All 4 ROP screening approaches (ROUTINE, CHOP-ROP, e-ROP IMAGING, and TARP) resulted in all 32 infants with type 1 ROP beginning eye examinations before the development of type 1 ROP (sensitivity, 100%; 95% CI, 89.3%-100%).

The Table summarizes the performance of each approach. Although both the CHOP-ROP approach and the e-ROP IMAGING approach resulted in a decrease in the number of infants receiving examinations, the TARP approach resulted in the greatest decrease in the number of infants having examinations and a reduction in the number of infants undergoing imaging. The CHOP-ROP approach resulted in the fewest total patient encounters (n = 730), whether imaging session or eye examination, while the TARP approach almost equaled the reduction in patient encounters (n = 734) and compared favorably with the ROUTINE or e-ROP IMAGING approaches (877 for both).

Discussion

We found that the use of a tiered approach to ROP screening theoretically would have resulted in a greater reduction in the

Table. Performance of 4 Approaches to Retinopathy of Prematurity (ROP) Screening

Screening Approach ^a	Retinal Imaging		Eye Examinations, No. (%)		Patient Encounters, No.
	Infants, No. (%)	Sessions, No.	Infants	Examinations	
ROUTINE	0	0	242 (100.0)	877 (100.0)	877
CHOP-ROP	0	0	184 (76.0)	730 (83.2)	730
e-ROP IMAGING	242 (100.0)	532	94 (38.8)	345 (39.3)	877
TARP	182 (75.2)	412	87 (36.0)	322 (36.7)	734

Abbreviations: CHOP-ROP, The Children's Hospital of Philadelphia Retinopathy of Prematurity; TARP, tiered approach to ROP screening.

^a The following 4 screening approaches were evaluated: ROUTINE (only diagnostic examinations by an ophthalmologist), CHOP-ROP (birth weight and

gestational age, with weekly weight gain initiating examinations when the risk cut point is surpassed), e-ROP IMAGING (trained reader grading of type 1 or 2 ROP initiates diagnostic examinations), and TARP (CHOP-ROP alarm initiates imaging, and imaging finding of severe ROP initiates diagnostic examinations).

number of infants undergoing eye examinations in this simulated pilot study than the use of a BW, GA, or growth-based model or telemedicine system alone. Application of the CHOP-ROP approach would have reduced the number of infants obtaining examinations by 24.0% compared with current BW and GA screening criteria, decreased the total number of examinations by 16.7%, and required no imaging sessions. Therefore, this approach had the fewest patient encounters of any of the 4 approaches we examined. However, the use of this weight gain-based predictive model would require abstracting weight measurements from the medical record and calculating the risk of ROP on a weekly basis until a model alarm indicated the need for examinations. In contrast, current BW and GA screening criteria are determined at birth, although a poor postnatal course for larger BW and older GA infants may also be considered.

The e-ROP IMAGING telemedicine approach resulted in a greater decrease in the number of infants requiring examinations (61.2%) and the number of diagnostic eye examinations (60.6%) than the CHOP-ROP approach. However, it would have required serial image acquisition, transmission of images to a reading center, and remote assessment of the images by trained graders. Furthermore, from the perspective of the infant and the neonatology care team, eye examinations were replaced one for one with imaging sessions, and the total number of patient encounters was identical between the e-ROP IMAGING approach and the ROUTINE approach. Therefore, the primary resource benefit of this approach lies in the shift from ophthalmologist time to retinal imager time and grader time. The preferred approach may vary among hospitals with the availability and costs of these human resources, as well as the cost of the digital camera. In addition, the relative stress for the infant associated with a diagnostic examination vs an imaging session has to be considered. Finally, image acquisition requires skilled imagers to maximize image quality for trained reader grading. In the e-ROP Study, of 39 950 individual retinal images, 91.7% (n = 36 364) were adequate quality, 5.6% (n = 2237) were poor quality, and 2.7% (n = 1079) were missing. In clinical practice, poor-quality images may require additional imaging sessions.

The TARP approach theoretically would have resulted in the maximum reduction in infants undergoing examinations (64.0%) and number of examinations (63.2%). It also would have resulted in 25% fewer infants undergoing imaging and 23% fewer imaging sessions so that there would be an equally significant

reduction in encounters for the infants as with the CHOP-ROP approach. The tiered approach has multiple steps and requires a greater degree of coordination of care to ensure that infants do not experience a delay in diagnosis of severe ROP. As with the CHOP-ROP and e-ROP IMAGING approaches, TARP necessitates medical record weight data abstraction and acquisition, transmittal, and grading of retinal images.

Strengths of this pilot study include prospectively conducted ROP diagnostic examinations performed by e-ROP Study-certified ophthalmologists with expertise in ROP, trained retinal image readers who graded images in a standardized fashion, and weight measurement data subject to multiple data quality measures that were followed in the G-ROP Study. These quality measures included a formal data collector certification process and extensive data cleaning procedures to identify errors.

Limitations

However, there are important limitations of the study to consider. The study cohort was small, with only 32 infants developing type 1 ROP. Therefore, the 95% CI around the point estimate of the sensitivity (100%) is wide (89.3%-100%). Studies in much larger cohorts are needed to ensure a sensitive system. In addition, the cohort in this study consisted of infants with a BW less than 1251 g and was therefore at higher risk for ROP. The savings with regard to reduction in examinations would likely be greater if larger BW, more mature infants were included, as would be done for routine ROP detection programs. Finally, the examination and imaging frequencies were not standardized in the e-ROP Study or the G-ROP Study; they were determined based on the decision of the examining ophthalmologists, who generally followed common clinical practice. The savings with regard to examinations and imaging sessions could be higher or lower than those observed in this pilot study depending on the schedule adopted. The savings could further be affected if the screening schedule is modified based on low-risk or high-risk status determined by weight gain parameters. Identification of the ideal screening schedule requires further investigation.

Conclusions

We found that both a postnatal weight gain predictive model and a telemedicine approach to ROP screening could result in

a decrease in the demand for ophthalmologist time. However, applying these 2 modalities in a serial tiered approach to ROP screening may improve the efficiency of the important ROP detection program more than the use of either modality alone while still ensuring that all infants requiring treatment are identified in a timely manner. Additional larger studies may

help determine the sensitivity of these approaches with higher precision, identify potential gaps in the process, and provide relative cost-effectiveness data to assist clinicians in their choice of an ROP screening process that best aligns with the resource availability and needs of their specific neonatal intensive care unit setting.

ARTICLE INFORMATION

Accepted for Publication: November 12, 2016.

Published Online: January 5, 2017.

doi:10.1001/jamaophthalmol.2016.5203

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

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding/Support: This work was supported by grants U10EY017014 (Dr Quinn) and R01EY021137 (Dr Binenbaum) from the National Institutes of Health.

Role of the Funder/Sponsor: The funding institution had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit manuscript for publication.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Meeting Presentations: This study was presented in part at the 42nd Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus; April 7, 2016; Vancouver, British Columbia, Canada; the Association for Research in Vision and Ophthalmology (ARVO) 2016 Annual Meeting; May 5, 2016; Seattle, Washington; and the 37th Annual Meeting of the Society for Clinical Trials; May 17, 2016; Montreal, Quebec, Canada.

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