

THE PHOTOGRAPHIC SCREENING FOR RETINOPATHY OF PREMATURITY STUDY (PHOTO-ROP)

Primary Outcomes

PHOTOGRAPHIC SCREENING FOR RETINOPATHY OF PREMATURITY
(PHOTO-ROP) COOPERATIVE GROUP*

Purpose: To evaluate the utility of remote digital fundus imaging as compared to indirect ophthalmoscopy to screen for retinopathy of prematurity (ROP).

Methods: This was a prospective, multicenter, masked clinical trial. Infants <31 weeks gestational age and <1000 g at birth were eligible for enrollment. Eligible enrolled infants were screened for ROP employing serial fundus imaging followed by indirect ophthalmoscopy. The main outcome measures were diagnostic sensitivity, specificity, positive and negative predictive values, and accuracy of image interpretation compared to ophthalmoscopy.

Results: Fifty-one infants (102 eyes) meeting eligibility criteria were enrolled between February 2001 and February 2002. Mean weekly examinations per infant (\pm SD) were 5.73 ± 3.22 (median 7; range 2–10). For the purposes of this study, the reading center established a definition of ROP seen on digital fundus images deemed sufficiently severe (termed clinically significant ROP, or CSROP) to warrant on-site examination by an ophthalmologist experienced in ROP. CSROP developed in 59 of 102 eyes (57.8%; 31 right eyes and 28 left eyes). Of the eyes with CSROP, 22% (13/59; 7 right eyes and 6 left eyes) progressed to ROP severe enough to require treatment according to the criteria of the Early Treatment for ROP Randomized Trial. Using onsite indirect ophthalmoscopic diagnosis as the reference standard, CSROP was identified by digital images with a sensitivity of 92% (94% right eyes and 89% left eyes) and specificity of 37.21% (40% right eyes and 35% left eyes), and Early Treatment for Retinopathy of Prematurity (ETROP) prethreshold Type I with a sensitivity of 92% (86% right eyes and 100% left eyes) and specificity of 67.39% (67% right eyes and 68% left eyes).

Conclusions: Remote interpretation of digital fundus images is a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy. Diagnostic sensitivity in this study was excellent. It was highly unlikely that severe ROP would be missed when image quality was high. Differences between the two screening approaches in timing of diagnosis of CSROP and ETROP were not statistically significant. Remote digital fundus imaging as deployed in this study is unlikely to supplant bedside ophthalmoscopic examination due to limitations in diagnostic sensitivity, specificity, and accuracy when image quality is poor.

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Retinopathy of prematurity (ROP) is a retinal vascular disorder of the premature infant and is a leading cause of preventable childhood blindness around the world. Accurate screening for ROP is of paramount importance since timely delivery of treatment is critical to maximize the chance of a favorable outcome.¹⁻³

Screening guidelines have been developed in many countries to ensure that premature infants at risk for ROP are examined at regular intervals.⁴⁻⁷ The standard method for diagnosis of ROP has been bedside indirect ophthalmoscopy for both routine clinical care and clinical trials. With this approach, the examiner's interpretations of the clinical findings are transcribed onto grading sheets, rather than a photographic record of the actual retinal features. The examiner's interpretation of fundus findings is presumed to be correct without opportunity for review.

This limitation also impacts clinical studies of treatments for ROP. In other retinal disorders, such as diabetic retinopathy and age-related macular degeneration, studies have demonstrated that digital photography with remote reading center evaluation by dedicated, trained graders is more sensitive than binocular indirect ophthalmoscopy in detecting retinal disease characteristics.⁸⁻¹³ The reading center paradigm has become the gold standard for the conduct of ophthalmic clinical trials. To date, however, all large ROP trials have gathered data by requiring examiners to draw the retinal findings as noted during the clinical examination. Neither the examiner nor study center has an opportunity to study an image of the fundus. For example, poor outcome despite adequate laser in the Early Treatment for Retinopathy of Prematurity (ETROP) was not distinguished from poor outcome due to incomplete peripheral retinal ablation.¹⁴ Photographic documentation of treatment is also essential to dis-

tinguish true therapeutic failure from poor outcome caused by incomplete treatment.

The task of screening all at-risk infants for ROP poses manpower challenges. Many physicians do not perform ROP screening for fear of litigation. In peripheral centers there may be no physician with expertise in ROP diagnosis and management. Experience with extreme prematurity may be limited. In Canada, for example, fewer than 100 subspecialists perform approximately 12,150 ROP examinations per year across the country.¹⁵

This combination of factors has fueled interest in a telemedicine approach to ROP screening. Evidence-based studies comparing remote photographic screening to on-site screening are critical to define the parameters of a telemedicine approach to ROP screening. The PHOTOROP Study was designed to evaluate the utility of remote imaging as an adjunct to indirect ophthalmoscopy in ROP screening.

Methods

Institutional review boards at all participating institutions reviewed and approved the study design and the consent forms to be used locally. Parents or guardians of infants studied gave signed informed consent before enrollment. Study design, methods, policies, and baseline characteristics of patients enrolled in The Photo-ROP Study are the subject of a separate report.¹⁶

Patient Eligibility and Enrollment

Eligibility requirements, clinical examinations, and data collection methods for The Photo-ROP Study are described elsewhere.¹⁶ Enrolled participants were premature infants born less than 31 weeks of postmenstrual age at birth and with a birthweight less than 1000 g. Consecutive infants from each of the six study centers were enrolled from February 1, 2001, to February 1, 2002. The last infant was imaged on May 30, 2002.

Examination Schedule and Procedures

The examination schedule and procedures are described in detail elsewhere.¹⁶ The center investigators performed the first ROP examination between 4 to 6 weeks of postnatal age, according to their country's screening guidelines. Both eyes of each infant were examined weekly by both digital photography and indirect ophthalmoscopy. Screening continued for up to 10 weeks or until the infant was discharged from neonatal intensive care, whichever came first. Masking of clinical centers for results of reading center digital image interpretation occurred as well as full

*The Writing Committee for the Photographic Screening for Retinopathy of Prematurity Cooperative Group includes Antonio Capone, Jr., MD, Anna Ells, MD, and Mamtha Balasubramanian, MS. The full list of participating centers (listed in alphabetical order) and investigators includes Alberta Children's Hospital, Calgary, Canada—Anna Ells, MD; Emory University, Atlanta, Georgia—G. Baker Hubbard, MD; Louisiana State University, New Orleans—Mary Elizabeth Hartnett, MD; National Children's Hospital, Dublin, Ireland—Michael O'Keefe, MD; University of California, Los Angeles, Jules Stein Eye Institute—Steven D. Schwartz, MD, Christine R. Gonzales, MD; The Western Eye Hospital, London, England—Alistair R. Fielder, FRCP, FRCS, FRCOphth, MD, Kenneth D. Cocker, MSc; William Beaumont Hospital (Study Center), Royal Oak, Michigan—Mamtha Balasubramanian, MS, Antonio Capone, Jr., MD, Michael T. Trese, MD.

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Reprint requests: Antonio Capone Jr, MD, 344 Medical Office Building, 3535 West 13 Mile Road, Royal Oak, MI 48073; e-mail: acaponejr@yahoo.com

masking of reading center image graders for results of indirect ophthalmoscopy examination.

Digital photographic imaging of both fundi was performed first. Next, indirect ophthalmoscopy was performed by the clinical center ophthalmologist on the right eye first, using a 25 or 28 diopter condensing lens and scleral depression. The retina was examined over 360 degrees to the ora serrata. The presence or absence of plus disease and ROP by zone, stage, and clock hour were recorded according to the International Classification of ROP on the ROP Data Form.¹⁷

The RetCam-120 camera system used in this study is a contact camera that directs transpupillary illumination to provide 130 degree images of 640×480 pixel resolution. Each image is approximately 900 Kilobytes in size with a resolution of 72 pixels/inch and a realistic color match. A standard image set for each eye consisted of the iris, followed by disk centered in the image, followed by images of temporal, nasal, superior, and inferior retinal fields (Figure 1). The goal for each examination was capture of 12 digital images (six images per eye) from each infant in each examination session. Images were initially stored on the RetCam-120 computer hard drive. The images were anonymized (using anonymizing software) and transferred uncompressed from the hard drive via the Internet employing a secure file transfer protocol (FTP) to a secure encrypted password protected institutional FTP server, or by mail on a ZIP diskette or writable compact discs (R-CDs). Images were stored on the institutional FTP server and posted for review by the reading center graders.

Remote Reading of Digitized Images

All image sets were read by two masked physician graders at the Reading Center experienced in ROP

diagnosis and management. Images were scored according to the highest stage of ROP, lowest zone, and the presence or absence of plus disease. Results were entered into the database.

Definition of Clinically Significant ROP and ETROP Type I Criteria

For the purposes of this study, the reading center established a definition of clinically significant ROP (CSROP) representing five descriptions of ROP sufficiently severe to warrant on-site examination by an ophthalmologist experienced in ROP (Table 1). Two of the definitions for CSROP address eyes for which images provide incomplete information regarding the presence of either ROP (CSROP 4) or plus disease (CSROP 5). The reading center also identified eyes requiring treatment based on the definitions of Type I prethreshold ROP in the ETROP Study (Table 1).¹⁸

Data Analysis and Statistical Methods

All pertinent data from each patient received at the Photo-ROP reading center were analyzed.

In keeping with the stated goal for the study, ROP staging based on Reading Center image interpretation was compared to ROP staging by ophthalmologists experienced in ROP screening performing bedside indirect ophthalmoscopic examinations, with the bedside examination determination as the gold standard.

In addition, ROP staging based on reading center image interpretation was compared to ROP staging by ophthalmologists experienced in ROP screening performing bedside indirect ophthalmoscopic examinations, with the reading center interpretation as the gold standard. This analysis was performed to speak to the

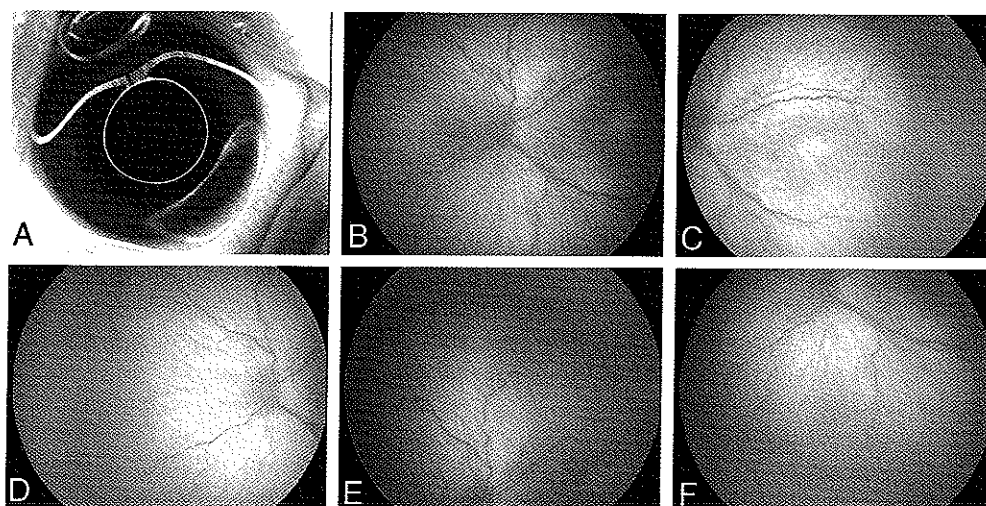


Fig. 1. PHOTO-ROP Standard Image Set.

Table 1. Reading Center Definitions of Clinically Significant ROP and ROP Requiring Early Treatment (Type I ETROP)

Clinically Significant ROP
Zone 1, any ROP, without vascular dilation or tortuosity
Zone II, stage 2, with up to one quadrant of vascular dilation and tortuosity
Zone II, stage 3, with up to one quadrant of vascular dilation and tortuosity
Any vascular dilation and tortuosity noted in eyes for which ridge characteristics were not interpretable (not imaged or poor image quality)
Any ROP noted in eyes for which disc features (plus disease) were not interpretable (not imaged or poor image quality)
Type I ETROP criteria for early treatment ¹²
Zone 1, any ROP, with plus disease (vascular dilation and tortuosity in at least two quadrants)
Zone 1, stage 3 ROP, without vascular dilation and tortuosity in at least two quadrants
Zone 2, stages 2 or 3 ROP, with vascular dilation and tortuosity in at least two quadrants

ROP = retinopathy of prematurity.

question as to whether remote imaging could supplant bedside indirect ophthalmoscopic examination as the primary approach to screening for ROP.

Finally, the two modalities were compared as to whether and when CSROP and ETROP were identified.

reading center data (digital image interpretations) and clinical site data (bedside indirect ophthalmoscopic examination diagnoses) were separately analyzed in the following fashion:

- For each patient at each examination date for each eye, the presence/absence of each of the 5 levels of CSROP and 3 levels of ETROP were coded as Yes/No (i.e., 1/0).
- In the interest of obtaining the overall picture as well as maintaining simplicity and clarity, all levels of CSROP were combined into a binomial response (i.e., presence/absence of CSROP) for each patient at each visit for each eye. The same was done for ETROP.
- The two data sets were then merged into one by patient ID and visit date.
- From the merged data set, a new data set was created that contained data on the presence or absence of CSROP and/or ETROP based on all visits for each patient for each eye, consistent with goal 3. As it was of primary interest to detect the first instance of ROP based on the clinical site data and then the reading center data, none of the previous or subsequent eye examinations/images were considered once ROP was detected. They were considered only to determine for each eye:

- If only CSROP was detected or if it was detected before or on the same day as ETROP,
- If ETROP was detected before CSROP,
- If only ETROP was detected but not CSROP,
- If neither CSROP nor ETROP was detected.

Thus each eye for each infant was counted in only one of these four mutually exclusive categories. This is tantamount to combining all data for an eye for each infant into a single diagnosis. Hence the correlation among multiple eye examinations/images of the same infant was no longer at issue.

There were a few infants for whom the first instance of CSROP was detected in one but not both eyes by one but not both centers. This was true of ETROP as well. And in some infants, only ETROP (and no CSROP) was detected, while in a few others ETROP was detected before CSROP—by either the reading center or clinical center, but not both. The calculations were performed for each eye for CSROP and then ETROP for those with CSROP—once using the Reading Center as the reference standard and then using the clinical site diagnosis as the reference standard. Hence, depending on what the reference standard is, these eyes were either included or excluded from these calculations, resulting in the difference in the frequency counts and diagnostic measures in Table 2. Each eye was analyzed separately in this regard, consistent with the clinical practice of making treatment decisions based on the findings of a given eye.

Sample size and statistical considerations are described in detail elsewhere.¹⁶ Sensitivities, specificities, positive predictive values, negative predictive values, and accuracies as well as their 95% confidence intervals (95% CI)¹⁹ for detecting CSROP and ETROP in each eye were computed for both the clinical and reading centers using definitions below based on the data set containing only one row of data for each infant. The parameters were determined first for the clinical center as the reference standard and then for the reading center as the reference standard:

Sensitivity = true positives/(true positives + false negatives)

Specificity = true negatives/(true negatives + false positives)

Positive predictive value (PPV) = true positives/(true positives + false positives)

Negative predictive value (NPV) = true negatives/(true negatives + false negatives)

Accuracy = (true positives + true negatives)/(all infants tested)

Continuous variables were summarized using means, standard deviations, and medians. The variables based on

Table 2. Postmenstrual Age (Weeks) at Examination for Each Eye*

Eye	No., Mean \pm Standard Deviation; Median (Minimum, Maximum)
Based on data from the clinical sites	
For CSROP	
R	30, 34.40 \pm 2.92; 34.14 (30.14, 40.14)
L	27, 33.97 \pm 2.79; 34.14 (30.14, 40.14)
For ETROP in eyes that first had CSROP	
R	7, 36.92 \pm 2.15; 36 (34.86, 41.14)
L	6, 36.52 \pm 2.40; 36 (34, 41.14)
Based on data from the reading center	
For CSROP	
R	37, 34.54 \pm 2.16; 34.14 (31.14, 42.57)
L	36, 34.21 \pm 2.30; 34.14 (26.14, 42.57)
For ETROP in eyes that first had CSROP	
R	13, 36.10 \pm 1.38; 36.14 (33.86, 38.14)
L	15, 35.91 \pm 1.99; 36 (32.43, 39.57)

*Excluding same day detection of clinically significant retinopathy of prematurity (CSROP) and early treatment retinopathy of prematurity (ETROP) as well as those with ETROP before CSROP.

differences in the time of visits were first assessed to determine their distributions. Based on this, either parametric (Student *t* test) or nonparametric (Wilcoxon Signed Rank Test) analyses were used.

P values less than an alpha of 0.05 (probability of Type I error) were considered statistically significant. Statistical analysis was performed using the SAS System for Windows version 9.1.3, Service Pak 2.

Results

Demographics and Examinations

Sixty-two infants were enrolled from six clinical centers. Eleven of the enrolled infants did not meet eligibility criteria for inclusion because either ROP severity was already at or beyond ETROP treatment threshold (whether treated or not) at initial examination (6 infants), or only a single examination was performed (5 infants). The remaining 51 infants (102 eyes) were considered eligible and are the subject of this article.

The mean gestational age (\pm SD) at the time of delivery was 26.80 \pm 1.73 weeks (median = 26.86 weeks, interquartile range [IQR] = 2.43 weeks). Mean postmenstrual age at first examination was 32.19 weeks \pm 2.86 weeks SD (median = 31.71 weeks, IQR = 2.29 weeks). Mean birthweight (\pm SD) was 830.51 \pm 219.57 g (median = 817 g, IQR = 225 weeks). Female infants comprised 49.02% of the patients. Race distribution was white 45.10%, African or Black 39.22%, Asian 9.8%, Hispanic 3.92%, and other races 1.96%. Mean number of examinations per infant (\pm SD) was 5.73 \pm 3.22 weeks (median = 7 weeks; range = 2 to 10 weeks).

Table 2 presents the results of postmenstrual age at the

time of diagnosis of CSROP and ETROP in each eye based on clinical site data and reading center data.

Three hundred image sets (3836 images) were acquired for remote reading at the reading center. Ninety-two percent (293/300) of the image sets were interpretable. An image set was defined as interpretable when one or more of the images in the set could be used to score zone, stage, and plus disease with confidence for a given eye. An image set was defined as uninterpretable when images in the set, individually or as a group, were of inadequate quality to allow the eye to be scored with confidence. Uninterpretable image sets were typically a consequence of 1) inadequate dilation limiting adequate illumination of the retina, or casting an obstructing shadow, 2) dark fundus pigmentation with poor image contrast, 3) vitreous haze due to extreme prematurity, or some combination of one or more of these features.

The two masked readers read the image sets of each infant in chronological order. A single clear wide-angle image of the posterior pole was often adequate to determine the presence of CSROP or ETROP. The CSROP or ETROP criterion most commonly scored on a single image of the posterior pole was plus disease. When images were of poorer quality (with regard to lighting, focus, clarity, field, or any combination thereof) the entire image set was used to make a determination as to the ROP status of the eye.

Two masked graders scored each image. If a grade for an image set was not agreed upon for either CSROP or ETROP, a consensus opinion was formulated. Disagreements were typically on the presence of nor-

mal posterior pole vessels versus posterior pre-plus vascular changes.²⁰

No adverse reactions or complications occurred as a consequence of either fundus imaging or indirect ophthalmoscopy.

Detection of Clinically Significant ROP and Subsequent ETROP Type I

Analysis Using Indirect Ophthalmoscopic Diagnosis as the Reference Standard.—Using the ROP diagnosis from the indirect ophthalmoscopic examinations (i.e., data from the clinical sites) as the reference standard, CSROP developed in 59 of 102 eyes (57.8%; 31 right and 28 left) with 22% (13/59; 7 right and 6 left) progressing further to ETROP Type I prethreshold ROP (i.e., excluding same-day detection).

Sensitivities, specificities, positive and negative predictive values, and accuracies for detecting CSROP and ETROP using the ROP diagnosis from the clinical sites as the reference standard are listed in Table 3.

Progression Interval: Clinically Significant ROP to ETROP Type I In the 22.03% (13/59; 7 right and 6 left) of eyes with CSROP that progressed to ETROP Type I, the mean interval to progression was 25.72 days (26.43 days for right eyes and 25 days for left eyes).

Timing of Diagnosis of CSROP or ETROP by the reading center Versus clinical centers Considering all images without regard for quality (i.e., including CSROP 4 and CSROP 5), there was no significant difference in timing of diagnosis of CSROP in either eye between the reading center and the clinical centers (*P* value = 0.4434 for right eyes and 0.1566 for left eyes). However, on average the reading center detected ETROP 5.7 days and 8 days sooner than the clinical

centers in right and left eyes respectively (*P* value = 0.1892 for right eyes and 0.0550 for left eyes).

When image quality was high (i.e., excluding CSROP 4 and CSROP 5) there was no significant difference in timing of diagnosis of CSROP in either eye between the reading center and clinical centers (*P* value = 0.0947 for right eyes and 0.1633 for left eyes). Using only CSROP images 1, 2, and 3, the reading center detected ETROP on an average 4.9 days and 6.9 days before the clinical centers in right eyes and left eyes, respectively (*P* value = 0.1862 for right eyes and 0.0989 for left eyes).

Analysis Using Remote Diagnosis of Digital Images as the Reference Standard.—Using the ROP diagnosis from the digital images (i.e., data from the Reading Center) as the reference standard, CSROP developed in 73 of 102 eyes (71.6%; 37 right eyes and 36 left eyes), with 38% (28/73; 13 right eyes and 15 left eyes) progressing further to ETROP Type I prethreshold ROP (i.e., excluding same-day detection).

Sensitivities, specificities, positive and negative predictive values, and accuracies for detecting CSROP and ETROP using the ROP diagnosis from the reading center as the reference standard are listed in Table 3.

Progression Interval: Clinically Significant ROP to ETROP Type I In the 38% (28/73; 13 right eyes and 15 left eyes) of eyes with CSROP that progressed to ETROP Type I, the mean interval to progression was 16.11 days (18.54 days for right eyes and 13.67 days for left eyes).

Timing of Diagnosis of CSROP or ETROP by the reading center versus clinical centers Considering all images without regard for quality (i.e., including

Table 3. Diagnostic Measures for Each Eye

	TP	FN	FP	TN	Sensitivity (95% CI)*	Specificity (95% CI)*	PPV (95% CI)*	NPV (95% CI)*	Accuracy (95% CI)*
Using clinical site diagnosis as reference standard									
Any CSROP for									
R	29	2	12	8	94 (79–98)	40 (22–61)	71 (56–82)	80 (49–94)	73 (59–83)
L	25	3	15	8	89 (73–96)	35 (19–55)	63 (47–76)	73 (43–90)	65 (51–76)
Any ETROP for those with any CSROP for									
R	6	1	8	16	86 (49–97)	67 (47–82)	43 (21–67)	94 (73–99)	71 (53–84)
L	6	0	7	15	100 (61–100)	68 (47–84)	46 (23–71)	100 (80–100)	75 (57–87)
Using reading center diagnosis as reference standard									
Any CSROP for									
R	28	12	2	8	70 (55–82)	80 (49–94)	93 (79–98)	40 (22–61)	72 (58–83)
L	25	15	2	8	63 (47–76)	80 (49–94)	93 (77–98)	35 (19–55)	66 (52–78)
Any ETROP for those with any CSROP for									
R	6	8	1	23	43 (21–67)	96 (80–99)	86 (49–97)	74 (57–86)	76 (61–87)
L	5	7	0	21	42 (19–68)	100 (85–100)	100 (57–100)	75 (57–87)	79 (62–89)

*Expressed as percentages rounded off.

TP = true positive; FN = false negative; FP = false positive; TN = true negative; CSROP = clinically significant retinopathy of prematurity; ETROP = early treatment retinopathy of prematurity.

CSROP 4 and CSROP 5), there was no significant difference in timing of diagnosis of CSROP in either eye between the reading center and the clinical centers (P value = 0.6887 for right eyes and 0.6392 for left eyes). However, on an average, the clinical centers detected ETROP 11 days and 12.3 days sooner than the reading center in right and left eyes respectively (P value = 0.0938 for right eyes and 0.0313 for left eyes). When image quality was high (i.e., excluding CSROP 4 and CSROP 5) there was no significant difference in timing of diagnosis of CSROP in either eye between the reading center and clinical centers (P value = 0.0947 for right eyes and 0.1614 for left eyes). Using only CSROP images 1, 2, and 3, the reading center detected ETROP on an average 4.25 days and 4.57 days before the clinical centers in right eyes and left eyes respectively (P value = 0.1840 for right eyes and 0.3160 for left eyes).

Discussion

The goal of screening for ROP is timely identification of infants requiring treatment. The foremost barriers to effective screening are manpower issues and lack of familiarity with the various clinical features of ROP. The screening ideal would be to have a world renowned ROP expert perform each infant's ROP screening examinations—an impractical ideal if the expert must be present in person at the bedside. In a national audit in the United Kingdom in 1997–1998, 8200 premature infants were examined for ROP and only 277 infants went on to treatment.²¹ Considered another way, 55 ROP examinations by an ophthalmologist occurred for every infant who was treated. In Canada and the United States, a similar ratio exists between infants screened and infants treated.^{4,22–24} Implementation of a longitudinal digital imaging paradigm with remote (reading center) image interpretation has the potential to maximize utilization of physician time and to broaden the availability of high level ROP diagnostic expertise.

The ROP severity definition CSROP was created for the purposes of this study in recognition of the fact that bedside ophthalmoscopy and digital fundus imaging are neither identical nor exactly interchangeable, but complementary. CSROP was designed to serve as a telemedicine referral threshold definition indicating the need for on-site examination by an experienced ophthalmologist. ETROP Type I criteria are similar to CSROP, although CSROP has a slightly greater funnel effect (or lower severity of disease referral threshold) for infants at risk for severe disease. In a remote screening paradigm it is desirable to have a "buffer zone" between the clinical findings

signaling higher potential risk of progression and the actual treatment criteria, in the interest of minimizing the likelihood of missing early treatable disease.

The findings of the current study demonstrate the effective funnel effect of CSROP criteria. Using the ROP diagnosis from the indirect ophthalmoscopy examination (i.e., the clinical sites) as the reference standard, CSROP developed in 59 of 102 eyes (57.8%; 31 right eyes and 28 left eyes) with 22% (13/59; 7 right eyes and 6 left eyes) progressing further to ETROP Type I prethreshold ROP (i.e., excluding same-day detection). Using the ROP diagnosis from the digital images (i.e., the reading center) as the reference standard, CSROP developed in 73 of 102 eyes (72%; 37 right eyes and 36 left eyes), with 38% (28/73; 13 right eyes and 15 left eyes) progressing further to ETROP Type I prethreshold ROP (i.e., excluding same-day detection).

The current study demonstrates the utility of remote imaging as an adjunct to indirect ophthalmoscopy in ROP screening. When the clinical center data are the reference standard, sensitivity in detecting both clinically significant ROP and ETROP Type I in each eye was excellent. Negative predictive value is a metric for the likelihood of missing true disease in each eye. The negative predictive value of 94% for right eyes and 100% for left eyes for detection of Type I ETROP in this study indicates that it was highly unlikely that severe ROP would be missed employing remote imaging with centralized interpretation. Positive predictive values were low in the study due to the reading center tendency to "overcall" pathology.

When using the reading center diagnosis as the reference standard to address the effectiveness of remote digital imaging as the primary screening methodology and how often clinicians performing indirect ophthalmoscopic examinations were in agreement, the specificity and positive predictive values are high, indicating excellent identification of eyes truly negative or positive for CSROP and ETROP using the RetCam. However, the poor sensitivity, negative predictive value, and accuracy suggest that bedside examinations cannot supplant indirect ophthalmoscopy for screening ROP.

Timely identification of ROP severe enough to require treatment is critical for an effective screening program. The ETROP¹⁸ reported better structural and functional outcomes in infants treated with severity less than threshold disease. This underscores the impact of timing of diagnosis on treatment outcome. In their pilot study of telemedicine screening for ROP,²⁵ Ells et al used definition for "referral warranted ROP" similar to CSROP as a telemedicine trigger. In that study referral warranted ROP was diagnosed remotely at least 1 week earlier than on-site indirect ophthal-

moscopy in 10 out of 23 eyes, all 10 of which went on to require treatment.²⁵ In the current study, there was no statistically significant difference in timing of diagnosis of CSROP or ETROP between the reading center and the clinical centers. When image quality was high (CSROP images 1, 2, and 3, in Table 1) there was a trend toward earlier detection of both CSROP and ETROP, although this finding was not statistically significant. In the current study, differences between the two screening approaches in timing of diagnosis of CSROP and ETROP were not statistically significant.

In summary, longitudinal (weekly) digital imaging was sensitive and specific for detection of CSROP and ETROP Type I in this study, with a high negative predictive value for the latter. These results support the concept of photographic screening as an adjunct to bedside evaluation of infants with characteristics of severe disease. The goal of integrating digital imaging into routine care is reasonable, particularly in view of the manpower issues related to this task. The one-time cost of the digital screening camera is easily offset by the reduction in physician time and medico-legal risk. Photographic screening would also minimize uncertainty in medicolegal cases, and provide a more consistent level of screening for all at-risk infants. The results of this study are intended to help formulate better screening methodologies for premature infants at risk for developing severe ROP.

Key words: retinopathy of prematurity, ROP, telemedicine, screening, RetCam-120.

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