Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness around the world. ROP screening is a hot topic. The goal of screening for ROP is timely identification of infants requiring treatment.

The screening ideal would be to have a recognized ROP expert perform each infant’s ROP screening exam, which is an impractical ideal if the expert must be present in person at the bedside. 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 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. One limitation to this approach is that the examiner’s interpretation of fundus findings is presumed to be correct without opportunity for review.

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 ETROP (Early Treatment for Retinopathy of Prematurity) trial was not distinguished from poor outcome due to incomplete peripheral retinal ablation. Photographic documentation would serve to confirm diagnosis and distinguish 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. Experience with extreme prematurity may be limited.

This combination of factors has fueled interest in a telemedicine approach to ROP screening. The Photographic Screening For Retinopathy Of Prematurity (Photo-ROP) Study was designed to evaluate the utility of remote imaging as an adjunct to indirect ophthalmoscopy in ROP screening.
MATERIALS AND METHODS

Enrolled participants were premature infants less than 31 weeks of gestational age at birth, with a birth weight less than 1000 grams. 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.

Examinations began at 31 weeks gestational age or 4 weeks postnatal age, whichever was later. Digital photographic imaging of both fundi was performed first. The RetCam-120 (Clarity Medical, Pleasanton, CA) camera system was used in this study. A standard set of six images per eye were captured from each infant in each exam session for each eye (iris and disc images, followed by images of temporal, nasal, superior, and inferior retinal fields). 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. Images were posted for review by the Reading Center graders.

Next, indirect ophthalmoscopy was performed by the Clinical Center ophthalmologist on the right eye first, using a 25-D or 28-D condensing lens and scleral depression. The presence or absence of plus disease and ROP (zone/stage/clock hour) were recorded as per the International Classification of ROP. Examinations were performed weekly for 10 weeks or until an infant was discharged from the hospital.

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.

For the purposes of this study, the Reading Center

Figures A-D. Examples of uninterpretable images. (A) Small pupil. (B) Fundus image of eye from top left with photographic artifact as a result of poor dilation. (C) Darkly pigmented fundus with poor fundus detail despite good dilation. (D) Poor fundus detail due to vitreous haze of prematurity.
established a definition of clinically significant ROP (CSROP) representing five descriptions of ROP sufficiently severe to warrant onsite 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 1 prethreshold ROP in the ETROP Study (Table 1).

Sensitivity, specificity, and positive and negative predictive values of Reading Center image interpretations were compared with clinical impressions based on bedside indirect ophthalmoscopy with the bedside examination determination as the “gold standard.”

RESULTS
Fifty-one infants (102 eyes) are the subject of this article. Mean gestational age was 26.80 ± 1.73 weeks (median = 26.86 weeks, interquartile range [IQR] = 2.43 weeks). Mean postmenstrual age at first examination was 32.19 weeks ± 2.86 weeks standard deviation (SD; median = 31.71 weeks, IQR = 2.29). Mean birth weight (±SD) was 830.51 ± 219.57 grams (median = 817 grams, IQR = 225). Female infants comprised 49.02% of the patients. Race distribution was white 45.10%, black 9.22%, Asian 9.8%, Hispanic 3.92%, and other races 1.96%. Mean number of examinations (1 per week) per infant (±SD) was 5.73 ± 3.22 weeks (median = 7 weeks; range = 2–10 weeks).

Three hundred image sets (3,836 images) were acquired for remote reading at the Reading Center. Ninety two percent (293/300) of the image sets were interpretable—ie, 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. 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 (Figure 1).

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.

Using the ROP diagnosis from the indirect ophthalmoscopic examinations as the reference standard, CSROP developed in 57.8% (59/102 eyes) with 22% (13/59 eyes) progressing further to ETROP Type I prethreshold ROP.

In the 22.03% (13/59; seven OD and six OS) of eyes with CSROP that progressed to ETROP Type I, the mean interval to progression was 25.72 days (26.43 days for OD and 25 days for OS).

When image quality was high (ie, excluding CSROP 4 and CSROP 5) there was no statistically significant difference in timing of diagnosis of CSROP or ETROP Type I between the Reading Center and Clinical Centers.

DISCUSSION
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 interchange-

**TABLE 1. READING CENTER DEFINITIONS OF CLINICALLY SIGNIFICANT ROP (CSROP) AND ROP REQUIRING EARLY TREATMENT (TYPE I ET-ROP)**

<table>
<thead>
<tr>
<th>Clinically Significant ROP (CSROP)</th>
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<tr>
<td>Zone 1, any ROP, without vascular dilation or tortuosity.</td>
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<tr>
<td>Zone II, stage 2, with up to one quadrant of vascular dilation and tortuosity.</td>
</tr>
<tr>
<td>Zone II, stage 3, with up to 1 quadrant of vascular dilation and tortuosity.</td>
</tr>
<tr>
<td>Any vascular dilation and tortuosity noted in eyes for which ridge characteristics were not interpretable (not imaged or poor image quality).</td>
</tr>
<tr>
<td>Any ROP noted in eyes for which disc features (plus disease) were not interpretable (not imaged or poor image quality).</td>
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<tr>
<th>Type I ET-ROP criteria for early treatment</th>
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<tr>
<td>Zone I, any ROP, with plus disease (vascular dilation and tortuosity in at least two quadrants).</td>
</tr>
<tr>
<td>Zone I Stage 3 ROP, without vascular dilation and tortuosity in at least two quadrants.</td>
</tr>
<tr>
<td>Zone II, stages 2 or 3 ROP, with vascular dilation and tortuosity in at least 2 quadrants.</td>
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able, 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 clinically significant ROP, although clinically significant ROP 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 OD and 28 OS) with 22% (13/59; 7 OD and 6 OS) 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 Site 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 OD and 100% for OS for detection of Type I ETROP in this study (Table 2) 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 exams were in agreement, the specificity and positive predictive values were high, indicating excellent identification of eyes truly negative or positive for CSROP and ETROP using the RetCam. However, poor sensitivity and negative predictive value suggest that bedside exams cannot supplant indirect ophthalmoscopy for screening ROP.

Timely identification of ROP severe enough to require treatment is crucial for an effective screening program. The ETROP reported better structural and functional outcomes in infants treated with severity of less than threshold disease. This underscores the impact of timing of diagnosis on treatment outcome. In a pilot study of telemedicine screening for ROP, Ells et al used a 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 onsite indirect ophthalmoscopy in 10 of 23 eyes, all 10 of which went on to

<table>
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<th>TABLE 2. DIAGNOSTIC MEASURES FOR EACH EYE</th>
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<tr>
<td><strong>Using Clinical Site Diagnosis as Reference Standard</strong></td>
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<tr>
<td><strong>Sensitivity</strong></td>
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<tr>
<td>(95%CI)**</td>
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<tr>
<td><strong>Any CSROP For:</strong></td>
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<tr>
<td>OD</td>
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<tr>
<td>OS</td>
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<tr>
<td><strong>Any ETROP for those with Any CSROP For:</strong></td>
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** Expressed as percentages rounded off
require treatment. 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, 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.

**SUMMARY**

Longitudinal (weekly) digital imaging was sensitive and specific for detection of CSROP and ETROP Type 1 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 medicolegal 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.

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