SUNDROP: six years of screening for retinopathy of prematurity with telemedicine

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ABSTRACT • RÉSUMÉ

Objective: To report the 6-year results of the Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) initiative in the context of telemedicine screening initiatives for retinopathy of prematurity (ROP).

Participants: Premature newborns requiring ROP screening at 6 neonatal intensive care units from December 1, 2005, to November 30, 2011.

Methods: Infants were evaluated via remote retinal photography by an ROP specialist. A total of 608 preterm infants meeting ROP examination criteria were screened with the RetCam II/III (Clarity Medical Systems, Pleasanton, Calif.). Primary outcomes were treatment-warranted ROP (TW-ROP) and adverse anatomical events.

Results: During the 6 years, 1216 total eyes were screened during 2169 examinations, generating 26 970 retinal images, an average of 3.56 examinations and 44.28 images per patient. Twenty-two (3.6%) of the infants screened met criteria for TW-ROP. Compared with bedside binocular ophthalmoscopy, remote interpretation of RetCam II/III images had a sensitivity of 100%, specificity of 99.8%, positive predicative value of 95.5%, and negative predicative value of 100% for the detection of TW-ROP. No adverse anatomical outcomes were observed for any enrolled patient.

Conclusions: The 6-year results for the SUNDROP telemedicine initiative were highly favourable with respect to diagnostic accuracy. Telemedicine appears to be a safe, reliable, and cost-effective complement to the efforts of ROP specialists, capable of increasing patient access to screening and focusing the resources of the current ophthalmic community on infants with potentially vision-threatening disease.

Retinopathy of prematurity (ROP) is a retinal vascular disease characterized by abnormal angiogenesis that may result in permanent visual impairment or complete blindness in premature and low-birth-weight infants. In the United States from 1997 to 2005, the total incidence rate of ROP was 0.12% to 0.17% overall and 15.58% for premature newborns with a length of stay of more than 28 days. According to the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and Early Treatment for Retinopathy of Prematurity (ETROP) trials reported in 1991 and again in 2005, ROP develops in an estimated 68% of premature babies weighing less than 1251 g, of which more than a third

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The 6-year results were presented by D.M.M. at the Massachusetts Eye and Ear Infirmary Grand Rounds “Telemedicine for ROP Screening,” 243 Charles St, Boston, MA 02114, July 2013.

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represent severe cases of the condition.\textsuperscript{6,7} Hence as neonatal survival worldwide continues to improve because of the increasing global presence of life-preserving technologies, ROP will persist internationally as a leading cause of childhood blindness.\textsuperscript{2} Consequently, there is an emergent need for scalable yet dependable approaches to the detection and management of ROP.

ROP treatments such as laser photocoagulation and anti-vascular endothelial growth factor drugs have been shown to possess vision-saving benefits when given early in the course of disease.\textsuperscript{2,6-8} ROP is a sequential disease that requires at-risk preterm infants to be examined at regular intervals to detect treatment-warranted changes before permanent damage occurs.\textsuperscript{9} To facilitate a standardized screening process, the American Academy of Pediatrics (AAP) in conjunction with the American Academy of Ophthalmology (AAO) and Association of Pediatric Ophthalmology and Strabismus (AAPOS) presented a revised statement of guidelines for an effective ROP screening program in 2013.\textsuperscript{9} With screening guidelines in place, the challenge will now be to deliver these recommendations to infants who are born in regions that lack trained ophthalmologists. Without effective means of delivering care to these infants, a large portion of premature infants will remain vulnerable to vision loss, blindness, and other ROP-related complications.\textsuperscript{10,11}

Telemedicine offers promise as a potential method to alleviate the burden of ROP screening by implementing remote interpretation of digital retinal photography to complement the work of pediatric ophthalmologists and retina specialists who treat ROP. Throughout the past decade, the sensitivity and specificity of digital screening technologies have improved, with recent studies indicating comparable outcomes between telemedicine-based retinal image photography and screening via indirect ophthalmoscopy.\textsuperscript{12-15} Moreover, by mediating online consultation and providing data for retrospective analysis as part of the electronic health record, digital imaging devices such as the RetCam (Clarity Medical Systems, Pleasanton, Calif.) may offer more objective information for ROP detection and historical comparison, thus paving the way for better care.\textsuperscript{16}

Other potential benefits of remote telemedicine screening include decreased cost of travel, reduced stress from bedside examinations of at-risk infants, and an extension of ROP diagnostic expertise into underserved regions on both a national and an international level.\textsuperscript{14,16,17}

The Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) is an ongoing telemedicine-based community initiative for in-hospital screening of high-risk infants for treatment-warranted ROP (TW-ROP) at 6 satellite neonatal intensive care units (NICUs) situated throughout Northern California. The goal of the SUNDROP initiative is to reduce blindness and poor visual outcomes from ROP by providing infants in rural and county hospitals with quaternary care. At each site, all infants meeting AAP/AAO/AAPOS criteria are screened using RetCam II images, which are subsequently sent to the Stanford University Byers Eye Institute reading centre for remote interpretation by an ROP specialist. The purpose of this study is to report the 6-year results of the SUNDROP initiative and present a review of telemedicine screening initiatives for ROP.

**METHODS**

The study was approved by the Institutional Review Board (IRB 8752) at Stanford University School of Medicine, which granted a waiver of consent for retrospective analysis of screening data from the first 6 years of the SUNDROP initiative. All research was conducted in compliance with human subject regulations and in accordance with the tenets of the Declaration of Helsinki.

All infants at 6 participating NICUs in Northern California who met AAP/AAO/AAPOS screening criteria for ROP were enrolled in the SUNDROP initiative. This study examined infants screened during the first 6 years of enrollment (December 1, 2005, to November 30, 2011) from level I, II, and III nurseries that included community, private, and county hospitals comprising a demographically, ethnically, and socioeconomically diverse population. Sex, estimated gestational age, birth weight, and multiple birth data were obtained from delivery records at each hospital. Birth weight was categorized as extremely low birth weight (ELBW; <1000 g) or other premature birth weights (1000–2500 g) to assess the percentage of TW-ROP that would be classified as ELBW by the World Health Organization. Multiple births were designated as singletons, twins, or triplets.

Nurses at each NICU were trained to capture wide-angle (130° lens) retinal photographs using the RetCam II/III as previously described.\textsuperscript{12,18-22} At each site, a team of 1 or 2 nurses was responsible for positioning the infant, monitoring vital signs, and performing digital imaging. Infants were dilated with 2.5% phenylephrine and 1% tropicamide 30 to 60 minutes before imaging, with feedings discontinued 2 hours before and after examination in accordance with aspiration precaution guidelines. Throughout each examination, vital signs, cardiopulmonary status, and oxygen saturation were closely monitored for possible bradycardia and apnea. If signs of either condition were present, imaging was halted until the patient was deemed stable to continue.

Directly before examination, 0.5% proparacaine was instilled in each eye as a topical anaesthetic. Eyes were opened with a sterile lid speculum and 2.5% hydroxypropyl methylcellulose was used to couple the digital camera lens to the infant’s cornea to provide adequate exposure for photography. In each eye, the goal was to obtain at minimum 5 clearly focused images with the 130° lens: (i) optic nerve centred, (ii) optic nerve superior, (iii) optic nerve inferior, (iv) optic nerve nasal, and (v) optic
nerve temporal. Photos were captured as necessary until they were deemed to be of sufficient quality as determined by the image interpreter. Later during the first year of the initiative, an iris image in each eye was also added to the protocol. In cases of inadequate exposure, artifact, poor visualization of the periphery, or lack of a complete standardized image set, a repeat telemedicine evaluation was performed within 48 hours.

Patient retinal photographs and data were transferred via secure and encrypted email, secure file transfer protocol, or on rare occasion via courier (DVD format), with families and NICU staff informed of the image interpretation within 24 hours. All study data were collected and managed in a Health Insurance Portability and Accountability Act–compliant manner using REDCap (Research Electronic Data Capture) tools hosted at Stanford University.

All enrolled infants underwent inpatient retinal image capture for ROP screening with remote evaluation at the Stanford Byers Eye Institute reading centre by an ROP specialist. For all patients, the frequency of screening examinations was consistent with those recommended by the joint criteria statement for ROP screening.

Primary outcomes of the study were TW-ROP and anatomic findings such as vision loss, retinal detachment, macular fold, or retrolental mass. Interpretation of images was performed according to the standardized international classification system criteria, with TW-ROP defined as follows: 1 = zone I any stage ROP with plus disease; 2 = zone I, stage 3 ROP with or without plus disease; 3 = zone II, stage 2 or 3 ROP with plus disease; 4 = any plus disease; or 5 = any stage 4 or higher disease.

To evaluate diagnostic accuracy of telemedicine screening, the clinical diagnosis determined using bedside binocular ophthalmoscopy (BIO) was considered the gold standard reference. All patients received at least 1 mandatory bedside BIO examination from a pediatric retina specialist within a week of NICU discharge. Infants with clinical TW-ROP, as determined by bedside BIO, comprised the TW-ROP telemedicine cohort for analysis.

All data were analyzed using Statistical Analysis Software (SAS) Enterprise Guide Version 5.3 (Cary, N.C.). Variables were first graphically examined for normal distributions and assessed for outliers to determine the appropriate statistical tests. Measures of central tendency and variation were used to describe the study population. All infants with TW-ROP were compared with the non-ROP cohort with respect to baseline characteristics using t test, χ² analyses, and Fisher’s exact test as appropriate. There were insufficient case counts to perform correlated testing (for multiple analysis) or statistical modeling to adjust for potential confounders; therefore, the crude bivariate analysis of cases compared with controls is presented. Statistical significance level was set as a 2-tailed test with α less than 0.05. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the detection of TW-ROP in the SUNDROP study during the first 6 years of enrollment. Telemedicine image interpretations were compared with the gold standard, beside BIO results from outpatient ophthalmology clinic.

Results

Over the 6-year study period, 608 preterm infants (1216 eyes) were screened for ROP with telemedicine as part of the SUNDROP initiative (Table 1). A total of 2169 examinations generated 26 970 retinal images, an average of 3.56 examinations (range 1–21) and 44.28 images (range 2–224) per patient. Data from delivery records on birth weight and gestational age were available for 556 (91%) and 538 (88%) patients, respectively. Mean values for birth weight and estimated gestational age were 1261 (range 420–3744) g and 28.8 (range 20–41) weeks. During the 72 months, slightly more males than females were screened (56% vs 44%). There were 95 multiples included in the study that were composed of 2 sets of triplets and 45 sets of twins. One twin did not survive to the first ROP screening secondary to extreme prematurity.

Twenty-two (3.6%) infants of the 608 total screened met criteria for TW-ROP (Table 2). On average, gestational age of the TW-ROP cohort was 4.2 weeks shorter than that of the remaining 586 infants (p < 0.0001). Similarly, measurements of birth weight in the study exhibited a mean difference of 564.2 g between the lighter patients with TW-ROP and the heavier group with no TW-ROP (p < 0.0001). Regarding multiplicity, a greater proportion of infants with TW-ROP (31.9%) was designated as part of a twin or triplet set (p = 0.06). No adverse anatomical outcomes were observed for any patient enrolled in the SUNDROP initiative.

A total of 133 (23.9%) of the 556 premature infants for which birth weight data were available were further categorized as infants with ELBW (<1000 g; Table 3). In comparison with the other preterm patients in the study, infants with ELBW averaged a significantly lower gestational age of 26.2 weeks (SD 1.9, p < 0.0001) and

Table 1—Demographic data for all infants enrolled in the Stanford University Network for Diagnosis of Retinopathy of Prematurity at 6 years (December 1, 2005, to November 30, 2011)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Mean Patient (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (eyes), N</td>
<td>608 (1216)</td>
<td>N/A</td>
</tr>
<tr>
<td>Examinations, N</td>
<td>2169</td>
<td>3.56 (1–21)</td>
</tr>
<tr>
<td>Images, N</td>
<td>26 970</td>
<td>44.28 (2–224)</td>
</tr>
<tr>
<td>Estimated gestational age (wk)</td>
<td>N/A</td>
<td>28.8 (20–41)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1281.1</td>
<td>(420–3744)</td>
</tr>
</tbody>
</table>

Infants were screened for retinopathy of prematurity if they met any 1 of the following American Academy of Pediatrics screening criteria: (i) birth weight of less than 1500 g or gestational age of 32 weeks or less; (ii) infants with a birth weight between 1500 and 2000 g or gestational age of more than 32 weeks with an unstable clinical course; and (iii) infants who are believed by their attending pediatrician or neonatologist to be at high risk.

*Gestational age was available for 538 patients.
†Birth weight was available for 556 patients.
SUNDROP: screening for retinopathy of prematurity—Wang et al.

Table 2—Comparison of baseline characteristics of infants with and without treatment-warranted retinopathy of prematurity at 72 months

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TW-ROP (n = 22) (mean ± SD)</th>
<th>No TW-ROP (n = 586) (mean ± SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Male, %</td>
<td>68</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>32</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Estimated gestational age, wk</td>
<td>24.8 ± 1.47</td>
<td>29.0 ± 2.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>718.7 ± 203.0</td>
<td>1282.9 ± 389.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiplicity</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Singlet (%)</td>
<td>68.1</td>
<td>84.9</td>
<td></td>
</tr>
<tr>
<td>Multiple (%)</td>
<td>31.9</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>No. of examinations</td>
<td>9.5 ± 4.6</td>
<td>3.4 ± 2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of images</td>
<td>129.0 ± 46.1</td>
<td>41.2 ± 31.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adverse outcomes</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

TW-ROP, treatment-warranted retinopathy of prematurity.

1The p values were obtained by comparing the data for infants with TW-ROP with those without TW-ROP using χ² test distributions for categorical variables and Student’s t test for continuous variables.

2Sex comparisons between TW-ROP and the no TW-ROP group are more likely to undergo additional screening examinations (p < 0.05). Twenty-one (95%) of the 22 cases of TW-ROP occurred in infants of birth weight less than 1000 g.

Compared with bedside BIO, remote interpretation of RetCam II/III images had a sensitivity of 100% and specificity of 99.8%, overcalling a single case of stage 3 ROP insufficient to warrant intervention. The PPV and NPV were 95.5% and 100%, respectively (Tables 4 and 5).

**DISCUSSION**

The 6-year results for the SUNDROP telemedicine initiative were highly favourable, exhibiting a sensitivity of 100%, specificity of 99.8%, PPV of 95.5%, and NPV of 100% compared with bedside BIO examination. In agreement with previously reported risk factors,18–27 TW-ROP infants from this study displayed significantly lower birth weight (p < 0.0001) and gestational age (p < 0.0001) when compared with the no TW-ROP cohort. Furthermore, our data suggest a greater risk for TW-ROP among patients from twin or triplet sets compared with singleton births (p = 0.06), consistent with some but not all published findings in the literature.28–31 Of the 608 infants enrolled in the SUNDROP program over 72 months, not a single case of TW-ROP went undetected as confirmed by bedside BIO, reinforcing the safety and efficacy of telemedicine screening in the identification of clinically significant ROP.

In 2013, the AAP, AAO, and AAPOS for the first time officially recognized the use of digital photographic retinal images captured and sent for remote interpretation as a developing approach to ROP screening.32 Consequently, as the practice of health care continues to shift toward greater cost efficiency, it is likely that telemedicine-based initiatives for routine ROP screening will become more widely accepted. Although the establishment of a telemedicine project often requires substantial initial funding, in the long term, telemedicine-based screening is appreciably more affordable than standard ophthalmoscopy for ROP management, costing an estimated US$3193 versus US $5617, respectively, per quality-adjusted life year.32 However, especially in the past 2 decades, the number of qualified ophthalmologists willing to treat ROP has declined for a variety of reasons including workforce shortages, legal concerns, unsatisfactory reimbursements, and time constraints.33 If telemedicine technology can indeed be used to supplement ROP screening without

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Table 3—Comparison of extremely low-birth-weight infants (<1000 g) with all other premature infants in the Stanford University Network for Diagnosis of Retinopathy of Prematurity initiative at 6 years

<table>
<thead>
<tr>
<th>Variables</th>
<th>ELBW (&lt;1000 g) (mean ± SD)</th>
<th>Other Premature Infants (&gt;1000 g and &lt;2500 g) (mean ± SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>133</td>
<td>423</td>
<td>N/A</td>
</tr>
<tr>
<td>Estimated gestational age, wk</td>
<td>26.2 ± 1.9</td>
<td>29.7 ± 2.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Examinations, N</td>
<td>6.8 ± 4.2</td>
<td>2.7 ± 2.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with TW-ROP, n (%)</td>
<td>21 (95.5%)</td>
<td>1 (0.5%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Gestational age was available for 538 patients. Birth weight was available for 556 patients.

1The p values were obtained by comparing the data for infants with treatment-warranted retinopathy of prematurity (TW-ROP) with those without TW-ROP using χ² test distributions for categorical variables and Student’s t test for continuous variables.

2p < 0.0001 for variable.

Table 4—Comparison of RetCam II examination findings with clinical assessment findings for detection of treatment-warranted retinopathy of prematurity

<table>
<thead>
<tr>
<th>Clinical Examination</th>
<th>Positive (+)</th>
<th>Negative (−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (+)</td>
<td>21</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Negative (−)</td>
<td>0</td>
<td>586</td>
<td>586</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>587</td>
<td>608</td>
</tr>
</tbody>
</table>

1The p values were obtained by comparing the data for infants with treatment-warranted retinopathy of prematurity (TW-ROP) with those without TW-ROP using χ² test distributions for categorical variables and Student’s t test for continuous variables.

2p < 0.001 for variable.
compromising the quality of care, then the burdens of infant transportation, physician time, and examination stress may all be greatly alleviated.14,34

Despite numerous publications in support of telemedicine as a reliable strategy for ROP detection,35–39 only a handful of studies to date have examined the more realistic scenario of screening without the safety net of simultaneously performed indirect ophthalmoscopy. In 2000, Schwartz et al.40 at UCLA collected wide-angle photographs using the RetCam 120 from 10 infants with relatively severe ROP, from which the images were digitally transmitted to a remote site for evaluation and treatment recommendations. Of the 19 eyes interpreted at the remote location, 18 (95%) were correctly classified as having plus disease, and 17 (89%) were accurately diagnosed for the presence of prethreshold or worse ROP, indicating to the authors that, in practice, telemedicine may ultimately be informative for ROP management decisions. Notably, the study by Schwartz et al.40 was, in part, restricted by the anatomical incompatibility of the 120-degree lens with the infant’s eye, a problem that in our protocol was mitigated by the use of a 130-degree lens and smaller lens coupling interface. Likewise, in 2009, Lorenz et al.41 reported on the experience of 5 NICUs in Germany using wide-angle retinal photographs also taken with the RetCam 120 to screen for ROP. Over the course of 6 years, 1222 at-risk premature infants were remotely examined and managed by a photographic reading centre, with any patient suspected to have treatment-requiring ROP referred for a more in-depth consultation via ophthalmoscopy. Remarkably, every instance of treatment-requiring ROP was first identified by telemedicine, consistent with observations of 100% sensitivity for remote ROP screening in the SUNDROP program.

Remote retinal image screening though telemedicine offers the prospect of better access to care for all infants, regardless of birthplace. In our 6-year assessment, there were no cases of missed TW-ROP or adverse anatomical outcomes, suggesting that even in a telemedicine-based program, it is still feasible for all patients to be properly screened. As demonstrated by our setup, the SUNDROP initiative did not replace the physician, but instead complemented screening by allowing a limited ROP specialist workforce to prioritize the highest-risk infants and administer laser treatments or anti–vascular endothelial growth factor agents as needed. In addition, in terms of accessibility, patients with ROP seen by NICU staff at any of the 6 participating hospitals throughout Northern California could all be remotely evaluated via telemedicine screening from 1 central location. Thus, particularly in rural regions where ROP specialists may be scarce, we anticipate worthwhile opportunities for telemedicine-based ROP screening to be implemented.

With representation from 6 distinct community, county, and private hospitals, the SUNDROP initiative draws from a highly diverse patient population, hinting at its broad applicability across ethnic, demographic, and socioeconomic spectrums. Nonetheless, based on the SUNDROP model, we acknowledge that there exist substantial financial and logistical obstacles to setting up a telemedicine-based screening system. Most importantly, successful implementation of a teledical ROP screening program demands the concerted effort of multiple personnel, including a referral centre capable of quickly turning around the readings of hundreds of images, a physician willing to travel to nurseries to examine high-risk infants, and the organization and cooperation of both NICU nurses and case management teams to ensure screening is provided at appropriate intervals. After discharge from the NICU, patients in most instances may also require additional follow-up, necessitating the involvement of a pediatric ophthalmology or vitreoretinal clinic to correlate the results of these examinations with those of earlier inpatient telemedicine screening. Other possible concerns with ROP telemedicine include suboptimal image quality, which a number of prior studies using the RetCam have noted,15,37,41 and the considerable upfront equipment costs requisite for remote evaluation. However, as the resolution, portability, speed, and affordability of retinal camera technology continue to improve, it is foreseeable that such methods will become increasingly suitable for real-world ROP screening. Similarly, it may be possible for the NICU to recoup the cost of the camera overtime by submitting billing for the photographs with interpretation.

Given the ever-growing number of premature infants at risk for ROP, it is crucial that efficient strategies for population-scale screening are leveraged to minimize the occurrence of preventable vision loss and blindness. Based on our 6-year findings from the SUNDROP initiative, we conclude that telemedicine is a safe, reliable, and cost-effective complement to the efforts of ROP specialists, capable of increasing patient access to screening and focusing the resources of the current ophthalmic community on infants with potentially vision-threatening disease.

Disclosure: The authors have no proprietary or commercial interest in any materials discussed in this article.

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