Current Trends in Telemedicine for Retinopathy of Prematurity

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Introduction

Retinopathy of Prematurity (ROP) is a vasoproliferative disease of the retina in premature infants that can progress to blindness. Clinical ROP management standards have been established by seminal studies such as the Cryotherapy for ROP (CRYO-ROP)1 and Early Treatment for ROP (ET-ROP)2 trials, and have significantly decreased the incidence of poor visual outcomes in ROP. However, ROP continues to be a leading cause of childhood blindness worldwide.3

The clinical effectiveness of ROP treatment guidelines begins with the accurate identification of infants with clinically significant ROP. Clinical examination by bedside indirect ophthalmoscopy has been the long-established standard for the screening, diagnosis and management of ROP. However, there is an insufficient number of skilled ROP examiners worldwide to meet the demand for the growing number of children at risk for ROP. The extensive training required in attaining proficiency in ROP management, medico-legal concerns of practicing within a pediatric population and financial reimbursement have all been described as possible reasons for a shortage of ROP experts.

Over the years, telemedicine has been studied as a modality that may improve access to care for children with ROP. ROP has several favorable characteristics that facilitate the application of telemedicine in clinical practice, and there is a very high intra-physician agreement between ophthalmoscopic examination and telemedical interpretation.4

ROP is a clinical diagnosis that is made on the appearance of disease in the retina, and there is a universally accepted evidence-based diagnostic classification standard for ROP. Telemedicine utilizes telecommunication and information technologies to enable the provision of clinical healthcare independent of the need for physical proximity. If effective, telemedicine can expand the geographic reach of clinical ROP expertise to currently underserved regions, which is particularly in need due to aforementioned reasons.

Approximately 90% of ROP cases may improve spontaneously without need for treatment, and fewer than 10% of infants examined for ROP may eventually require treatment.2 A telemedicine approach to ROP screening has the potential to greatly reduce the number of bedside indirect ophthalmoscopy examinations and simultaneously increase the number of infants who receive timely retinal evaluation. Telemedicine, however, may not completely replace or eliminate the need for bedside indirect ophthalmoscopy. Rather, accurate identification, by telemedicine approaches, of infants with fundus appearances concerning for more advanced disease that require further bedside indirect ophthalmoscopy examinations may help optimize the use of resources and expertise of ROP specialists.

Imaging is increasingly influencing clinical decisions in medical specialties such as radiology, cardiology, dermatology, as well as ophthalmology. For telemedicine to be established as standard of care in ROP screening, its safety, reliability and accuracy performance, technical validity, risks, workflow, financial costs, as well as resource requirements have to be rigorously tested. There are several reports that provide evidence supporting the use of telemedicine in ROP screening that will be examined in greater detail in this review.

The Current State of Telemedicine for Retinopathy of Prematurity

Evidence for Telemedicine for ROP

In 2012, the American Academy of Ophthalmology Ophthalmic Technology Assessment Committee (OTAC) reported on the detection of clinically significant retinopathy of prematurity using wide-angle digital retinal photography.7 The report noted at least
five independent level 1 original research studies that demonstrated digital retinal photography had a high accuracy (>90% sensitivity) for the detection of clinically significant ROP.6-10 Three level 1 studies demonstrated lower accuracy, reporting 77% sensitivity for detection of type 2 or worse ROP,11 76% sensitivity for detection of type 2 or worse ROP at 31 to 33 weeks,7 and 57% sensitivity for detection of stage 3 disease.11 The report additionally examined studies from 3 independent study sites with level III evidence that reported high accuracy of detection of clinically significant ROP through telemedical interpretation of wide-angle retinal images.12-17

A joint technical report published in 2015 by the American Academy of Pediatrics and the American Academy of Ophthalmology systematically examined the current literature for the implementation of telemedicine for the evaluation of ROP.13 This report reaffirmed the findings and conclusions of the 2012 OTAC report on level I evidence for high accuracy of wide-angle digital retinal photography on the detection of clinically significant ROP. The report further stated that telemedicine serves as a useful adjunct to but not a replacement of binocular indirect ophthalmoscopy. The joint technical report further elaborates on the components and considerations of a telemedicine-based remote digital fundus imaging system of ROP evaluation. It describes the need for an imaging system, personnel and training required for retinal image acquisition and interpretation, cost of acquisition and maintenance of equipment, security of transmission and backup of data, various responses to interpretation of incidental findings and urgent cases, as well as the duty to ongoing care and necessary criteria for discharge from further screening. It also explored potential pitfalls, patient consent, and malpractice liability that may be associated with a ROP telemedicine system.

**Potential Cost/Benefit of a ROP Screening Program**

Visual impairment from ROP results in lifelong reduction in quality of life on an individual level, as well as decreased productivity and increased financial costs on a societal level. Current methods of traditional ROP screening remain suboptimal largely due to insufficient penetrance. The Economic Model of Retinopathy of Prematurity (EcROP) demonstrated a significant financial impetus to implementing an ideal (100% penetrance) national screening and treatment program that contributes significantly to quality of life in both high-income (United States) and middle-income (Mexico) nations.19 EcROP is a cost-effectiveness, cost-utility and cost-benefit analysis of an ideal national screening program, compared to estimates of current practice. EcROP incorporated in its calculations verified societal impacts of the loss in parental or caregiver productivity, as well as the loss in future earnings of blind individuals. Previous cost utility studies concluded that ROP screening is cost effective based on dollars invested per Quality Adjusted Life Years (QALYs) gained. Data from EcROP goes a step further by predicting that investments in national ROP screening programs will not only be completely recouped, but result in financial gain in the long term through a reduction in the lifelong burden of visual impairment.

**ROP Telemedicine Screening Programs**

There has been recognition of the importance of expanding evaluation and management options available for ROP surveillance. The Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) study is a National Eye Institute-funded study that evaluates the use of digital wide-angle photography in ROP.20 The e-ROP study proposed and described a centralized system of grading ROP digital images by non-physician trained readers under the supervision of an ophthalmologist reading center director. Babies enrolled in the e-ROP study underwent both digital retinal imaging by certified non-physician ROP imagers and indirect ophthalmoscopic examinations by ophthalmologists on the same day. Five wide-field retinal images (center, nasal, temporal, superior, inferior) were captured using the RetCam imaging system (Clarity Medical Systems, Pleasanton, CA) and subsequently graded by non-physician trained readers using a standardized protocol to identify eyes with Referral-Warranted ROP (RW-ROP). RW-ROP was defined as plus disease, zone 1 ROP, or stage 3 ROP or above. The grading results were then compared to findings from clinical indirect ophthalmoscopic examinations from the same day. The e-ROP study reported 81.9% sensitivity and 90.1% specificity rates for the detection of RW-ROP when retinal image grading of an eye was compared to the results of its corresponding clinical diagnostic examination from a single session. When retinal images from both eyes of an infant at a single session were considered together, the study reported 90.0% sensitivity and 87.0% specificity rates. Over multiple sessions, detection of infants with RW-ROP in the study was 97.1% sensitive and 75.9% specific.

There are other ongoing ROP telemedicine screening programs in the United States,21 Canada, Germany,22 New Zealand,23 and India.22 Aside from telemedicine approaches, numerous clinical models and algorithms for the prediction of retinopathy of prematurity have been proposed with the aim of reducing the burdensome number of ROP screening examinations. Although clinical predictive models are still early in their developmental stages, there may be potential in combining telemedical screening with clinical prognostic models to streamline future screening programs.23-27

**Retinal Imaging**

The crux of any telemedicine model depends on the ability to acquire high quality retinal images for review by a medical expert geographically distant from the patient. Early efforts at retinal imaging, such
as with the NM-200D camera (NIDEK, Inc, Fremont, CA) that provided a 30° field of view, were limited in clinical effectiveness due to a restricted field of view. Advances in imaging technology have significantly increased the ability to image the pediatric retina. RetCam (Clarity Medical Systems, Inc, Pleasanton, CA) is a mydriatic wide field fundus imaging system that achieves a 130° field of view with a handheld contact camera system. Many ophthalmologists and neonatal intensive care units (NICUs) have adopted RetCam in the clinical management and documentation of ROP. More recently, retinal imaging systems suited to digital wide-field retinal imaging in ROP include the PanoCam LT (Visunex Medical Systems, Fremont, CA) and 3nethra neo (Forus Health, Bangalore, India) systems. The PanoCam LT has a compact wireless, contact-based system that achieves a 130° field of view, while the 3nethra neo is a lightweight compact, contact-based system for high definition imaging that achieves a 120° field of view. Optomap (Optos plc, Dunfermline, Scotland) is a non-contact, non-mydriatic ultra-wide field imaging system that achieves a 200° field of view. Optomap has been used in ROP imaging in infants, but may require a ‘flying baby’ technique of manually holding infants to the imaging device.29 This process can be technically challenging and difficult to integrate into the NICU workflow, and Optomap has not yet been widely adopted for digital retinal imaging in ROP.

The advantages of wide-field retinal imaging and telemedicine for ROP extend beyond its potential for ROP screening. It is an effective modality that enables clinicians to share clinical findings with other physicians, healthcare staff and patient families. Wide-angle photography has been shown to be safe,29 and allows for objective documentation of examination findings, improved detection of disease progression over time by comparison to baseline photographs, and may enable a more precise review of subtle clinical findings that may have been missed from limited bedside binocular indirect ophthalmoscopic examination. There is evidence suggesting that use of digital wide-field retinal imaging in telemedicine may detect moderate to severe ROP earlier than traditional ophthalmoscopy.30 Inherent difficulties with ophthalmoscopy such as infant movements, small pupils, and paper-based hand-drawn documentation of retinal findings may also lead to inadequate assessments with traditional ophthalmoscopy.

**Limitations and considerations**

Although a telemedicine approach to ROP screening and evaluation has many potential advantages, there are several notable limitations. Evidence supports the cost effective nature of telemedicine in ROP screening, but there are nevertheless significant initial investment costs associated with the implementation of an ROP telemedicine system. Logistical challenges of integrating a telemedical screening system have to be resolved at a NICU, hospital, local, national, and even international level. Often, infrastructure and access to resources such as Internet and computers needed to enable telemedicine are poorest where the need for expanded medical expertise is greatest.

A system intended for the screening of ROP may not solely be limited to the identification of ROP. A widespread retinal imaging screening program also has the potential to identify other incidental findings that may independently result in vision loss. Practice guidelines to the reporting of incidental findings have to be established to minimize associated liability risk. Images concerning for an abnormal fundus with or without ROP may be flagged for repeat imaging or bedside clinical examination. Careful checks can be incorporated into the system to reduce or eliminate the occurrence of missed disease.

### The Future of Telemedicine for Retinopathy of Prematurity

As we look to the future, further research will aim to increase, standardize and regulate the quality, reliability, as well as efficiency of telemedicine for ROP. This may eventually enable the establishment of a digital retinal imaging screening system with an expanded geographical reach that overcomes many limitations to optimal ROP care the current system is restricted by.

**Fluorescein Angiography**

There is growing evidence supporting the role of fluorescein angiography in the diagnosis and management of retinopathy of prematurity. Fluorescein angiography is an established diagnostic modality utilized in the assessment of retinal vasculature in vasoproliferative disorders such as diabetic retinopathy,31 and exudative age-related macular degeneration32 in adults. In the pediatric population, fluorescein angiography has been described to be of importance in disorders such as Coats’ disease33, choroidal neovascular membranes34, sickle cell retinopathy35, ocular tumors36, and other diseases.37-38 Fluorescein angiography has been utilized to describe vascular abnormalities in ROP, changes in vasculature after intervention with anti-VEGF therapy,40-42 or scleral buckling43, and different patterns of vessels at the junction between vascular and avascular retina that may not be visible with indirect ophthalmoscopy alone.44-47 However, clear diagnostic and management criteria have yet to be established based on fluorescein angiography findings in ROP.

Our group has reported significant improvement of sensitivity of diagnosis of ROP by experts for zone, stage 2 or worse, stage 3 or worse, pre-plus or worse, and type 2 ROP or worse disease with the
combined use of fluorescein angiography and corresponding color fundus photographs compared to color fundus photographs alone (Figure 1).48,49 Accuracy and inter-grader agreement for diagnosis of ROP was also significantly improved with the combined use of fluorescein angiography and color fundus photographs.49-50 These findings suggest that fluorescein angiography may have an important role in improving image-based diagnosis for ROP.

**Image Montaging and Mosaics**

Many studies in ROP telemedicine currently utilize multiple images of different regions of the retina to produce a comprehensive digital representation of a patient’s fundus. Advances in montage software programs have enabled the automated construction of mosaic photographs from multiple individual images that matches or exceeds the field of view of individual ultra-widefield images, combining technical ease of image acquisition with the clinical utility of ultra-widefield imaging (Figure 2). Our group recently investigated the use of digital mosaic images in the diagnosis and management of ROP. When compared to the interpretation of multiple individual photographs, interpretation of a single mosaic photograph resulted in increased accuracy and inter-grader agreement in the diagnosis of stage of ROP, presence of plus disease, and consequently clinically significant ROP (In press, JAMA Ophthalmology).51 It has been suggested that peripheral fundus findings contribute to the clinical diagnosis of plus disease despite the use of a narrow-angle reference photograph of the posterior pole as a basis for comparison.52-53 Dynamic flickering of superimposed imaged pairs has also been shown to increase the speed for detection of structural progression in ROP and inter-grader agreement in other ophthalmic conditions.54-55 Mosaic images have other advantages including ease of viewing and smaller average file sizes.

**Computer-Based Image Analysis and ROP**

The current age of burgeoning computational capacity is attracting investments focused on the development of computer-facilitated analysis of health data. Classification and management of ROP depends heavily on the characterization of zone, stage and plus disease. Currently, computer-based image analysis systems have already been shown to be comparable to ROP expert image interpretation in the detection of plus disease in ROP (Figure 3).53,56-58 In combination with the clinical exam, a fully automated computer-based analysis system for evaluating an ROP fundus is not only theoretically possible, but also becoming more feasible in real world telemedicine programs.

**Tele-Education for ROP**

Telemedicine for ROP is not limited to the direct assessment of patients. A widely accepted public health concept with improving care in underserved areas is the establishment of a self-sustaining system, which often involves education. Tele-education allows remote access to high quality education, circumventing the need for an increase in local expert human resources.59 The use of web-based systems with thousands of validated fundus images has been reported to improve exposure to as well as diagnostic accuracy and reliability of ROP education in the United States60 and internationally.59 Additionally, a tele-education system has the potential for greater standardization of ROP training through the grading of image interpretation competency. There may be a role for web-based ROP tele-education systems in certifying care providers prior to participation in a ROP telemedicine screening system.

**Conclusion**

Teledmedicine has the potential to significantly improve upon current methods of screening, evaluation, and management