Retinopathy of prematurity screening: A narrative review of current programs, teleophthalmology, and diagnostic support systems

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Abstract:

PURPOSE: Neonatal care in middle-income countries has improved over the last decade, leading to a “third epidemic” of retinopathy of prematurity (ROP). Without concomitant improvements in ROP screening infrastructure, reduction of ROP-associated visual loss remains a challenge worldwide. The emergence of teleophthalmology screening programs and artificial intelligence (AI) technologies represents promising methods to address this growing unmet demand in ROP screening. An improved understanding of current ROP screening programs may inform the adoption of these novel technologies in ROP care.

METHODS: A critical narrative review of the literature was carried out. Publications that were representative of established or emerging ROP screening programs in high-, middle-, and low-income countries were selected for review. Screening programs were reviewed for inclusion criteria, screening frequency and duration, modality, and published sensitivity and specificity.

RESULTS: Screening inclusion criteria, including age and birth weight cutoffs, showed significant heterogeneity globally. Countries of similar income tend to have similar criteria. Three primary screening modalities including binocular indirect ophthalmoscopy (BIO), wide-field digital retinal imaging (WFDRI), and teleophthalmology were identified and reviewed. BIO has documented limitations in reduced interoperator agreement, scalability, and geographical access barriers, which are mitigated in part by WFDRI. Teleophthalmology screening may address limitations in ROP screening workforce distribution and training. Opportunities for AI technologies were identified in the context of these limitations, including interoperator reliability and possibilities for point-of-care diagnosis.

CONCLUSION: Limitations in the current ROP screening include scalability, geographical access, and high screening burden with low treatment yield. These may be addressable through increased adoption of teleophthalmology and AI technologies. As the global incidence of ROP continues to increase, implementation of these novel modalities requires greater consideration.

Keywords: Pediatric, retinopathy, screening

INTRODUCTION

The incidence of retinopathy of prematurity (ROP) and sight-threatening ROP is largely determined by the availability of high-quality neonatal care and is therefore region- and country-dependent. Low-income nations have the lowest incidence of ROP due to high infant mortality rates for premature infants. High-income nations report an increasing rate of ROP in extremely premature and low birth weight infants, as the result of improving survival for these at-risk patients.[1] Middle-income countries including China, India, and those within Latin America and Africa are experiencing a significant increase in ROP incidence,[2] resulting in a “third epidemic” of the disease. Improved neonatal care in these countries has led to the increased survival of premature infants, without concomitant improvements in the infrastructure for ROP case detection and treatment. In 2010, global estimates...
approximated 185,000 of the surviving cohort of preterm infants to have some degree of ROP, with 54,000 having severe disease with potential to progress to visual impairment.[3]

ROP is a disease of the retina characterized by disruption of normal retinal angiogenesis due to premature birth,[4] leading to arrest of retinal vascularization. ROP is diagnosed through visualization of the retinal vasculature status and can be classified according to the International Classification of Retinopathy of Prematurity (ICROP) guidelines by Zone (1–3) and Stage (0–5) [Figure 1].[5] The presence of “plus disease” defined as dilatation and tortuosity of the posterior vessels involving at least 2 quadrants, is also an important indicator of disease severity. ROP has several characteristics which enable it to be suitable for screening. These include (a) an easily identifiable at-risk population; (b) a clearly defined disease stage which is distinct and detectable; (c) a known and relatively predictable natural history; (d) accurate and cost-effective methods for case detection; (e) severe visual sequelae if disease is missed; and (f) effective treatment options that reduce adverse outcomes.[6] Screening is thus a cornerstone of ROP management. Despite this, access to ROP screening is limited globally, with screening programs highly heterogenous in access, inclusion criteria, screening frequency and duration, modality, and published accuracy.[7] Further, international guidelines that have been previously established for inclusion for screening are highly variable due to regional differences in patient demographics and available infrastructure.

As ROP incidence continues to increase, novel methods for case detection are under investigation to increase access to screening. Recent developments including teleophthalmology and artificial intelligence (AI)-based technologies represent promising methods to address this growing incidence of disease,[8] especially in the context of recent revisions to international ROP screening and diagnostic criteria.[5] These recent revisions have the stated goal of accommodating advances in the field of retinal imaging, while simultaneously acknowledging the subjectivity of appraisal.

Given existing regional differences and the increased recent focus on ROP screening, we have sought in this present study to review representative guidelines and programs globally. This review was also carried out considering recent developments in teleophthalmology and AI for ROP and the identification of opportunities for adoption of these technologies within ROP screening.

**Methods**

This study represents a critical narrative review of the literature. It is intended as a summary of the field as it currently exists, encompassing screening recommendations, methods, and their benefits and limitations within the clinical and social contexts they are employed. Literature was not chosen within a formal meta-analytical or systematic framework. Publications selected for review were intended to highlight both common features of existing programs and novel developments in areas of increasing need. A search was conducted via PubMed and Medline for publications related to ROP screening practices and techniques. Only studies from 1990 onward were included to encompass the goals of this review, with summarized themes and representative regional practices presented here.

**Results**

**Current screening programs**

**Inclusion criteria**

The onset of serious ROP has been shown to better correlate with an infant’s postmenstrual age (PMA) than with chronologic postnatal age. Timing for the initiation of screening is therefore

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**Figure 1:** Examples of retinopathy of prematurity stages, plus disease, and aggressive retinopathy of prematurity according to International Classification of Retinopathy of Prematurity guidelines

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often based on the former, as demonstrated by the country frameworks listed in Table 1. In addition to ROP, all premature infants have an increased risk of developing ophthalmic morbidities later in life, including strabismus, cortical processing problems, and significant refractive errors. Inclusion criteria are based on a combination of gestational age and/or birth weight, with some centers also including special consideration for unstable clinical course. Variations in guidelines are noted both between countries and within countries. Broadly, guidelines recommend ROP screening for at-risk patients ≤30–32 weeks gestational age and/or ≤1250–1500 g birth weight.

In contrast, in many middle-income countries, larger and more mature babies are developing ROP. This reflects regional variations in neonatal care and the continued use of unmonitored supplemental oxygen for premature infants in countries like India; similar in nature to the cases of the “first epidemic” of ROP in the 1940–1950s. A recent analysis showed that the mean birth weight and gestational age of infants treated for severe ROP, or who had developed severe stage 4 or 5 ROP, in the United Kingdom (UK), the US, and Canada were <800 g and <26 weeks. The mean gestational age and birth weight for comparable infants in ten middle-income countries were >1000 g and ranged from >26 to 35 weeks. Proposed national screening guidelines for India recommend that all infants born <2000 g and <34 weeks gestation are screened. Similar, more inclusive screening criteria have also been employed on a region- or unit-specific basis in China, Latin America, and Africa, although national guidelines remain lacking.

### Screening schedule

Recent revised joint AAO and AAP guidelines recommend that screening commences at 31 weeks PMA for all infants born <28 weeks gestation and at 4 weeks postnatal for infants born older. For the most premature infants born <24 weeks gestation, limited evidence on their clinical course, comorbidities, and speculation that severe AP-ROP may occur before 31 weeks PMA, has led to the recommendation that clinicians should exercise clinical judgment on if ROP screening should be initiated earlier for this patient group.

The frequency of follow-up examinations is dependent on diagnostic findings. These range from 1 to 3 weeks and vary according to ROP disease severity and location [Table 2]. Screening examinations can be ceased when any of the following criteria are met:

- Full retinal vascularization in proximity to the ora serrata for 360°
- Zone III retinal vascularization reached without previous zone I or II ROP
- Regression of ROP, indicated by the development of dry white ridges/lies, development of laser-induced scar tissue and transgression of vessels across the demarcation line
- Infant reaches 45 weeks PMA and there is no type 1 or worse ROP present

### Table 1: Comparison of international retinopathy of prematurity screening criteria

| Country          | Gestational age (weeks) | Birth weight (g) | Notes |
|------------------|-------------------------|------------------|-------|
| US[16,29]        | ≤30                     | ≤1500            | The majority of US NICUs use a wider gestational age criteria of ≤31 or 32 weeks. Selected infants with birth weight 1500–2000 g or >30 weeks gestation with an unstable clinical course are also recommended for ROP screening[28] |
| UK[31]           | ≤31                     | ≤1500            | Proposed in 1996, these national guidelines have been rescinded. Actual criteria used by NICUs in Australia vary. Queensland has recently adopted a new state-wide guideline to screen infants born <31 weeks gestation or ≤1250 g.[19] Royal Prince Alfred Hospital screens infants born <30 weeks gestation, ≤1250 g or following clinician discretion for infants at high-risk of developing ROP[21] Infants with an unstable clinical course are also included for screening |
| Canada[32]       | ≤31                     | ≤1500            | Any infant ≤36 weeks gestation receiving supplemental oxygen more than 49 days also screened. Special attention given to infants who receive blood transfusions |
| Australia (NHMRC)[33] | <32                   | <1500            | Proposed national guidelines |
| New Zealand[17,18] | ≤31                     | ≤1250            | Infants with an unstable clinical course are also included for screening |
| Saudi Arabia[34] | ≤32                     | ≤1500            | Any infant ventilated for at least 1 week or who received supplemental oxygen for <30 days also screened. National guidelines remain unavailable |
| India[34]        | <34                     | ≤2000            | Any infant exposed to high/prolonged oxygen supplementation or ventilation, sepsis, or poor weight gain as recommended by a neonatologist. Guidelines introduced in 2018, trialed in 4 public hospitals |
| China (Shanghai)[35] | ≤34                  | ≤2000            | Screening of infants >1500 g also conducted if they have risk factors such as unblended oxygen supplementation |
| Kenya[27]        | ≤32                     | ≤1500            | |
| South Africa[27] | <32                     | <1500            | |

US: United States, UK: United Kingdom, NICUs: Neonatal intensive care units, ROP: Retinopathy of prematurity
If intravitreal bevacizumab is used, given the risk of very late recurrence, ROP screening should continue to 54 weeks PMA.

Screening modalities

Binocular indirect ophthalmoscopy

ROP screening examinations have traditionally been completed by an experienced specialized ophthalmologist conducting serial examinations using binocular indirect ophthalmoscopy (BIO). Screening with BIO requires extensive training, is labor-intensive, technically challenging, and can represent a significant time burden. Specialist ophthalmologists experienced in BIO screening are clustered in large centers, thus requiring either the ophthalmologist to travel to remote centers, or infants to be transferred for repeated screening examinations. Transfer increases both the risk of infant morbidity and mortality and cost of screening—a recent Australian analysis indicating that the average cost, per eye, per screening examination for transferred infants was $5110 AUD.\(^{[36,37]}\) Screening episodes typically have a low treatment yield of approximately 8%, meaning a large number of infants are screened to find the relative few requiring treatment.\(^{[38]}\) Further, this practice is comparatively poorly reimbursed. Despite increasing ROP incidence and demand for screening, these complex clinical, logistical, and medico-legal factors have led to a decrease in the number of clinicians who are willing to carry out ROP screening.\(^{[15]}\) One of the main challenges for ROP care globally therefore remains providing equitable and sufficient access to timely screening.

To achieve an adequate view for BIO, pupil dilatation is required. When dilatation has been achieved, the infant is swaddled, topical anesthetic instilled on the ocular surface, and a neonatal lid speculum inserted [Figure 2]. Oral sucrose and a dummy may be used in conjunction with swaddling to reduce the neonatal pain response. BIO examination and the scleral depression needed to adequately view the far retinal periphery are associated with increased blood pressure, decreased oxygen saturation, and infant distress.\(^{[39,40]}\) Examinations should therefore be short to minimize cardiorespiratory risk. The image viewed by the clinician through the condensing lens is also inverted both horizontally and vertically. Examination results are then documented via hand drawn annotations [Figure 3]. This analog documentation, along with significant variability in ROP diagnosis has led to a high medico-legal risk associated with this traditional screening practice.\(^{[41-43]}\)

Significant inter-clinician subjectivity and regional variation in the diagnosis of plus disease within fundal images is well documented and may lead to delayed treatment and poorer visual outcomes.\(^{[44-47]}\) Campbell et al. in 2016 demonstrated mild mean inter-expert agreement (weighted $\kappa$ of 0.30) in ROP diagnosis between eight expert clinicians within a reference standard diagnosis set of 134 images.\(^{[48]}\) Similarly, Chiang et al. in 2007 demonstrated that among 22 ROP experts, all experts agreed on the same diagnosis in only 4 of 34 studied ROP fundal images.\(^{[49]}\) Diagnostic variation may be due to individual ophthalmologists evaluating differing features, focusing on wider fields of view than the standard photograph for diagnosis, or having different cutoff points for vascular abnormality required for determination of plus disease.\(^{[48]}\) Geographical variation in diagnosis has also been established.\(^{[47]}\)
Wide-field digital retinal imaging

The advent of wide-field digital retinal imaging (WFDRI) technology for infants has addressed some of the challenges associated with traditional BIO screening. RetCam (Clarity Medical Systems, Pleasanton, CA, USA) is the most established of WFDRI systems available and uses a wide-angle contact camera to capture fundal images at a standard 130° field of view [Figure 4]. Like BIO screening, pupil dilatation, topical ocular anesthetic, and an eyelid speculum are required. A viscous gel couples the camera lens to the ocular surface while images are captured. Images should be reviewed to ensure they are clear and gradable, and if necessary, retaken. Notably, if the camera is held heavily against the eye, blanching of the posterior pole vasculature may occur, which may minimize the appearance of plus disease. Appropriate close cardiac and respiratory status monitoring is required in the NICU, although image capture via WFDRI has been shown to carry less risk of cardiorespiratory stress compared to traditional BIO.[50]

The minimum number of fundal images captured per eye vary depends on the implementation and local guidelines. These range from 3: posterior pole, nasal retina, and temporal retina; to 6, including five images of the retina (one posterior pole, four of each peripheral aspect), and one noncontact image of the anterior segment.[17,51,52] The AAO and others have confirmed WFDRI to be as equally accurate to BIO for the diagnosis of ROP.[53,54]

Compared to BIO, WFDRI has decreased magnification and lacks stereopsis. The field of view may not always be able to capture the full retina up to the ora serrata unless scleral indentation is applied. Although this may not influence the diagnosis of treatment-requiring ROP, it may restrict ability to capture very peripheral disease, reflected in decreased sensitivities in the diagnosis of mild–moderate ROP seen in early studies.[17,55] WFDRI also carries with it similar concerns regarding interclinician variability in diagnosis, though medicolegal risk is diminished due to ease of seeking a second opinion and objective photographic documentation.

Teleophthalmology

Teleophthalmology is a division of telemedicine that enables ophthalmic care to be delivered using telecommunications technology and digital medical equipment [Figure 5].[56] Teleophthalmology allows clinicians to provide care to patients present in different geographic locations. Using WFDRI, fundal images of premature infants at-risk of developing ROP can be captured at one location, with grading of images and management decisions carried out by an ophthalmologist at a different location. Early implementations which evaluated the safety and efficacy of teleophthalmology versus traditional BIO employed the use of trained ophthalmologists to capture images.[52,57-61] As these screening models have matured, implementations typically now employ trained neonatal nurses, ophthalmic photographers, and trained technicians.[17,24,51,62-66]

Captured fundal images can be reviewed in different ways. Images can either be interpreted directly at the bedside, or more typically, a “store-and-forward” model is employed. This “store-and-forward” model involves transmission of the image electronically for evaluation by an expert grader based remotely who is typically a specialized ophthalmologist experienced in ROP care.[55] Images may be captured from across several different NICUs and transmitted to a central reading and treatment center for evaluation.[17] Images may be transmitted via a secure electronic server or electronic health record and may be accompanied with further patient demographic and clinical information which may assist the grader’s evaluation. Novel models in settings in which access to expert graders is limited and images are evaluated by appropriately trained nonphysician readers are also showing promise.[24,67,68]

Reporting of imaging findings and disease follow revised ICROP guidelines or any local ROP screening guidelines. The frequency of follow-up and criteria for termination of screening should follow the same international or local ROP screening guidelines described earlier [Table 2].[16,54]
Several technical limitations remain however for teleophthalmology implementations of ROP screening. The quality of images captured may at times be inadequate. Several studies have reported that up to 8%–21% of images captured may be difficult to interpret.\(^{60,70,85}\) Adequate-quality images may be particularly difficult to capture for infants with dark fundi and small palpebral fissures, which limit adequate contact between the RetCam lens and the corneal surface. These challenges however appear to be improved with newer, updated versions of the RetCam device and appropriate training of staff capturing images, to assess for image quality.

Further, a significant initial capital outlay is required to purchase imaging equipment and to adequately train clinical staff for screening. Setup costs, estimated to be up to $125,000 USD, may limit the uptake of teleophthalmology programs, particularly in middle-income countries where the current burden of disease is at its highest.\(^{65}\) The emergence of new fundal camera systems will likely significantly decrease these costs.\(^{86-88}\) This is particularly relevant in the context of AI screening, as it has been noted that certain algorithms are only validated for use with particular brands or models of imaging devices.\(^{89}\) However, it is important to consider these costs in the context of overall costs required for patient transfer and hospitalization.

The ongoing implementation of teleophthalmology has been shown to be cost-effective when measured in quality-adjusted life years (QALYs).\(^{89}\) In the US reimbursement setting, substantial cost-savings can be achieved with teleophthalmology, with $3193 per QALY gained using this screening practice versus $5617 per QALY gained using traditional bedside ophthalmoscopy.\(^{89}\) An early study from UK showed that teleophthalmology models using image capture by visiting nurses and grading by visiting nurses or remote ophthalmologists, were cost-effective compared to traditional bedside ophthalmoscopy at £172 and £201, respectively, versus £321 per infant examined.\(^{89}\)

### Current Implementations and Efficacy

Successful implementations of teleophthalmology models for ROP screening have been carried out in several real-world settings, including the ART-ROP network in New Zealand; SUNDROP in Northern California; the KIDROP, ROPE-SOS, and Vittala ROP networks in South India; the Bavarian ROP-Telemedicine Project in Germany; and a national telemedicine study in Chile\(^{[17,24,51,52,62,65,67,78-79]}\) [Table 3].

Several studies have evaluated the accuracy and safety of teleophthalmology for ROP. For the diagnosis of any ROP, including mild or worse disease, teleophthalmology has been shown in a systematic review to have a sensitivity of 0.82–0.86 and specificity of 0.91–0.96, when compared to an expert BIO reference standard.\(^{85}\) Higher accuracy has been reported for detecting ROP in fundal images captured of infants at later PMAs.\(^{[82,83]}\) This has been attributed to improved image quality and acquisition due to more accommodating external and anterior chamber anatomy. For prethreshold or worse ROP, sensitivities of 0.72–1.00 and specificities of 0.90–0.98 have been reported.\(^{[55,83,85]}\) Detection of moderate-to-severe ROP showed sensitivities of 0.92–1.00 and specificities of 0.37–0.96.\(^{[58,60]}\) While there is still improvement to be made with detection of early or very peripheral disease, models of ROP screening care which use WFDRI and remote expert diagnosis without any BIO examinations increasingly appear to be safe and effective.\(^{[17,80]}\)

![Figure 5: Example workflow diagram for teleophthalmology services, including use of computer-based image analysis/artificial intelligence for initial screening of retinopathy of prematurity](image_url)

### Computer-based image analysis and artificial intelligence

The adoption of WFDRI and teleophthalmology have improved access to ROP screening and diagnosis. However, accurate diagnosis of treatment-requiring ROP or plus disease is highly variable and subjective. This can lead to delay in treatment or unnecessary treatment. Computer-based image analysis (CBIA) systems have been previously developed to assist ROP diagnosis. These systems are dependent on the evaluation of fundal image features selected a priori to determine plus disease risk, including arteriole or venule diameter, tortuosity, curvature, image field of view, or a transformation and combination of these individual features.\(^{[49,91-100]}\) These image features are then programmed into rules-based computer systems to provide an objective evaluation of plus disease risk and to reach a diagnostic conclusion. Table 4 highlights several examples of these systems.

AI methods of identifying ROP are still under development, and none have yet been implemented in routine clinical
Table 3: Selected implementations and trials of teleophthalmology for retinopathy of prematurity screening

| Implementation or trial | Screening model | Efficacy | Notes |
|-------------------------|-----------------|----------|-------|
| ART-ROP screening Network(17,78,79) | Image acquisition by trained ROP specialist nurses | Treatment-requiring ROP – 100% sensitivity, 97.9% specificity, 84.6% PPV, 100% NPV | Minimum of three photos capturing posterior pole, nasal, and temporal retina |
| Four NICU network in Auckland, New Zealand | Diagnosis conducted remotely by consultant pediatric ophthalmologist | No simultaneous BIO | |
| e-ROP cooperative Group | Image acquisition by trained non-physician imagers | Referral-warranted ROP – 81.9% sensitivity, 90.1% specificity, 62.5% PPV, 97.3% NPV | Standard six image set consisting of anterior segment, posterior pole and four retinal fields |
| 12 US and Canada clinical centers(84,76,77) | Diagnosis conducted remotely by trained non-physician readers and compared to expert readers and BIO | 3 of 162 infants treated by ROP specialists not detected on WFDRI | Strong support for the validity of remote evaluation by trained non-physician readers captured by trained non-physician imagers |
| SUNDROP | Image acquisition by trained NICU nurses | Treatment-warranted ROP – 100% sensitivity, 99.8% specificity, 92.9% PPV, 100% NPV | Minimum of five fundal images captured, one of each retinal quadrant and one centered on the optic nerve. Further image captured of anterior segment to assess pupillary dilatation and iris vascular engagement associated with plus disease |
| 6 NICU network in Northern California(79,78-80) | Diagnosis conducted remotely by expert ROP specialist (retinal or pediatric ophthalmologist) within 24 h | No patient progressed to retinal detachment or adverse anatomical outcome | |
| KIDROP | Image acquisition by trained technicians | Treatment-requiring ROP – 95.7% sensitivity, 93.2% specificity, 81.5% PPV, 98.6% NPV | Non-physician technicians trained with KIDROP stat tile-education program. Technicians trained to assess for image quality, diagnosis and make clinical management decisions |
| 33 NICUs in India(24,67) | Diagnoses conducted remotely initially by ROP experts. Subsequent training of non-physician technicians | 94.3% of technician-led decisions agree with ROP expert. 0.4% of treatment-requiring ROP missed by technician | |
| PHOTO-ROP study | Image acquisition by expert physicians, also carrying out simultaneous BIO | Clinically significant ROP – 92.0% sensitivity, 37.2% specificity | Standard six image set consisting of pupil, posterior pole, and four retinal fields |
| 7 NICUs in Canada, Ireland, UK, US(80,63,81) | Diagnoses conducted remotely by masked ROP experts. Results of BIO and WFDRI diagnoses compared | Type 1 ROP – 92.0% sensitivity, 67.4% specificity | WFDR1 deemed as useful adjunct to conventional bedside ROP, with severe ROP highly unlikely to be missed when image quality is high |
| Chilean national pilot program for telemedicine screening of ROP(96) | Image acquisition by trained mixed staff (nurse, midwife, or technician) | 4% of patients imaged referred for treatment | Five images minimum (posterior pole and four quadrants) per eye. Independent reviewers also rated image quality in addition to disease severity |
| 11 NICUs in Chile | Diagnosis same day by two independent masked ROP expert ophthalmologists | 98% agreement between clinical examinations and images | Patients with non-interpretable images were re-imaged within 72 h. Ophthalmologist examination performed if meeting criteria for treatment or second imaging still interpretable |

ROP: Retinopathy of prematurity, e-ROP: Evaluating Acute-Phase ROP, PHOTO-ROP: Photographic screening for ROP, SUNDROP: Stanford university network for diagnosis of ROP, KIDROP: Karnataka internet assisted diagnosis of ROP, ART: Auckland regional telemedicine, NICU: Neonatal intensive care unit, US: United States, UK: United Kingdom, BIO: Binocular indirect ophthalmoscopy, WFDRI: Wide-field digital retinal imaging, PPV: Positive predictive value, NPV: Negative predictive value

Practice. Deep learning (a subset of machine learning), in which algorithms train themselves using multiple layers of neural networks, has been applied with success to ROP screening. Those highlighted in Table 5 each use convolutional neural networks to process input images. These algorithms are trained on a learning set of images, typically labeled with known diagnoses, and regions of each image are weighted by the algorithm based on their contribution to the overall diagnosis. Using these weightings, test images are introduced, and the output is analyzed to determine the algorithm’s performance.

Current AI models show some variation in their classification of disease. Both ROP-AL(108) and i-ROP-DL(110,111) focus on the detection of plus disease, while Huang et al.(112,113) model their detection criteria around ICROP staging. DeepROP(109) does not use strict ICROP criteria, with their “minor ROP” category corresponding to Zone 1 or 2 and Stage 1 or 2 disease as per ICROP and “severe ROP” corresponding to type 1, 2 AP-ROP or Stage 4 or 5 disease. All algorithms demonstrate comparable sensitivity and specificity to already implemented screening techniques, of more than 80% in both internal and external validation. Huang et al. have also demonstrated the viability of using CNNs pre-trained on non-ROP data to produce results of similar performance. Despite these promising results, these systems have so far seen limited implementation in real-world settings beyond initial development and validation.

Discussion

In this review, we have identified nine different regional screening programs, with significant heterogeneity in screening criteria both between and within countries. This may be in response to differing population factors and the risk factors of infants who are developing ROP locally. The ROP screening schedule should ensure that all eyes at risk of requiring
Table 4: Published studies of computer-based image analysis in retinopathy of prematurity diagnosis

| Study       | Fundal image features selected a priori                                                                 | Results                                                                                                                                                                                                 | Notes                                                                 |
|-------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| RISE[91,92] | Venule and arteriole diameter, tortuosity and integrated curvature (cumulative vessel angles normalized to length) | 34 images, RISE compared to reference standard diagnosis based on 22 ROP expert graders[92] In classifying plus disease, venule integrated curvature individually – AUROC 0.853. Combination of arteriole integrated curvature, tortuosity, venule integrated curvature, diameter, and tortuosity index – AUROC 0.967 | Required significant image pre-processing including manual identification and segmentation of retinal vessels Median diameters of arterioles and venules in plus disease shown to be approximately 12 μm greater |
| i-ROP[98,99] | Vessel cumulative tortuosity index, integrated curvature, integrated squared curvature normalized by curve length, integrated squared curvature normalized by curve length, integrated curvature normalized by chord length, integrated squared curvature normalized by chord length, acceleration, curvature, average segment diameter, average point diameter, image field of view | 73 images, i-ROP compared to reference standard diagnosis based on 11 ROP expert graders[98] In classifying plus disease, using the widest image field of view and incorporating arterial and venous tortuosity – 95% accuracy 77 images, i-ROP compared to reference standard diagnosis based on 3 ROP expert graders[99] In classifying plus and pre-plus disease – 95% accuracy | Required significant initial manual segmentation of retinal vessels. Subsequent computer-based image pre-processing to develop vasculature trees Provided three-level diagnosis including plus, pre-plus disease and normal retina |
| ROP tool[96,97] | Vessel tortuosity and dilatation                                                                        | 335 images, Retool compared to reference standard diagnosis by 3 ROP expert graders or lay reader[96] In detection of any vascular abnormality – AUROC 0.917, 91% sensitivity, 82% specificity 185 images, Retool compared to reference standard diagnosis by 3 ROP experts and 3 non-expert pediatric ophthalmologists[97] In detection of tortuosity sufficient for plus disease – 95% accuracy, 97% sensitivity, 94% specificity | Required operator input to semi-automatically identify fundal image quadrants prior to segmentation of retinal vessels |
| CAIAR[101-104] | Venule and arteriole tortuosity, width and combined                                                      | 111 images, CAIAR compared to clinical diagnoses via BIO[102] In detection of plus disease, arteriole tortuosity – AUROC 0.920. Venule width – AUROC 0.909 | Used narrow-field retinal images. Semi-automated segmentation of retinal vessels |
| Vessel Map[105] | Venule and arteriole diameter                                                                            | 78 eyes from 39 infants, unknown number of images, Vessel Map compared to clinical diagnoses via BIO[105] In detection of fundi progressing to severe ROP requiring treatment – AUROC 0.75-0.94 | Used narrow-field retinal images. Semi-automated segmentation of retinal vessels |

ROE: Retinal image multiScale analysis, DL: Deep learning, ROP: Retinopathy of prematurity, i-ROP: Imaging and Informatics in ROP, BIO: Binocular indirect ophthalmoscopy, CAIAR: Computer-aided image analysis of the retina, AUROC: Area under receiver operator characteristic

It allows for objective photographic documentation, mitigating the medicolegal risk associated with BIO, and its subjective method of ROP grading and documentation. In addition, serial retinal imaging offers photographic monitoring of ROP progression and ease in seeking a second opinion. Images can also be used for education and training to improve ROP management. However, both BIO and WFDRI demonstrate similar and significant interoperator variability in diagnosis.

Six teleophthalmology-based screening models across countries of varying income levels were chosen to illustrate representative program characteristics. Teleophthalmology in combination with WFDRI addresses many of the challenges associated with traditional ROP screening and provides an effective alternative model of care. The use of trained nonophthalmologists to capture images can also release ophthalmologists from a significant portion of the image grading and decision-making for treatment.

While BIO remains the gold standard for ROP diagnosis, it is becoming increasingly difficult to apply this practice widely within at-risk populations. The relative lack of trained experts is exacerbated by the growing incidence of disease, especially in middle-income settings where specialized clinicians are already lacking. Limitations in the supply of clinicians willing to carry out BIO is further worsened by the additional medicolegal risk associated with this screening practice. WFDRI carries significant benefits to address these challenges.
Table 5: Published artificial intelligence-based systems for retinopathy of prematurity diagnosis

| Study          | Datasets                                                                 | Results                                                                                                                                                                                                 | Notes                                                                 |
|----------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| ROP.AI[107]    | 6974 images of normal and plus-disease retinae sourced from New Zealand ART-ROP image library. Image diagnoses provided by expert appraisal. Internal validation through 80:20 image split into training: test sets. External validation on set of 90 images from independent center | Internal validation: 96.6% sensitivity, 98.0% specificity for detection of plus disease  
External validation: 93.9% sensitivity and 80.7% specificity | Data also gathered on detecting pre-plus disease: 81.4%/80.7% sensitivity/ specificity |
| DeepROP[109]   | 20795 images sourced from both local data and web searches. Divided into two subsets of data for identification task (normal versus ROP) and grading task (minor ROP versus severe ROP). 90:10 split of cases for internal validation. External validation via submission of 944 clinical cases to website | Internal validation: 96.6% sensitivity, 99.3% specificity for identification, 88.5% sensitivity, 92.3% specificity for grading  
External validation: 84.9%/86.9% sensitivity/specificity in identification, 93.3%/73.6% sensitivity/specificity in grading | Unlike other algorithms, DeepROP takes a case-based approach, assigning multiple images to single patients  
Comparison also made with 3 human experts. AI appears to outperform one expert |
| i-ROP-DL[110,111] | 5511 retinal images sourced from 8 study centers. Images consisted of 82.3% normal, 14.6% pre-plus, and 3.1% plus based on expert appraisal. 80:20 split of images into training: Test sets. Independent test set of 100 images (54/31/15 normal/pre-plus/plus). Further testing of algorithm's ability to detect clinically significant ROP based on grading/staging criteria | Internal validation: plus disease 93% sensitivity, 94% specificity; pre-plus or worse disease 100% sensitivity, 94% specificity  
Internal validation: treatment-requiring ROP (Type 1 ROP): 94% sensitivity, 79% specificity | Algorithm correctly identified 91 of the test images and did not generate false negatives |
| Huang et al.[112,113] | 11372 images consisting of no ROP, stage 1, and stage 2 disease. 90:10 split of cases for internal validation. Test set of 94/44/106 images consisting of no ROP/stage 1/ stage 2 disease respectively for external validation  
Second study on the use of small datasets in conjunction with translational learning for pre-existing AI models.  
6500 total images across 210 patients collected from Taiwanese and Japanese NICUs | Internal validation: No ROP: 96.1% sensitivity, 96.0% specificity; stage 1: 91.8% sensitivity, 94.5% specificity; stage 2: 89.8% sensitivity, 99.0% specificity  
Translational learning: Best model (VGG19) demonstrated 99.2% sensitivity, 99.3% specificity for ROP/no ROP; 98.7% sensitivity, 98.5% specificity for ROP severity | Second study demonstrates that models pre-trained with non-ophthalmic datasets can be adapted for ROP diagnosis |

ROP: Retinopathy of prematurity, i-ROP: Imaging and Informatics in ROP, AI: Artificial intelligence, DL: Deep learning, ART: Auckland regional telemedicine, NICUs: Neonatal intensive care units, VGG: Visual Geometry Group

Nonophthalmologist image acquirers may also be able to capture images in units or regions where ROP screening may not have been previously available, reducing the need for infant transfer and addressing access limitations which constrain traditional BIO-based models of screening. Evidence for these models is emerging with pilot studies in the US[81] and Mexico[14] demonstrating positive outcomes, including high sensitivity and overall performance.

The COVID-19 pandemic has encouraged further interest in the application of teleophthalmology for ROP screening and within ophthalmology in general.[115,116] Studies from India and the US[117,118] have demonstrated significant enthusiasm from patients and clinicians. Most current guidelines still advise teleophthalmology be accompanied where possible by at least one in-person examination. Applying CBIA and AI technologies to teleophthalmology-based screening may further address current limitations in the capacity and distribution of the ROP workforce.

Second, further development of portable or low-cost retinal cameras may increase access to retinal imaging and teleophthalmology-based screening. Currently available retinal cameras are limited by portability and cost, reducing adoption in geographically large and low- and middle-income countries that have reduced capacity for costly equipment capital outlays. Third, training and deploying nonphysician image acquirers and graders may reduce need for specialized ophthalmology input for diagnosis and mitigate present issues in access to

with sufficiently validated algorithms, may allow for the point-of-care diagnosis of treatment-requiring ROP in settings without previous access to case detection.[88] Significant real-world testing and prospective trials will be required to validate the accuracy of these early-stage algorithms before their routine use and meaningful uptake. Recent studies such as the investigational use of an AI system within clinical practice in Nepal and Mongolia are highly promising for their potential in improving screening access within traditionally resource-constrained settings.[119] Based on this review, several recommendations for the future development of ROP screening emerge. Firstly, increased development of country- or region-specific guidelines is required. Ensuring screening guidelines reflect area-specific demographic factors and have sufficient sensitivity in detecting vision-threatening disease will require population-level studies that help determine appropriate thresholds that optimize sensitivity against breadth and cost of screening.

Most recent AI technologies may enable automated diagnosis and reduce need for specialized ophthalmology services to diagnose disease. In high-demand regions, including middle-income countries, AI may enable more effective triage, accurately identifying cases that demand further clinician review. Further, these technologies may have potential in assisting clinicians in objectively quantifying and monitoring the severity of ROP disease. The use of WFDRI and novel portable neonatal retinal imaging systems, coupled
screening. Here, AI may be highly valuable, providing clinical decision support or triage to identify high-risk cases that require specialized review and even automated point-of-care diagnosis, thus improving access and efficiency. At last, AI algorithms for ROP remain largely validated in silico with limited real-world testing. Prospective trials will be required to evaluate their real-world performance and cost-effectiveness, which will be essential to large-scale adoption within routine clinical care. Given regional differences in ROP demographics, special care must be given to validating performance in diverse patient populations and ethnicities and ensure that algorithms are generalizable and do not perpetuate existing health equity gaps. Routine adoption of these tools also requires consideration of the understandability of their outputs and address broader liability, regulatory, and ethical concerns that are common to AI systems at large.

**CONCLUSION**

The “third epidemic” of ROP is attributable in part to current limitations in ROP screening. As improved neonatal services result in increased survival of premature infants globally, the number of patients at-risk of developing ROP will likely continue to grow. While BIO remains the traditional gold standard for ROP screening, it is likely not feasible given current workforce and geographical distribution limitations for each neonate to be directly examined via BIO by a specialized ophthalmologist. Advances in retinal imaging and increasing reception for adoption of teleophthalmology may mitigate geographical barriers to screening. Ongoing limitations however remain in interoperator consistency, and the low treatment yield of ROP screening. AI technologies may have application in the initial triage of ROP images, reducing the number of at-risk images that need to be reviewed by trained ophthalmologists. In areas of increasing need, these technologies have the potential to play a critical role in addressing the growing burden of ROP globally.

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There are no conflicts of interest.

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