Advanced Training in Neonatal/Perinatal Medicine

EXAMPLE PROJECT

PROJECT TITLE: Screening for Retinopathy of prematurity (ROP) using wide angle digital retinal photography by non-ophthalmologists – A systematic review.
Screening for Retinopathy of prematurity (ROP) using wide angle digital retinal photography by non-ophthalmologists- A systematic review

Keywords:

Retinopathy of prematurity, Digital retinal photography.

Word count: Excluding references and Tables - 3868
Abstract

Introduction: Retinopathy of prematurity (ROP) is one of the leading and preventable causes of blindness. The incidence of ROP is rising with increasing survival of preterm infants. The gold standard test for diagnosing ROP is Binocular Indirect Ophthalmoscope (BIO) done by ophthalmologists. Since the number of ophthalmologists available to do BIO examination is limited, there is a need for an alternate, feasible and easy to administer test. Telemedicine imaging with Digital Retinal Photography (DRP) is one such alternate diagnostic test which can be performed easily by non-ophthalmologists, with adequate training.

Aim: To do a systematic review to evaluate the accuracy of DRP performed by trained personnel (non-ophthalmologists) in diagnosing clinically significant ROP.

Methods: Medline, EMBASE, CINAHL were searched independently by two authors. Eligible studies were assessed using the QUADAS-2, an evidence-based tool for the assessment of quality in systematic reviews of diagnostic accuracy studies.

Results: Initial literature search provided 415 citations, of which 190 were from Medline, 207 from EMBASE and 18 from CINAHL. After removing duplicates, 291 articles were screened, out of which six were included in the review (three prospective; N=120, three retrospective; N=579). Studies had methodological limitations on QUADAS-2. Because of the heterogeneity of studies, data could not be pooled to derive single effect size estimates for sensitivity and specificity. The included studies reported sensitivity of 45.5% to 100% with the majority being more than 90%; specificity 61.7% to 99.8% with the majority being more than 90%, positive predictive value 61.5% to 96.6% and negative predictive value of 76.9 to 100% for diagnosing clinically significant ROP.
Conclusion: DRP imaging performed by non-ophthalmologists may be a useful tool to identify significant ROP in preterm infants. The ongoing prospective study (ClinicalTrials.Gov NCT01264276) which is aiming to recruit 2000 participants is expected to answer this question definitively.
Background:

Retinopathy of prematurity (ROP) is a proliferative disease of the retinal vasculature predominantly affecting the premature and low birth weight infants (Hunter and Mukai 1992). Advances in medical technology have enabled increased survival rates for preterm infants even at very low gestational ages resulting in an increased incidence of ROP (Costeloe et al. 2012). ROP is one of the leading causes of childhood blindness and the disease burden is even higher in middle income countries where the standard of neonatal care has improved in recent times (Gilbert 2008).

Cryotherapy for Retinopathy Of Prematurity Study CRYO-ROP (1988) and the Early Treatment for Retinopathy of Prematurity ET-ROP (Early Treatment For Retinopathy Of Prematurity Cooperative 2003) have confirmed the success of treatment and hence, screening is mandatory. The revised ROP screening guidelines (2006) expanded the eligible screening population, which includes infants with birth weight of less than 1500g or gestational age of ≤32 weeks at birth and more mature high-risk infants. The recent update in 2013, includes “selected infants with a birth weight between 1500 and 2000 g or gestational age of >30 weeks with an unstable clinical course, including those requiring cardio respiratory support and who are believed by their attending paediatrician or neonatologist to be at high risk for ROP” (Fierson 2013). The revised guidelines together with the increased number of survivors of preterm infants, has resulted in an enormous workload on the screening ophthalmologists.
Although more infants require ROP surveillance, there are only a limited number of ophthalmologists who are trained in diagnosing and treating ROP. A random survey of 1504 ophthalmologists in USA showed that only 11% were performing ROP screenings and only 6% were treating ROP (Kemper, Freedman, and Wallace 2008). In another survey by the American Academy of Ophthalmology it was shown that only 50% of retinal specialists and paediatric ophthalmologists were managing ROP, and that nearly 25% intended to stop because of issues such as logistical difficulties, medico legal liability and financial concerns (AAO Communication). In Canada more than 12,150 ROP examinations are performed by fewer than 100 subspecialists per year (Lee et al. 2001).

Binocular Indirect ophthalmoscope (BIO) has been the gold standard method for ROP screening. The timely screening of ROP with BIO has achieved great success and prevented blindness; however there are few drawbacks of this screening program. First of all, it is very labour intensive and time consuming for ophthalmologists (Richter, Sun et al. 2009). Secondly, the documentation detailing zone, stage, extent (clock hours), and the presence of plus or pre-plus disease can be subjective. Thirdly, there are no stored images for future (Richter et al. 2009).

Screening for ROP with digital imaging using wide angle digital retinal photography (DRP) has been proposed as a potential alternative. Telemedicine strategies ie.,capturing retinal images and transferring them to off-site ophthalmologists for evaluation have been tried in various clinical settings such as diabetic retinopathy (Wilson et al. 2008) etc. DRP imaging are done through a hand held digital retinal camera (130° field of view) which is placed gently on the cornea interfaced with ophthalmic lubricant. The images done through DRP can diagnose disease up to anterior zone 2 which accounts for over 90% of ROP requiring...
treatment (Hartnett and O'Keefe 2011, Wilson, Ells, and Fielder 2013). Additional advantage is that, the images can be documented for future reference. Screening with digital retinal photography has been shown to be associated with a significantly lower stress-related response than BIO (Mukherjee et al. 2006). The technology of DRP has evolved over last ten years and the most recent is the RetCam Shuttle, which has an additional advantage of portability and can be easily transferred between units (Calafati, Naqi, and Ahmed 2009).

A recent systematic review (Chiang et al. 2012) has shown that wide angle digital retinal photography has the potential to complement standard ROP screening by ophthalmologists. Based on the review from 10 studies, the authors reported that digital retinal photography has high accuracy for detection of clinically significant ROP. However, majority of the studies included in that review, the retinal photography was taken by ophthalmologists.

Clinical staffs that are most suitable to take up this task are neonatal nurses. The advantages of nurses performing this procedure are 1. The nurses are aware of neonatal pathophysiology 2. They are tuned to the needs of preterm babies such as procedural pain and hunger. 3. Nurses are always available in the unit on a shift basis 4. Competent neonatal nurses may be able to interpret the digital images and prioritise ophthalmology reviews. 5. This approach has the potential to improve the outcomes even in medium human development countries where there may be shortage of trained paediatric ophthalmologists. Other non-ophthalmology personnel who may be able to do DRP are trained photographers, neonatal paediatricians.

However, it is important that the images taken by non-ophthalmologists need to be of high quality so that correct interpretation is possible when read by ophthalmologists who are off site. Hence, we conducted this systematic review to evaluate the diagnostic accuracy of screening of ROP by non-ophthalmologists using DRP. So far, to our knowledge, no such systematic review has been conducted.
Methods

We followed methods for conducting and reporting systematic reviews recommended by the Cochrane Collaboration Diagnostic Test Accuracy Working Group and the PRISMA (Moher et al. 2009).

Study selection.

To be considered for the review, the studies should have met the following essential criteria: (1) Provision of adequate description of the clinical test used for diagnosing ROP i.e., digital retinal photography (2) a report of the measures of diagnostic accuracy (e.g., sensitivity and specificity), and (3) an acceptable reference standard for comparison, i.e., BIO examination.

Both prospective and retrospective studies were included for the review as long as the above criteria were met. The following types of studies were eligible for inclusion.

1. Studies where DRP was done by non-ophthalmologists, but not interpreted by the non-ophthalmologists. All images sent electronically to ophthalmologists for interpretation. BIO also done in all study infants simultaneously with DRP.

2. Studies where DRP was done by non-ophthalmologists but not interpreted by them and all images are sent electronically to ophthalmologists for interpretation. BIO was done by ophthalmologists at some stage in the neonatal period.

3. Studies where DRP was done and interpreted by non-ophthalmologists and compared with BIO done by ophthalmologists.

Excluded studies:

The studies where the DRP was done by ophthalmologists were excluded from the review.
Participants:

Preterm infants at risk for developing ROP.

Index test:

The index test was DRP screening done by trained personnel.

Target conditions:

The target conditions were referral warranted (RW-ROP) and treatment warranted ROP (TW-ROP) as described in ETROP study.

RW-ROP was defined as ROP of sufficient severity to require expert ophthalmologic opinion (1) Any Zone 1 disease (2) Any stage 3 diseases, (3) presence of plus disease

TW-ROP was defined as any one of the following: (1) Zone I any stage with plus disease; (2) Zone I, stage 3 with or without plus disease; (3) Zone II, stage 2 or 3 ROP with plus disease; (4) any zone, plus disease and (5) any zone, stage 4 or higher disease (Good and Hardy 2001).

Reference standard.

BIO examination performed by pediatric ophthalmologists.

Outcomes

Primary

Accuracy of DRP to diagnose TW-ROP when compared to BIO.
Secondary Outcome:

Accuracy of DRP to diagnose RW-ROP when compared to BIO.

Accuracy of DRP to diagnose various stages of ROP when compared to BIO.

Search Methods

Study Selection

Two reviewers (SEA and SCR) independently screened the databases Medline (1966-June 2013), Embase (1980-June 2013) using the Ovid platform. CINAHL (dates) and the Cochrane library (Issue number, June 2013) were also searched to identify relevant studies. Abstracts of the accumulated citations were read independently by both authors to identify potentially eligible studies. Full-text articles of such studies were read to decide upon final eligibility for inclusion. Any disagreements about study selection were resolved by discussion all other authors (SKP, GL., CD). No language restrictions were applied.

Data Extraction and analysis

Two authors (SEA and SCR) independently completed a pre-specified data extraction form for all included studies. The following details were collected: title of the article, journal, year when study was conducted, year of publication, study design (prospective versus retrospective), sample size, baseline characteristics including gestational age, and ROP classification were collected. In addition, any reported side effects or complications due to DRP were collected.
Initial plan was to pool the data to derive summary statistics for sensitivity, specificity, positive predictive value and negative predictive value with appropriate confidence intervals. However, in view of clinical heterogeneity regarding the study design, data provided, outcomes assessed among the included studies, we decided to do narrative synthesis.

Results

Results of the search

The search provided 415 citations of which 190 were from Medline, 207 from EMBASE and 18 from CINAHL. After removing duplicates there were 291 articles screened and 20 were short listed and 6 were included for the final review. The details of study selection process are given in figure 1. The list of excluded studies and the reasons for their exclusion is provided in table 1.

Included studies

Three were prospective studies (Yen et al. 2002, Skalet et al. 2008, Chiang et al. 2007) and three were retrospective (Roth et al. 2001, Weaver and Murdock 2012, Fijalkowski et al. 2013) Further details about methodology, time of the study and instrument used and other additional study characteristics are given in table 2 and 3. In Total there were 699 infants from the six included studies.
Roth (Roth et al. 2001)

In this retrospective study from Miami University, the DRP images were taken by trained photographers at the time of standard screening by BIO examination done by ophthalmologists. The DRP images were stored and the interpretation of images was done by masked readers several months later. The sensitivity, specificity, PPV and NPV were 82.4%, 93.8%, PPV 96.6%, NPV 76.9% respectively. The author's concluded that the low sensitivity was due to the technical limitation of the camera, and the ROP that was missed by DRP were the ones which involved the peripheral zone 2 and 3.

Yen (Yen et al. 2002)

In this prospective study from Utah, USA, DRP images were taken by the nurses and all study infants had simultaneous BIO examination done by ophthalmologists. The authors reported that the sensitivity and specificity were 100% for identifying threshold ROP. For pre-threshold disease sensitivity was 64 and specificity was 97% at 38-40 weeks of age.

Chiang (Chiang et al. 2007)

In this prospective study from Columbia University, USA neonatal nurses took the DRP images and all study infants had simultaneous BIO examination done by ophthalmologists. The interpretation of the images were done by three different ophthalmologists and the sensitivity for diagnosing TW-ROP was 100% for all three readers and the specificity ranged from 80.6-94.1% at 35-37 weeks.
There were 3 further publications using the same cohort of infants addressing other outcomes such as single image VS multiple image telemedicine examination (Lajoie et al. 2008), intra-physicians agreement where the same ophthalmologists who did the BIO earlier interpreted the image reading 4-12 months later (Scott et al. 2008) and interpretation of images by ophthalmology fellows compared to web based evaluation by ophthalmologist (Myung et al. 2011).

Skalet (Skalet et al. 2008)
This is the only study in our review which was conducted in middle income country (Peru) which evaluated the feasibility of retinal imaging and remote grading of images. Images from 26 infants out of 28 were included for review and both the sensitivity and specificity for 5 different readers ranged from 45.5% to 95.2%, 61.7 and 96.2% respectively.

Weaver (Weaver and Murdock 2012)
In this retrospective study nurses took the DRP and images were interpreted by two remote ophthalmologists. In this study, the infants who had RW-ROP were referred as opposed to TW-ROP in SUNDROP study and underwent reference standard Bio examination immediately. Of the 137 infants screened 13 were referred and 9 got treated with a positive predictive value of 61.5%. This study had a high risk for bias on the reference standard and flow and timing because the babies didn’t have simultaneous BIO examination. However, all infants who had been discharged had been confirmed to have no ROP as an outpatient BIO examination on later date giving a negative predictive value of 100% (Weaver and Murdock 2012).
SUNDROP study (Fijalkowski et al. 2013)

SUNDROP study from Stanford University was a retrospective study where trained nurses performed the DRP and images were interpreted by remote ophthalmologists. The earlier publications from the same centre (Murakami et al. 2008, Silva et al. 2009, Murakami et al. 2010, Silva et al. 2011) been superseded by a more recent publication (Fijalkowski et al. 2013). This study is the largest study till date included 410 infants with 820 eyes which showed 100% sensitivity and 99.8% specificity for identifying TW-ROP. The study infants did not have simultaneous BIO examination and hence scored high on risk for bias in reference standard and flow and timing. However, all the infants who had the diagnosis of TW-ROP were confirmed with Bio-examination within 8-12 hours of arrival into referring hospital. The rest of the infants were confirmed as no ROP with a BIO examination either at the time of discharge or within a week of discharge from hospital giving a negative predictive value of 100 % for TW-ROP

Assessment of the Methodological Quality of Individual Studies

Eligible studies were independently assessed by two reviewers (SEA and SCR ) using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies), an evidence-based tool for the assessment of quality in systematic reviews of diagnostic accuracy studies which evaluate the presence of bias and variation in diagnostic accuracy studies (Whiting et al. 2011). As recommended, we scored each item as “Low,” “High,” or “Unclear”. (Table 4)

Studies had methodological limitations on assessment using the QUADAS 2 tool. All the six studies were considered to include a representative patient population. We scored this item as “yes” when infants at risk of developing ROP were screened and there were no concerns for bias or applicability. Our review showed that the majority of studies were considered to have a spectrum of patient’s representative of those that would be tested in real clinical practice.
All studies used similar index test, except (Skalet et al. 2008) which used a different camera. Only three of the studies (Chiang et al. 2007, Yen et al. 2002, Weaver and Murdock 2012) had simultaneous BIO examination, which is considered to be the gold standard test for diagnosing ROP. The flow and timing was variable and all six studies were scoring either high or unclear on this domain. Detailed description of the QUADAS 2 parameters for all included studies is described in table 4 and figure 2.

Discussion

To our knowledge, this is the first systematic review to investigate the accuracy of DRP screening done by trained non-ophthalmologists for diagnosing ROP in preterm infants. While the results from a total of 699 infants from six studies suggest that this method has the potential to be implemented in neonatal units, it is important to note that the largest sample size (579/699) came from the three retrospective studies; prospective studies contributed to only 17% of the total sample size.

Unlike the only other systematic review (Chiang et al. 2012), which included screening done by professional ophthalmologists, we included only those studies where screening photography was done by non-ophthalmologists. When trained personnel are able to capture high-quality digital retinal images, the remotely located ophthalmologists will be able to interpret, which in turn will reduce the burden on the ophthalmologists while not compromising patient safety.

To be a good screening tool, the new test should be validated by comparison against an established gold standard in an appropriate spectrum of subjects (Greenhalgh 1997). Four indices of test validity have been widely used and they are sensitivity, specificity, positive predictive value and negative predictive value. (Grimes and Schulz 2002). "A test is valid if
it detects most people with the target disorder (high sensitivity) and excludes most people without the disorder (high specificity), and if a positive test usually indicates that the disorder is present (high positive predictive value)" (Greenhalgh 1997). It seems that DRP fits all these above mentioned criteria. The sensitivity of DRP in the included studies was high except for (Yen et al. 2002, Roth et al. 2001). The included studies reported sensitivity of 45.5% to 100% with the majority being more than 90%, specificity 61.7% to 99.8% with the majority being more than 90%, positive predictive value 61.5% to 96.6% and negative predictive value of 76.9 to100% for diagnosing clinically significant ROP.

SUNDROP, which is the largest study included in our review reported highest sensitivity and specificity. This study has demonstrated high degree of diagnostic reliability and ability to identify infants needing treatment. The reported high levels of sensitivity/ specificity and 100% negative predictive value gives a hope for "a cost effective, reliable and accurate screening method for ROP" (Fijalkowski et al. 2013). Similar levels of high sensitivity/specificity and NPV were reported by another large included study (Weaver and Murdock 2012). "Negative predictive value means if a person tests negative, what is the probability that he or she does not have the condition" (Greenhalgh 1997).

Because of the variations in methodology in these six studies, it was not possible to calculate the pooled sensitivity and specificity estimates. On the QUADAS tool all these six studies were similar in patient selection and represented the true patient spectrum which would need this diagnostic testing. However majority of included studies had methodological limitations, because the gold standard BIO was not performed simultaneously (Figure 2, Table4 ).
Hence, a methodologically robust prospective study with adequate sample size is essential to address this issue definitively. One such multicentre clinical trial is currently under way in USA and Canada (Clinicaltrials.Gov 2013) NCT01264276 and aims to recruit 2000 participants. The study infants will undergo both DRP and clinically indicated indirect ophthalmoscopic examinations (BIO) on the same day. Wide-field digital images (DRP) of both eyes will be captured by non-physician Certified ROP Imagers (CRIs) using standardized imaging protocols. The accuracy of DRP done by this CRIs will be compared with the simultaneously performed BIO by ophthalmologists. This trial also looking into the reliability, feasibility, safety and cost-effectiveness of DRP imaging as compared to BIO.

The incidence of ROP is on the rise in middle income countries where the pattern of ROP is different from those seen in the developed part of the world. The ROP pattern in these countries are due to poor control of supplemental oxygen and uneven screening programmes available for ROP in very preterm infants. The ROP is seen even among more mature (>32 weeks’ gestation) and heavier (>1500 g birth weight) infants (Darlow, Gilbert, and Quiroga 2013). The review by Darlow et al (Darlow, Gilbert, and Quiroga 2013) highlights the need for ROP programs emphasising on primary prevention through improved obstetric and neonatal care, and secondary prevention through appropriate case detection and treatment.

The screening programme in middle income countries faces two problems. Firstly, due to lack of awareness of ROP and the need for screening, secondly, the lack of specialists who could perform procedure even when parents are ready. The KIDROP (Karnataka Internet assisted Diagnosis of ROP) programme is an Indian based not for profit organisation which has taken the ROP surveillance to the community because of the above mentioned problem faced in India, and it serves 51 neonatal intensive care units (NICU) in rural and semi-urban regions of south India. In this project the DRP screening is done by trained non-physicians
using the digital camera (RetCam Shuttle) at each district headquarters and since 2008 this surveillance programme has screened 9058 infants, of whom 718 babies (7.9%) had clinically significant ROP (Vinekar, Wilson, Ells, and Fielder 2013).

In summary, while there are arguments for and against a telemedicine approach to ROP, definitely there is a trend towards the telemedicine. In Developed countries this would benefit the already overworked specialists. Additional advantage of this approach is a permanent digital image for accurate documentation of ROP. In developing nations, telemedicine screening has the potential to increase the access of ROP care (Wilson, Ells, and Fielder 2013, Carden and Good 2011).

Main strengths of our review was that we used a standard protocol for search and a comprehensive search strategy by two independent reviewers at all stages of the review process, and assessment of methodological quality of individual studies with the QUADAS-2 tool. Our review also had limitations; the majority of studies were looking only for RW-ROP and TW-ROP and not considered to include the pickup rate for patients with milder form of ROP. Clearly, having more studies of similar nature would have allowed us to say with confidence, the ability of DRP to identify patients at risk.
Conclusion

DRP imaging done by non-ophthalmologists has a high sensitivity and has the potential to identify the TW-ROP & RW-ROP in at risk infants. Hence, DRP imaging performed by non-ophthalmologists may be a useful tool to identify clinically significant ROP. Diagnostic accuracy of DRP must be established, preferably prospectively, in a wide spectrum of patients, against the gold standard BIO (Binocular indirect ophthalmoscope examination). The ongoing prospective study (ClinicalTrials.Gov NCT01264276) which is aiming to recruit 2000 participants is expected to answer this question definitively.
References:


Depistage et suivi de la retinopathie du premature par camera de retine (Retcam 120): Experience d'une equipe de neonatalogistes a propos de 145 cas." Archives de Pediatrie no. 10 (8):694-699.

Vincar, Anand. "The KIDROP Experience in India."


Table 1 - Studies by author, year and reason for exclusion.

<table>
<thead>
<tr>
<th>Study &amp; Authors</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ells, A. (Ells et al. 2003)</td>
<td>Both DRP screening &amp; BIO done by ophthalmologist</td>
</tr>
<tr>
<td>Hungi, B (Hungi et al. 2012)</td>
<td>A team under the supervision of ophthalmologist (trained technicians) did the screening. BIO was not compared with DRP</td>
</tr>
<tr>
<td>Photographic Screening for Retinopathy of Prematurity Cooperative, G. 2008</td>
<td>DRP Screening done by ophthalmologists</td>
</tr>
<tr>
<td>Shah, P. K. (Shah et al. 2006)</td>
<td>Both DRP screening &amp; BIO done by ophthalmologist</td>
</tr>
<tr>
<td>Dhaliwal, C (Dhaliwal et al. 2009)</td>
<td>Both DRP screening &amp; BIO done by ophthalmologist</td>
</tr>
<tr>
<td>Dai, S (Dai, Chow, and Vincent 2011)</td>
<td>Both DRP screening &amp; BIO done by ophthalmologist</td>
</tr>
<tr>
<td>Williams, S. L., (Williams et al. 2010)</td>
<td>Multiple reviewers in the DRP arm (fellows, medical students, nurse did the DRP)</td>
</tr>
<tr>
<td>Sommer, (Sommer et al. 2003)</td>
<td>Screening done by neonatologist and compared by the ophthalmologist, but no simultaneous BIO examination done</td>
</tr>
<tr>
<td>Myung, J. S. (Myung et al. 2011)</td>
<td>DRP Screening done by ophthalmology fellows</td>
</tr>
<tr>
<td>Paul Chan, (Paul Chan et al. 2010)</td>
<td>DRP Screening done by Retinal fellows</td>
</tr>
<tr>
<td>B Lorenz (Lorenz et al. 2009)</td>
<td>DRP Screening done by general Ophthalmologists</td>
</tr>
</tbody>
</table>

DRP: Digital Retinal Photography  
BIO: Binocular Indirect Ophthalmoscope
## Table 2. Summary table of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample size</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV</th>
<th>NPV</th>
<th>Author's Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2001</td>
<td>32 Infants 100 eyes</td>
<td>82.4%</td>
<td>93.8%</td>
<td>96.6%</td>
<td>76.9%</td>
<td>Authors concluded that the low sensitivity is due to the technical limitations of the DRP.</td>
</tr>
<tr>
<td>Yen 2002</td>
<td>25 Infants 50 eyes</td>
<td>64% for prethreshold 100% for Threshold disease</td>
<td>97% for prethreshold 100% for threshold</td>
<td>88% Pre-threshold 100% Threshold</td>
<td>88% Pre-threshold 100% Threshold</td>
<td>The DRP had insufficient sensitivity to be recommended as a substitute for BIO in screening for ROP.</td>
</tr>
<tr>
<td>Chiang 2007</td>
<td>67 Infants 248 Eyes</td>
<td>100%</td>
<td>94.1% 93% 80.6% (3 readers)</td>
<td>NA</td>
<td>NA</td>
<td>DRP imaging has the potential to improve existing Shortcomings of ROP management, particularly at later Post Menstrual Ages.</td>
</tr>
<tr>
<td>Skaled 2008</td>
<td>28 infants</td>
<td>45.5-95.2% (5 readers)</td>
<td>61.7-96.2% (5 readers)</td>
<td>NA</td>
<td>NA</td>
<td>A telemedicine approach for ROP screening using DRP obtained by non-ophtalmologists is feasible in middle income countries.</td>
</tr>
<tr>
<td>Weaver 2012</td>
<td>137 infants 582 Eyes</td>
<td>100%</td>
<td>96.3%</td>
<td>61.5%</td>
<td>100%</td>
<td>Telemedicine ROP screening detected patients at a remote site in need of treatment, allowing prompt transfer with no poor outcomes.</td>
</tr>
<tr>
<td>Fijalkowski 2013</td>
<td>410 infants 820 Eyes</td>
<td>100%</td>
<td>99.8%</td>
<td>92.9%</td>
<td>100</td>
<td>The SUNDROP initiative was able to capture all infants with TW-ROP and DRP offers a cost-effective, reliable and accurate screening methodology for identifying infants with TW-ROP.</td>
</tr>
</tbody>
</table>

DRP: Digital retinal Photography

BIO: Binocular Indirect Ophthalmoscope
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Study Period</th>
<th>Study design</th>
<th>Eligibility criteria</th>
<th>Who did screen</th>
<th>Who did the interpretation</th>
<th>Reference standard</th>
<th>Remote/onsite interpretation</th>
<th>Camera - used</th>
<th>Outcome</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2001</td>
<td>Miami University &amp; Columbia</td>
<td>October 1997- May 1998</td>
<td>Retrospective</td>
<td>32-34 weeks, and then 2 weekly</td>
<td>Experienced ophthalmic photographers</td>
<td>Paediatric ophthalmologist</td>
<td>BIO by Ophthalmologists</td>
<td>Images were interpreted after several months</td>
<td>RETCAM-120 Clarity Medical system</td>
<td>Threshold ROP</td>
<td>Treatment was based on BIO only and the images were interpreted several months later</td>
</tr>
<tr>
<td>Ven 2002</td>
<td>University of Utah Salt lake City USA</td>
<td>July 1-1999- December 15 1999</td>
<td>Prospective</td>
<td>1st Exam: 32-34 weeks 2nd Exam: 38-40 weeks</td>
<td>Trained Neonatal nurses</td>
<td>Ophthalmologist</td>
<td>BIO by ophthalmologist</td>
<td>Onsite</td>
<td>RetCam 120 Massie Research Laboratories, Dublin, Calif</td>
<td>Threshold/ Prethreshold ROP</td>
<td>Simultaneous Bio &amp; Reteam</td>
</tr>
<tr>
<td>Chiang 2007</td>
<td>Columbia University</td>
<td>November 1,2005-October 31,2006</td>
<td>Prospective</td>
<td>31-33 weeks &amp; 35-37 weeks</td>
<td>Trained Neonatal nurses</td>
<td>3 paediatric ophthalmologist</td>
<td>BIO by ophthalmologist</td>
<td>Onsite</td>
<td>RETCAM-11 Clarity Medical system</td>
<td>TW-ROP†</td>
<td>Bio &amp; RetCam done simultaneously</td>
</tr>
<tr>
<td>Skakel 2008</td>
<td>Lima, Peru</td>
<td>April-May 2006</td>
<td>Prospective Feasibility study</td>
<td>28-44 weeks post menstrual age</td>
<td>Trained Neonatal nurses</td>
<td>5 different readers (ophthalmologist)</td>
<td>BIO by ophthalmologist</td>
<td>Remote</td>
<td>NIDEK NM 200-D posterior pole retinal camera</td>
<td>RW-ROP†</td>
<td>Primary outcome is RW-ROP</td>
</tr>
<tr>
<td>Weaver 2012</td>
<td>Great Falls, Montana</td>
<td>January 1 2007-June 30 2011</td>
<td>Retrospective</td>
<td>AAP criteria for screening, until discharge</td>
<td>Trained Neonatal nurses</td>
<td>2 paediatric Ophthalmologist</td>
<td>BIO for infants with RW-ROP</td>
<td>Remote</td>
<td>RETCAM-11 Clarity Medical system</td>
<td>RW-ROP†</td>
<td>Primary outcome is RW-ROP</td>
</tr>
<tr>
<td>Fijalkowski 2013</td>
<td>Stanford University Network</td>
<td>December 2004-November 2009</td>
<td>Retrospective</td>
<td>AAP criteria for screening, until discharge</td>
<td>Trained Neonatal nurses</td>
<td>Paediatric ophthalmologist</td>
<td>BIO for only those who had TW-ROP within 24 hours and rest within a week</td>
<td>Remote within 24 hours</td>
<td>RETCAM-11 Clarity Medical system</td>
<td>TW-ROP†</td>
<td>Diagnosis of TW-ROP resulted in BIO within 8-24 hours</td>
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</tbody>
</table>

TW-ROP† was defined as Early Treatment ROP (ETROP) Type 1 which includes: (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 and (5) any stage 4 or higher disease.

RW-ROP† is defined as ROP Of sufficient severity to require expert ophthalmologic opinion (1). any Zone 1 Disease (2). any stage 3 disease, (3). presence of plus disease
Table 4: Methodological quality of included studies evaluating the digital retinal photography

<table>
<thead>
<tr>
<th>Study Name</th>
<th>PATIENT SELECTION</th>
<th>INDEX TEST</th>
<th>REFERENCE STANDARD</th>
<th>FLOW AND TIMING</th>
<th>PATIENT SELECTION</th>
<th>INDEX TEST</th>
<th>REFERENCE STANDARD</th>
<th>APPLICABILITY CONCERNS</th>
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</thead>
<tbody>
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Figure Legends

Figure 1: Flow of studies in the review of RetCam screening for the diagnosis of retinopathy of Prematurity.

Figure 2: Methodological quality graph of all studies evaluating the digital retinal photography (given in %)
Figure 1. Flow of studies in the review of digital retinal photography (DRP) screening for the diagnosis of retinopathy of prematurity.

Records identified through EMBASE (n = 207)

Records identified through MEDLINE (n = 190)

Records identified through CINAHL (n = 18)

Records after duplicates removed (n = 291)

Full-text articles assessed for eligibility (n = 20)

Full-text articles excluded, with reasons (n = 11)

Studies identified for review (n = 9)

Excluded 3, because of same cohort of patients

Studies included for final review (n = 6)
Figure 2. Methodological quality graph of all studies evaluating the digital retinal photography (given in %)