Validity of a Telemedicine System for Evaluations of Acute-phase ROP (e-ROP)
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For the e-ROP Cooperative Group

Supported by Cooperative Agreements from the National Eye Institute, National Institutes of Health, DHHS
clinicaltrials.gov national registry number: NCT01264276

Case
- You are seeing a new patient, Eliza for the first time in your clinic.
- She is a former 1120 gram 29 1/7 week gestation infant who is DOL 42.
  - What is her Postmenstrual Age?
- She was discharged 3 days ago from the community hospital with a Level II NICU where you have privileges.
- Eliza was born at the community hospital and transferred to the Regional Level VI NICU after stabilization.

Case – reviewed by systems
- Neuro – no IVH on 2 HUS – 1 at Level IV and 1 the week before discharge
  - Caffeine for apnea of prematurity stopped at DOL 28.
- CV – had a PICC for access
- Resp – Surfactant for RDS and extubated on DOL 1, then HFNC and weaned to RA on DOL 19
- FEN/GI – TPN for nutrition until full feeds on DOL 14. Fed only EBM that was exclusive human milk fortified until returned to community hospital (DOL 21) where fortification was changed to bovine base. She was discharged breastfeeding with supplemental 22 kcal/oz formula.

Case
- Heme – transfused X2 from Pedi pack and then had Fe and EPO; discharged HCT – 28%, retic 6.9. Discharged with MVI with Fe.
- ID – Initial 48 hours of Amp/Gent. Had 2 sepsis evaluations for apnea and bowel distension that were negative.
  - No immunizations because mom refused
- Social – Parents very attentive and wanted baby back at community hospital and pushed for return transfer
- What is missing?

Where is the Ophthalmology Report?
- Baby returned to community hospital (PMA 32 1/7 weeks) prior to her scheduled ROP exam
- Community hospital did not have a Pediatric Ophthalmologist
- Transfer summary from Level IV stated that she needed a ROP exam in the next week (PMA 33 weeks) after she was transferred.
- Receiving Pediatric hospitalist at community hospital tried to get an Ophthalmologist to see the baby but was told that was not in his scope of practice
- What do you need to do?

Objectives
- To understand the pathogenesis of Retinopathy of prematurity and to identify those babies are at risk.
- To manage in your medical home those babies who are being evaluated and followed by Ophthalmologist for Retinopathy of prematurity.
- To understand the need telemedicine to assist with Retinopathy of prematurity screening due to lack of trained Ophthalmologists available to all babies at risk.
What is ROP?

- Leading cause of childhood blindness worldwide
- Developmental vascular proliferative disorder that occurs in preterm infants whose retina has not completely vascularized.

Normal retinal development

- Retinal vessels began forming at about 16 weeks gestation
  - 6 weeks – anterior segment of eye – hyaloid artery that originates from optic nerve, passes through vitreous and supplies vessels to lens and iris – resorbed by 34 weeks gestation
  - Retinal blood vessels extend from optic disc and grow peripherally. Nasal retina completes at 36 weeks whereas temporal retinal finishes by 40 weeks
  - Delayed in preterm infants

ROP Pathogenesis

- Premature birth interrupts normal processes of retinal vascularization
  - Postnatal developing retina exposed to less stable, relatively hyperoxic environment.
  - Process of retinal vascularization slows
- Programmed development of retinal neural cells continue – proliferation, differentiation, increase metabolic activity – leading peripheral avascular retina to become critically hypoxic.
- VEGF increases leading to abnormal angiogenesis.

Two Stages of ROP

- Preproliferative stage (hyperoxia-vasoocessation)
- Proliferative stage (hypoxia-vasoproliferative)
  - Pathological neovascularization
  - Fronds of aberrant blood vessels that tend to be leaky and friable, flourish and grow into vitreous along with myofibroblasts - hemorrhage and exudation followed by fibroplasia.
  - Contraction of vascular complexes results in traction retinal detachment and blindness.

Is Eliza at risk? Does she need a retinal exam?

- AAP, AAO, AAPOS, 2013 Policy Statement
- Infants with a birth weight of ≤1500 g or < 30 weeks gestational age and selected infants with a birth weight between 1500 and 2000 g or > 30 weeks gestational age with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk for ROP, should have retinal screening examinations.
Retinal examinations in preterm infants should be performed by an ophthalmologist who has sufficient knowledge and experience to identify accurately the location and sequential retinal changes of ROP using the ICROP.

- USA – 11% Ophthalmologist can perform ROP screening and only 6% can provide treatment.

The initiation of acute-phase ROP screening should be based on the infant’s postmenstrual age.

How does ROP “screening” happen?

- Neonatologist identifies babies at risk using birth weight, gestational age and sickness criteria and consults ophthalmology
- Ophthalmologist performs diagnostic examination using Binocular indirect ophthalmoscopy after pupillary dilatation at bedside
- Documentation
  - Presence or absence of retinopathy
  - Assess severity of ROP
  - Treatment indications
  - Follow-up schedule

### Initial Screening Examination of Premature Infants for Retinopathy of Prematurity

<table>
<thead>
<tr>
<th>GA at birth</th>
<th>Postmenstrual Age</th>
<th>Chronological Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>23</td>
<td>31</td>
<td>8</td>
</tr>
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<td>24</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>25</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>26</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>28</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>29</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>30</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>High risk factors</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
Stage 2: The Ridge

Stage 3: Extra retinal fibro-vascular proliferation

Stage 4a: extra-foveal partial retinal detachment

Stage 4b: foveal partial retinal detachment

Pre plus disease

Vascular abnormality of posterior pole insufficient to call plus but demonstrate more arterial tortuosity than venous dilation

Plus disease

Venous dilation, anterior tortuosity of posterior pole vessels; Iris vascular engorgement; vitreous haze
Limitations of current paradigm

- Liability and medico-legal risk
  - Small window of time to determine treatment
  - High risk due to blindness
  - Increase in liability insurance
- Logistics of traveling to NICU
- Reimbursement not commensurate with time, effort and expertise
- Lack of Ophthalmologists with training

What are the manpower demands for detection of serious ROP?

8200 babies ~20K exams
55 examinations were performed for every infant identified with treatable ROP.
363 infants treated

A Fielder et al; 2002
UK cohort study 1997/8

Shift from diagnostic examination to ROP screening

Referral-warranted ROP (Ells et al, 2003)
1) Any ROP in zone 1
2) Any stage 3
3) Presence of plus disease (2 or more quadrants)

Principles to consider when adopting telemedicine in ROP

- Define purpose
  - Identify serious ROP – i.e. case detection – however “case” may be defined
- Ensure performance is sufficient compared to “appropriate criterion standard”
  - diagnostic examination by ophthalmologist
- Establish technical validity

Establish technical validity: the toughest challenge

- Series of studies using evaluation of digital images
  - PHOTO-ROP
  - SUNDROP
  - Chiang et al
  - Skale, Quinn et al
  - Wu, Petersen, & VanderVeen
  - Yen et al
  - Schwartz et al
  - Wallace et al
- Limitations
  - Small samples (PHOTO-ROP n=51, SUNDROP n=97)
  - Varying criteria for case detection

Objective of e-ROP

To evaluate a telemedicine system to detect eyes of at-risk babies in need of a diagnostic examination by an ophthalmologist experienced in ROP:

- Validity
- Reliability
- Feasibility
- Safety
- Cost-effectiveness
**Clinical Centers**

- Eligible infants
  - BW <1251g with RW-ROP
  - Eligible for ROP exams
- Exclusion criteria
  - ROP treatment
  - PMA 40 weeks or greater unless transferred for treatment
  - Regressing or regressed ROP

Clinical Centers
12 centers in US
1 center in Canada

**e-ROP Study Organization**

**Outcome Measure**

- Comparison of results of diagnostic examination by Study certified ophthalmologist with grading of retinal image by Trained non-physician Readers
- Primary outcome measure – detection of RW-ROP on digital retinal images
  - Validity (sensitivity, specificity, NPV, PPV)
- Sufficiently large sample to address:
  - Reliability
  - Feasibility
  - Safety
  - Cost-effectiveness

**Referral warranted ROP**

- Concept developed for identifying on digital retinal images those eyes with ROP that needs to be evaluated by an ophthalmologist experienced in ROP
- Features of RW-ROP
  - Zone I ROP
  - Stage 3 ROP
  - Plus disease

**Flow of Study Procedures**

- Baby with BW <1251g
- ROP consent
- Diagnostic exam
- Imaging by CRI
- NICU review form
- Study Center Coordinator
- Images graded by trained and expert readers

**Sessions at Clinical Centers**

- Ophthalmologist
  - Diagnostic eye examination
- Non-physician Retinal Imager
  - Digital retinal imaging – wide field, using RetCam Shuttle
- Study Center Coordinator
  - Consents, scheduling procedures
  - Completion of data forms and uploading data

All using standard protocols
Characteristics of Infants
- 1284 premature infants with BW <1251g among 2147 eligible (60%) were enrolled from May 2011 to October 2013
- 1257 infants had ROP examinations
  - Mean birth weight (BW) - 864g (± 212)
  - Mean gestational age (GA) – 27 weeks (± 2.2)
  - 49% female
  - Race:
    - White - 56.1%,
    - Black – 29.3%
    - Unable to answer – 9.8%
    - Mixed/other – 1.8%
    - American Indian – 1.7%
    - Asian – 1.4%
  - Ethnicity:
    - Hispanic/Latino – 9.7%
    - Non Hispanic/Latino – 86.3%
    - Unable to answer – 4.0%

Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Infants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>429</td>
<td>34.2%</td>
</tr>
<tr>
<td>751-1500</td>
<td>455</td>
<td>36.2%</td>
</tr>
<tr>
<td>1001-1250</td>
<td>373</td>
<td>29.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥24</td>
<td>242</td>
<td>19.3%</td>
</tr>
<tr>
<td>&gt;24-27</td>
<td>614</td>
<td>48.9%</td>
</tr>
<tr>
<td>&gt;27-30</td>
<td>328</td>
<td>26.1%</td>
</tr>
<tr>
<td>≥30</td>
<td>74</td>
<td>5.9%</td>
</tr>
<tr>
<td>Multiple births</td>
<td>375</td>
<td>29.9%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>638</td>
<td>50.8%</td>
</tr>
<tr>
<td>Female</td>
<td>619</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Flow Chart for e-ROP Data Collection

Study Completion
1117 (87%) study babies met the study endpoint
- Mature retinal vessels (30%)
- Immature Zone III on two exams ≥7 days apart (15%)
- ROP regressing on two exams ≥7 days apart (11%)
- ROP regressed (4%) - Treated for severe ROP (14%)
- Reached 40 weeks PMA with no ROP or only stage 1 or 2 (33%)

Major reasons for not meeting endpoint in 167 babies were:
- Consent withdrawn (27%)
- Lost to follow-up (23%)
- Transferred/discharged/other (46%)
- Death (5%)

Sessions per Infant

<table>
<thead>
<tr>
<th>Number of Babies</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic exams</td>
<td>1257*</td>
<td>3.4 (2.1)</td>
</tr>
<tr>
<td>Imaging sessions</td>
<td>1241*</td>
<td>3.2 (2.0)</td>
</tr>
</tbody>
</table>

Diagnostic Examinations
- Among 1257 who had at least one diagnostic examination:
  - 19% had single exam
  - 40% had 4 or more exams
  - Overall mean 3.4 exams with range of 2.3 to 3.8 per infant across centers
- Interval day between two examinations
  - 51% within 10 days, 12% >2 weeks
  - Median 9 days (range 1-37)
ROP Status from Diagnostic Examination

<table>
<thead>
<tr>
<th></th>
<th>Number of infants</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>801</td>
<td>63.7%</td>
</tr>
<tr>
<td>No</td>
<td>456</td>
<td>36.3%</td>
</tr>
<tr>
<td>RW-ROP characteristics on eye examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>244</td>
<td>19.4%</td>
</tr>
<tr>
<td>No</td>
<td>983</td>
<td>78.2%</td>
</tr>
<tr>
<td>Unknown</td>
<td>30</td>
<td>2.4%</td>
</tr>
<tr>
<td>RW-ROP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>214</td>
<td>87.8%</td>
</tr>
<tr>
<td>Unilateral</td>
<td>30</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

RW-ROP Findings Based on Diagnostic Examination

- RW-ROP was observed in 244 infants (19.4%) and 174 required treatment (13.8%)
- RW-ROP rate varied across centers from 8.8% to 29.7%

RW-ROP Rate by Birth Weight (BW)

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>RW-ROP Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=500 (n=42)</td>
<td>56.8</td>
</tr>
<tr>
<td>501-750 (n=387)</td>
<td>37.7</td>
</tr>
<tr>
<td>751-900 (n=271)</td>
<td>15.9</td>
</tr>
<tr>
<td>901-1000 (n=194)</td>
<td>9.8</td>
</tr>
<tr>
<td>1001-1100 (n=164)</td>
<td>4.9</td>
</tr>
<tr>
<td>1101-1250 (n=209)</td>
<td>2.9</td>
</tr>
</tbody>
</table>

RW-ROP Rate by GA

<table>
<thead>
<tr>
<th>GA (Weeks)</th>
<th>RW-ROP Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=23 (n=83)</td>
<td>63.5</td>
</tr>
<tr>
<td>24 (n=129)</td>
<td>44.0</td>
</tr>
<tr>
<td>25 (n=194)</td>
<td>26.3</td>
</tr>
<tr>
<td>26 (n=216)</td>
<td>19.9</td>
</tr>
<tr>
<td>27 (n=204)</td>
<td>7.8</td>
</tr>
<tr>
<td>28 (n=173)</td>
<td>6.4</td>
</tr>
<tr>
<td>29 (n=228)</td>
<td>6.4</td>
</tr>
</tbody>
</table>

PMA at First and Last Imaging Session

- 986 babies completed at least 2 image sessions
- PMA at the first image session:
  - Median: 33 wks (range: 32 – 42 wks)
  - 25% at 32 wks
- PMA at the last image session:
  - Median: 38 wks (range: 32 to 47 wks)
  - 29% at 40 wks or later

Retinal Imaging

- In 202 (4.8%) image sessions, babies were not approached for imaging, due to:
  - Infant too unstable (41%)
  - Parent/guardian refusal (27%)
  - Other contraindications (47%)
Completeness of Image Sets

When babies approached for imaging
• 87% sessions had complete image sets in both eyes
• 9% had complete image sets in one eye only
• 4% sessions had incomplete image set in both eyes

Reasons for incomplete image set
• Poor access to eye (44%)
• Poor dilation (21%)
• Baby became unstable (13%)
• Technical problem (6%)
• Other reasons (36%)

Number of Retinal Images in a Submitted Image Set
(N=7905)

% of Image Taken by Image Type (N=7905)

Image Grading in Reading Center

• Images selected for grading by Reading Center
• All images from babies with RW-ROP (n=244)
• All images from random sample of babies without RW-ROP (n=613)
• Total of 5520 image sets
• Independently graded by two Trained Readers
• Adjudicated by Reading Supervisor if discrepancy met the adjudication criteria

Retinal Image Quality by Type
(N=5520 Image Sets)
The cross-tabulation of RW-ROP* from diagnostic examination vs. image grading of all sessions per eye

<table>
<thead>
<tr>
<th>RW-ROP from image grading</th>
<th>No</th>
<th>Yes</th>
<th>Indeterminate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3703 (67.1%)</td>
<td>854 (15.5%)</td>
<td>91 (1.7%)</td>
<td>4648 (84.2%)</td>
</tr>
<tr>
<td>Yes</td>
<td>161 (2.9%)</td>
<td>632 (11.5%)</td>
<td>20 (0.4%)</td>
<td>813 (14.7%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>47 (0.9%)</td>
<td>9 (0.2%)</td>
<td>3 (0.1%)</td>
<td>59 (1.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>3911 (70.9%)</td>
<td>1495 (27.1%)</td>
<td>114 (2.1%)</td>
<td>5520 (100.0%)</td>
</tr>
</tbody>
</table>

*RW-ROP = referral warranted retinopathy of prematurity.

Primary Analysis of Outcomes

- **Validity:** Sensitivity/specificity
  - Sensitivity = $a / (a+c)$ or TP/(TP+FN)
  - Specificity = $d / (b+d)$ of TN/(TN+FN)

<table>
<thead>
<tr>
<th>Diagnostic examination of RW-ROP</th>
<th>Present</th>
<th>Absent</th>
</tr>
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<tbody>
<tr>
<td>Image Evaluation of RW-ROP</td>
<td>+</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>c</td>
</tr>
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</table>

Single Session per Infant (N=855)

<table>
<thead>
<tr>
<th>Diagnostic examination findings of RW-ROP</th>
<th>Present</th>
<th>Absent</th>
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</thead>
<tbody>
<tr>
<td>Image Evaluation of RW-ROP</td>
<td>+</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>24</td>
</tr>
</tbody>
</table>

- Sensitivity = 90.0% (85.4-93.5%)
- Specificity = 87.0% (84.0-89.5%)
- PPV* = 62.5%
- NPV* = 97.3%

* Assumed RW-ROP rate of 19%

Any Session per Infant (N=855)

<table>
<thead>
<tr>
<th>Diagnostic examination findings of RW-ROP</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image Evaluation of RW-ROP</td>
<td>+</td>
<td>232</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

- Sensitivity = 97.1% (94.0-98.6%)
- Specificity = 75.9% (72.2-79.1%)
- PPV = 44.2%
- NPV = 99.1%

* Assumed RW-ROP rate of 19%

ROP Treatment per Infant (N=855)

<table>
<thead>
<tr>
<th>ROP treated by Clinician</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image Evaluation of RW-ROP</td>
<td>+</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

- Sensitivity = 98.2% (94.4-99.4%)
- Specificity = 80.2% (77.0-79.1%)
- PPV = 44.3%
- NPV = 99.6%

* Rate of ROP treatment is 14%
Comparison of Time of Detection of RW-ROP from Image vs. Diagnostic Examination among the 447 Eyes with RW-ROP

<table>
<thead>
<tr>
<th># of eyes</th>
<th>%</th>
<th>Time difference in Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Image earlier than diagnostic examination</td>
<td>191</td>
<td>42.7%</td>
</tr>
<tr>
<td>Same</td>
<td>200</td>
<td>44.7%</td>
</tr>
<tr>
<td>Image later than diagnostic examination</td>
<td>24</td>
<td>5.37%</td>
</tr>
<tr>
<td>Missed detection by image</td>
<td>32</td>
<td>7.16%</td>
</tr>
</tbody>
</table>

Subgroup Analyses of Sensitivity and Specificity of RW-ROP from Trained Readers Grading

Birth Weight Groups

<table>
<thead>
<tr>
<th>Single Session Per Eye Analysis**</th>
<th># of eyes RW-ROP present from exam</th>
<th># of eyes RW-ROP image grading</th>
<th>Sensitivity (95% CI)</th>
<th># of eyes RW-ROP image grading</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤750 g (n=455)</td>
<td>117</td>
<td>264</td>
<td>83.3% (77.9-87.6%)</td>
<td>338</td>
<td>81.1% (75.7-86.5%)</td>
</tr>
<tr>
<td>&gt;750, ≤1000 g (n=655)</td>
<td>74</td>
<td>62</td>
<td>83.8% (73.3-90.7%)</td>
<td>270</td>
<td>87.2% (81.7-91.1%)</td>
</tr>
<tr>
<td>&gt;1000 g (n=697)</td>
<td>56</td>
<td>40</td>
<td>71.4% (55.5-83.4%)</td>
<td>641</td>
<td>96.1% (94.0-97.3%)</td>
</tr>
</tbody>
</table>

Gestational Age Groups

<table>
<thead>
<tr>
<th>Single Session Per Eye Analysis**</th>
<th># of eyes RW-ROP present from exam</th>
<th># of eyes RW-ROP image grading</th>
<th>Sensitivity (95% CI)</th>
<th># of eyes RW-ROP image grading</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24 weeks</td>
<td>128</td>
<td>106</td>
<td>82.8% (73.0-89.6%)</td>
<td>58</td>
<td>83.0% (87.0-89.6%)</td>
</tr>
<tr>
<td>&gt;24, ≤26 weeks (n=538)</td>
<td>214</td>
<td>183</td>
<td>85.3% (79.9-89.8%)</td>
<td>314</td>
<td>80.6% (74.9-85.2%)</td>
</tr>
<tr>
<td>&gt;26 weeks (n=992)</td>
<td>105</td>
<td>77</td>
<td>73.3% (62.3, 82.2%)</td>
<td>886</td>
<td>94.0% (91.9-95.6%)</td>
</tr>
</tbody>
</table>

Subgroup Analyses of Sensitivity and Specificity of RW-ROP from Trained Readers Grading

Based on Image Quality

<table>
<thead>
<tr>
<th>Good/adequate quality in all retinal images</th>
<th>Single Session Per Eye Analysis*</th>
<th># of eyes RW-ROP present from exam</th>
<th># of eyes RW-ROP + image grading</th>
<th>Sensitivity (95% CI)</th>
<th># of eyes RW-ROP + image grading</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>(n=400)</td>
<td>372</td>
<td>315</td>
<td>84.7% (80.0-88.4%)</td>
<td>933</td>
<td>90.6% (84.2-91.9%)</td>
</tr>
<tr>
<td>Yes</td>
<td>(n=1305)</td>
<td>315</td>
<td>933</td>
<td>90.6% (84.2-91.9%)</td>
<td>886</td>
<td>94.0% (88.2-92.5%)</td>
</tr>
</tbody>
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e-ROP Study Primary Outcomes

- Strong support for validity of telemedicine system comprised of:
  - Trained non-physician imagers in the NICU
  - Non-physician readers of digital images
  - Sensitivity for detecting RW-ROP in an infant 90.0% with a specificity of 87.0% and negative predictive value of 97.3%
  - Among infants treated by the ophthalmologists, sensitivity increased to 98.2%

Strengths of e-ROP Study

- Successful use of non-physician imagers to obtain standard image sets for grading by non-physician trained readers using a standard grading protocol
- Standardized eye exams by ophthalmologists with experience in ROP studies
- Subset of image sets were also graded by ophthalmologists expert in ROP
  - Results of Expert and Trained Readers were very similar
### Limitations of e-ROP Study

- Comparing image grading to results of diagnostic examination
  - A criterion standard with known variability in diagnosis of:
    - “threshold ROP” in CRYO-ROP study
    - Plus disease
    - Zone of disease
- Enrolled only infants with birth weights of <1250g and not all infants who need ROP examinations in the NICU

### False Negatives

- e-ROP outcomes, RW-ROP rate of 19.4% and NPV of 97.3% still means that this system might miss some infants with serious disease
- Steps to improve the odds:
  - More frequent and targeted imaging schedule
  - Incorporate other methods such as early weight gain to predict high risk and lower risk infants even before ROP examinations would start

### Other Issues in Telemedicine in ROP

- Availability of ophthalmologists to examine infants if needed
- Licensing and liability issues, in particular the inter-state licensing issues
- Establishing and maintaining consistent and reliable imagers and a reading center
- Ensuring timely feedback to the infant’s NICU
- Dealing with poor quality images

### Background – The Need

Premature infants are at risk of ROP but access to necessary ophthalmologist screening in the NICU might be limited in some regions of the US and many other countries.

- Approximately 50-60K premature babies are born at <31 weeks pregnancy or <3.3 pounds in the US each year.
- ROP is a major cause (13% prevalence) of childhood blindness in the US.
- Early detection is essential to helping reduce vision loss; ROP can develop and advance quickly.
- The NEI has invested in research to address ROP for over 30 yrs.

### Why it Matters

- Use of Telemedicine for ROP potentially gives every hospital access to excellent ROP screening
  - Telemedicine could help identify premature babies who may need to be evaluated for ROP, even in remote or underserved areas
  - Allows for more frequent screening, not dependent upon physicians’ availability and schedule
  - Can be more baby-centered, avoid unnecessary transfers
  - Could reduce screening costs by shifting the demand from physicians to other specially trained staff
  - Can increase awareness of ROP among NICU staff and families
  - Findings are generalizable to other parts of the world with high ROP rates

### Take home message

- This NIH/NEI-funded Study shows that telemedicine can reliably detect blinding disease in premature babies
- Compared to exams in the NICU, remote evaluation of retinal images by non-physicians is as reliable as, and potentially earlier at, identifying babies who need referral for ROP
Finally, Eliza

- She needs to get her eyes examined and it is worth it to refer her back to the Regional Level IV hospital to get her into an Ophthalmologist that can examine her.
- Telemedicine may be helpful to the community hospital but the cost of the wide-field digital cameras are high (up to $100,000) and they would need to train personal to do the imaging.

For them, so they can see their world!