Telemmedicine in Retinopathy of Prematurity

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Background

- ROP is a major cause (13% prevalence) of childhood blindness in the US.
- Early detection and access to treatment is essential to helping reduce vision loss; ROP can develop and advance quickly.
- Approximately 50-60K premature babies are born at <31 weeks pregnancy or <3.3 pounds in the US each year.
- Current US guidelines for identifying infants for exams are based on birth weight and gestational age.

15 million premature babies per year

Visual impairment due to ROP in premature babies (2010 data)

What are the manpower demands for detection of serious ROP?

8200 babies ~20K exams
363 infants treated

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)

RW-ROP indicates need for a diagnostic examination to determine whether treatment is indicated
Telemedicine and ROP

Using a telemedicine system may maximize the opportunity to detect serious ROP in at-risk premature babies?

Principles to consider when adopting telemedicine in ROP

- Define purpose
  - Case detection of serious ROP
- Ensure performance is sufficient compared to “appropriate criterion standard”
  - Diagnostic exam by ophthalmologist

Adapted from P Lee on diabetic retinopathy in Arch Ophthal 1999;117:1639-40

Previous studies for ROP using retinal imaging

<table>
<thead>
<tr>
<th>Reference</th>
<th># Eyes</th>
<th>Disease</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>% NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2000</td>
<td>10</td>
<td>Plus</td>
<td>100 (85-100)</td>
<td>0 (0-88)</td>
<td>-</td>
</tr>
<tr>
<td>Yen et al, 2001</td>
<td>63</td>
<td>Plus pred at 30-34 wks</td>
<td>90</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Ells et al, 2003</td>
<td>44</td>
<td>RW-ROP</td>
<td>90 (55-100)</td>
<td>66 (48-84)</td>
<td>94 (90-99)</td>
</tr>
<tr>
<td>Chang et al, 2006</td>
<td>64</td>
<td>Type 2 or worse</td>
<td>77 (70-84)</td>
<td>91 (86-96)</td>
<td>94 (90-99)</td>
</tr>
<tr>
<td>Wu et al, 2006</td>
<td>64</td>
<td>Type 2 or worse</td>
<td>90 (65-100)</td>
<td>97 (92-100)</td>
<td>100 (92-100)</td>
</tr>
<tr>
<td>Yen et al, 2003</td>
<td>67</td>
<td>Type 2 at 31-33 wks</td>
<td>78</td>
<td>66 (40-84)</td>
<td>94 (90-99)</td>
</tr>
<tr>
<td>PHOTO-ROP</td>
<td>51</td>
<td>Clinically significant ROP</td>
<td>92 (83-99)</td>
<td>33 (23-42)</td>
<td>78 (66-90)</td>
</tr>
<tr>
<td>Ells et al, 2000</td>
<td>61</td>
<td>Stage 3</td>
<td>92 (83-99)</td>
<td>68 (63-73)</td>
<td>68 (63-73)</td>
</tr>
<tr>
<td>Luan et al, 2000</td>
<td>1322</td>
<td>Suspect treatment requiring</td>
<td>98 (95-100)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Silva et al, 2011</td>
<td>530</td>
<td>Type 2 or worse</td>
<td>98 (95-100)</td>
<td>97 (94-100)</td>
<td>98 (95-100)</td>
</tr>
<tr>
<td>Ells et al, 2009</td>
<td>100</td>
<td>Treatment requiring</td>
<td>98 (73-100)</td>
<td>93 (83-100)</td>
<td>100 (94-100)</td>
</tr>
</tbody>
</table>

Table concept adapted from Chiang et al, 2012

Digital imaging and ROP detection

- Sensitivity:
  - ≥ Type-2 ROP: 76-100%
  - ≥ Type-1 ROP: 87-100%
  - (one 57% for stage 3)
- Specificity: 80-100%

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

Funded by NEI/NIH July 2010

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 1 ROP
  - Stage 3 ROP
  - Plus disease
- Consistent with Type 1 ROP (treatment indicated) and Type 2 ROP (increased observation)
Clinical Centers

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

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

Flow of Study Procedures

- e-ROP Image Reading Center
  - Images graded by masked non-physician trained readers to determine presence of:
    - Zone I ROP
    - Stage 3 ROP or worse
    - Plus disease
  - Sample also graded by masked ROP experts

Outcome Measure

- Primary outcome measure – detection of RW-ROP on digital retinal images
  - Comparison of results of diagnostic examination by Study certified ophthalmologist with grading of retinal image by Trained non-physician Readers

Characteristics of e-ROP 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 (sd 212)
- Mean gestational age (GA) – 27 weeks (sd 2.2)
- 49% female, 56.1% white, 29.3% black

<table>
<thead>
<tr>
<th>Number of infants</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
<th>1</th>
<th>2-3</th>
<th>4-5</th>
<th>&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td># diagnostic exams</td>
<td>1257*</td>
<td>3.4 (2-1)</td>
<td>3 (1, 12)</td>
<td>240 (19%)</td>
<td>811 (41%)</td>
<td>316 (25%)</td>
</tr>
<tr>
<td># imaging sessions</td>
<td>1241*</td>
<td>3.2 (2.0)</td>
<td>3 (1, 12)</td>
<td>255 (21%)</td>
<td>529 (43%)</td>
<td>290 (23%)</td>
</tr>
</tbody>
</table>

*Among those who completed the study and had at least one diagnostic examination or imaging session after enrollment.
ROP Status from Diagnostic Examination

<table>
<thead>
<tr>
<th>ROP Status</th>
<th>Number of Infants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP Yes</td>
<td>801</td>
<td>63.7%</td>
</tr>
<tr>
<td>ROP No</td>
<td>456</td>
<td>36.3%</td>
</tr>
<tr>
<td>RW-ROP Bilateral</td>
<td>214</td>
<td>87.8%</td>
</tr>
<tr>
<td>RW-ROP Unilateral</td>
<td>30</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

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

The cross-tabulation of RW-ROP* from diagnostic examination vs. image grading of all sessions per eye

<table>
<thead>
<tr>
<th>Diagnostic examination findings of RW-ROP</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3703 (67.1%)</td>
<td>854 (15.5%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>47 (0.9%)</td>
<td>9 (0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>3911 (70.9%)</td>
<td>1495 (27.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Image Evaluation of RW-ROP</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>215</td>
<td>24</td>
</tr>
<tr>
<td>Absent</td>
<td>137</td>
<td>554</td>
</tr>
</tbody>
</table>

*RW-ROP = referral warranted retinopathy of prematurity.

Single Session per Infant (N=855)

<table>
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<th>Diagnostic examination findings of RW-ROP</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>215</td>
<td>24</td>
</tr>
<tr>
<td>-</td>
<td>137</td>
<td>554</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>+</td>
<td>215</td>
<td>144</td>
</tr>
<tr>
<td>-</td>
<td>24</td>
<td>453</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 treatment by clinician</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>159</td>
<td>137</td>
</tr>
<tr>
<td>-</td>
<td>3</td>
<td>554</td>
</tr>
</tbody>
</table>

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

* ROP treatment rate of 14%
RW-ROP Rate by GA

- RW-ROP Rate (%)
- GA (Weeks)
- RW-ROP decreased with increasing GA
- Only one infant with GA >29 weeks had RW-ROP among the 228 infants with RW-ROP in one or both eyes

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

- Imaging done on same schedule as clinical examinations for ROP
- Enrolled only infants with BW <1251g rather than all eligible for ROP examinations

Where do these efforts lead?

- Use of Telemedicine for ROP potentially gives every hospital access to excellent ROP screening
- In US and countries with well developed NICU systems
  - May allow physicians to examine only the most at-risk babies
  - Will likely decrease early transfers for treatment
  - Allow ROP screening in underserved areas
  - May be most useful in level II nurseries
- Other regions of the world
  - Very useful in NICUs with no current coverage or limited ROP expertise
  - Countries with widely dispersed population (Canada, Russia)

Unresolved issues in ROP telemedicine

- How to minimize missed cases
  - Alter schedule for high risk infants?
  - Use other parameters for identifying high risk such as early weight gain, risk factors
- When to discharge infant from acute ROP detection program
- Extending service to underserved regions of the world
- Liability and licensing issues