Telemedicine Diagnostic Challenges for Retinopathy of Prematurity (ROP)

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Image based diagnosis and telemedicine for ROP has been shown to be reliable, accurate, and cost-effective:

- Prospective and retrospective studies investigating the use of telemedicine and image-based diagnosis for detection of ROP
- Telemedicine screening can be more time efficient for the examiner
- Telemedicine for ROP is cost effective

Active Clinical ROP Telemedicine Programs:

- SUNDROP (USA)
- FOCUS ROP (USA)
- ROPE-SOS (India)
- KIDROP (India)
- ARTROP (New Zealand)
Who is qualified to perform ROP telemedicine diagnosis?

• “Referral Warranted ROP”
  – ROP telemedicine programs have focused on prevention of retinal detachment by identifying disease that may soon progress to treatment-requiring ROP

• Potential diagnostic challenges
  – Inter-expert variability in Plus disease diagnosis
  – Studies have shown that experience matters
  – Stage 4, Stage 5, and AP-ROP

• Variability in Training for Image Grading in ROP Telemedicine Programs

Telemedicine Diagnostic Challenges for ROP
Diagnostic Accuracy – Board Eligible Ophthalmologists

• Board Eligible Ophthalmologists
  - Retina fellows
  - Variability in diagnostic accuracy

• Poor diagnostic accuracy for clinically significant ROP
  - Type 2-Prethreshold


Telemedicine Diagnostic Challenges for ROP
Diagnostic Accuracy – Board Eligible Ophthalmologists

- Board Eligible Ophthalmologists
  - Pediatric ophthalmology fellowship
  - Variability in diagnostic accuracy

- Variability in diagnostic accuracy for both type 2 and treatment-requiring ROP
  - Higher accuracy for mild ROP

Mean Sensitivity/Specificity

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild ROP</td>
<td>0.85</td>
<td>0.919</td>
</tr>
<tr>
<td>Type-2 ROP</td>
<td>0.527</td>
<td>0.938</td>
</tr>
<tr>
<td>Treatment-Requiring ROP</td>
<td>0.515</td>
<td>0.949</td>
</tr>
</tbody>
</table>

Table 3. Reasons for discrepancy by ROP diagnoses provided by five pediatric ophthalmology fellows, compared to diagnosis provided by expert reference standard

<table>
<thead>
<tr>
<th>Reasons for discrepancy</th>
<th>Number of images</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of stage</td>
<td>43</td>
<td>91.5%</td>
</tr>
<tr>
<td>Identification of plus disease</td>
<td>19</td>
<td>40.4%</td>
</tr>
<tr>
<td>Identification of zone</td>
<td>16</td>
<td>34.0%</td>
</tr>
<tr>
<td>Identification of type-2 ROP</td>
<td>2</td>
<td>4.3%</td>
</tr>
<tr>
<td>Poor image quality</td>
<td>2</td>
<td>4.3%</td>
</tr>
<tr>
<td>Total number of images</td>
<td>47</td>
<td>—</td>
</tr>
</tbody>
</table>


Telemedicine Diagnostic Challenges for ROP
Diagnostic Accuracy – Ophthalmology Trainees (US and International)

~ 250 Ophthalmology Trainees

ROP Case Presentations

Trainees were asked to diagnose plus disease, zone, stage, and category (none, mild, type-2 ROP or pre-plus, treatment-requiring ROP) for each eye.

Swamy L, Patel S, Jonas KE, Ostmo S, Chiang MF, Chan RVP, Characterization of errors in retinopathy of prematurity (ROP) diagnosis by ophthalmology residents, JAAPOS, August 2016, Volume 20, Issue 4, Page e44
What factors lead to an incorrect diagnosis of ROP?

Failure to diagnose treatment-requiring ROP was most commonly associated with **error in recognizing plus disease**.

Over-diagnosis of Type 2 as treatment-requiring was most commonly due to **error in recognizing plus disease and zone**.

Telemedicine Diagnostic Challenges for ROP
Diagnostic Accuracy – Ophthalmology Trainees (US and Canada)

Diagnostic Error Rate (Percent of Incorrect Diagnosis)

<table>
<thead>
<tr>
<th></th>
<th>Country A</th>
<th>Country B</th>
<th>Country C</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error Rate (% incorrect) All categories of ROP</td>
<td>48%</td>
<td>58.9%</td>
<td>48.1%</td>
<td>50.5%</td>
</tr>
<tr>
<td>Error Rate Treatment-requiring ROP</td>
<td>45.2%</td>
<td>42.9%</td>
<td>31.6%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Error Rate Type 2 ROP</td>
<td>73.6%</td>
<td>77.3%</td>
<td>78.9%</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

Telemedicine Diagnostic Challenges for ROP
Diagnostic Accuracy – Ophthalmology Trainees (US and International)

- **Inadequacies in Diagnostic Accuracy for ROP**
  - US and International trainees misdiagnosed ROP more than 50% of the time
  - Rates and reasons for misdiagnoses for each country were similar
  - Raises concerns for mismanagement by inexperienced examiners according to established guidelines

- **Implications for ROP telemedicine and image based diagnosis**
  - Wrong diagnosis of plus disease and zone are major factors leading to incorrect diagnoses
  - **Need to improve diagnostic accuracy of type 2 ROP**
  - Need for targeted education for ROP diagnosis


- **Ophthalmology trainees misdiagnosed ROP more than half of the time**

- Identification of **plus disease** and **zone** being the salient factors leading to incorrect diagnosis.

General ophthalmologists may provide ROP care. Therefore, it is important to improve competency in ROP diagnosis.
Telemedicine Diagnostic Challenges for ROP
Diagnosis of Stage 4 and Stage 5

Telemedical Diagnosis of Stage 4 and Stage 5 Retinopathy of Prematurity

Purpose: To determine the accuracy of image-based diagnosis for stage 4 or worse retinopathy of prematurity (ROP) disease.

Participants: We prospectively obtained data, from 8 major ROP centers, for 1220 eye examinations from 230 infants.

Methods: An ophthalmologist at each center provided a clinical diagnosis using indirect ophthalmoscopy. Wide-angle retinal images (RetCam; Clarify Medical Systems, Pleasanton, CA) were then obtained, and these were independently read by 2 ROP experts using a web-based system for an image-based diagnosis.

Main Outcome Measures: Sensitivity and specificity of image-based diagnosis from the ROP experts were calculated using the clinical diagnosis as the reference standard.

Results: Of 1220 examinations, 28 (2%) had a clinical diagnosis of stage 4 or worse. Sensitivity and specificity for stage 4 or worse disease were 75% and 99% for expert 1, and 86% and 99% for expert 2.

Conclusions: There were inconsistencies in the accuracy of image-based diagnosis of stage 4 and stage 5 ROP when compared with the clinical diagnosis. Ophthalmology Retina 2017;1–6 © 2017 by the American Academy of Ophthalmology

Table 2. Sensitivity and Specificity of Image-based Retinopathy of Prematurity Diagnosis by Retinopathy of Prematurity Experts

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Expert 1*</th>
<th>Expert 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>Stage 4 or worse (N = 28)</td>
<td>75 (55–89)</td>
<td>99 (99–100)</td>
</tr>
<tr>
<td>Stage 5 (N = 13)</td>
<td>69 (39–91)</td>
<td>99 (99–100)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Sensitivity and specificity for the image-based diagnosis of both experts were computed using the clinical diagnosis by indirect ophthalmoscopy as the reference standard.
Clinical Diagnosis: Stage 4a
Examiner 1: Stage 4a
Examiner 2: Stage 3 (no treatment)
Outcome: Vitrectomy

Telemedicine Diagnostic Challenges for ROP
Clinical Diagnosis of ≥Stage 4 and an Image-based Diagnosis of <Stage 4

Telemedicine Diagnostic Challenges for ROP
Diagnosis of Aggressive Posterior-ROP (AP-ROP)

Abstract
Purpose: To determine the accuracy and reliability of diagnosing aggressive posterior retinopathy of prematurity (AP-ROP) using two imaging-based systems for ROP.

Methods: A total of 1280 eye examinations from 136 infants were prospectively obtained at 8 major ROP centers. All infants were medical and clinical data were independently read by 2 ROP experts using a computer-based system for an image-based diagnosis. Sensitivity and specificity of this diagnostic model using two separate systems were calculated using the reference standard of clinical diagnosis. Results: The intra-rater agreement of the 1280 examinations had a clinical diagnosis of AP-ROP sensitivity and specificity for the presence of AP-ROP were 35% and 96% for expert 1 and 17% and 99% for expert 2. Using the clinical diagnosis, an image-based versus clinical diagnosis agreement for the diagnosis of AP-ROP was 5/164 (2%) for expert 1 and 11/164 (6%) for expert 2. Agreement for the diagnosis of AP-ROP between the two systems for expert 1 was 5/164 (2%) and for expert 2 was 11/164 (6%). Conclusion: There are inconsistencies between the clinical diagnosis of AP-ROP (as determined by indirect ophthalmoscopy) and the image-based diagnosis of AP-ROP. This may have important implications for ROP management and the current international ROP classification system.

Keywords: aggressive posterior retinopathy of prematurity, retinopathy of prematurity, telemedicine
Telediagnosis of Aggressive Posterior-ROP (AP-ROP)

A: Clinical diagnosis of no AP-ROP. Both experts provided an image-based diagnosis of AP-ROP.

B: Clinical diagnosis of AP-ROP. Both experts provided an image-based diagnosis of no AP-ROP.

C: Clinical diagnosis of AP-ROP. Expert 1 provided an image-based diagnosis of AP-ROP. Expert 2 provided an image-based diagnosis of no AP-ROP.


Telediagnosis of Aggressive Posterior-ROP (AP-ROP)

Tele-Education

• GEN-ROP
  • Improved diagnostic accuracy through a web-based learning platform.
  • Implications for ROP training and telemedicine.

Imaging

• Fluorescein Angiography for ROP
  • May improve diagnostic accuracy for certain categories of ROP (e.g. stage 2 or worse, stage 3 or worse, pre-plus or worse, and type-2 ROP or worse)

• Digital Mosaic Images for ROP
  • May improve diagnostic accuracy and intergrader agreement of clinically-significant ROP (e.g. Plus disease)


Telemedicine Diagnostic Challenges for ROP
Improvement in Diagnostic Accuracy with Tele-Education

United States and Canada Trainees

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity, % (SE)</th>
<th>Specificity, % (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 or worse</td>
<td>81 (2)</td>
<td>82 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 2 or worse</td>
<td>79 (5)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 3 or worse</td>
<td>79 (2)</td>
<td>90 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zone 1</td>
<td>81 (5)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zone 2</td>
<td>80 (5)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plus</td>
<td>78 (2)</td>
<td>90 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Category</td>
<td>79 (2)</td>
<td>90 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild or worse</td>
<td>80 (3)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 or worse</td>
<td>78 (2)</td>
<td>90 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment requiring</td>
<td>80 (3)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence APROP</td>
<td>81 (4)</td>
<td>90 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence ROP</td>
<td>81 (3)</td>
<td>90 (3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APROP, aggressive posterior retinopathy of prematurity; ROP, retinopathy of prematurity.

International Trainees

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity, % (SE)</th>
<th>Specificity, % (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All programs (N=81)</td>
<td>81 (2)</td>
<td>82 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild or worse</td>
<td>81 (5)</td>
<td>90 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate or worse</td>
<td>79 (2)</td>
<td>90 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe (treatment requiring)</td>
<td>79 (2)</td>
<td>90 (1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Program 1 (N=27) | 83 (3) | 90 (2) | <0.001 |
Program 2 (N=43) | 80 (3) | 90 (2) | <0.001 |
Program 3 (N=11) | 78 (2) | 90 (1) | <0.001 |

Telemedicine Diagnostic Challenges for ROP
Summary

“There is more to ROP Telemedicine than just reading an image”

• Challenges in image based diagnosis of ROP
  – Variability in diagnostic accuracy for type 2 ROP and Plus disease
  – Discrepancies between image based diagnosis and clinical diagnosis for Stage 4, Stage 5, AP-ROP

• Potential strategies to improve ROP telemedicine
  – Tele-Education and a standardized certification process
  – Improved imaging and multimodal imaging with FA, OCT, OCTA
  – Computer-based image analysis and Deep learning

• Who should be responsible for ROP telemedicine programs?
  – The nature of ROP care is time sensitive
  – Skilled Ophthalmologists should be responsible for determining diagnostic and management decisions for ROP