

# The “Eyes Have It” What’s New in Pediatric Ophthalmology?



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WREIC 2019***



***Low vision center with early intervention services in India, Aravind Eye Hospital, Madurai***

# What you need to know:

## 1. ***Back of the EYE***

OCT: Optical Coherent tomography

Lebers congenital amaurosis

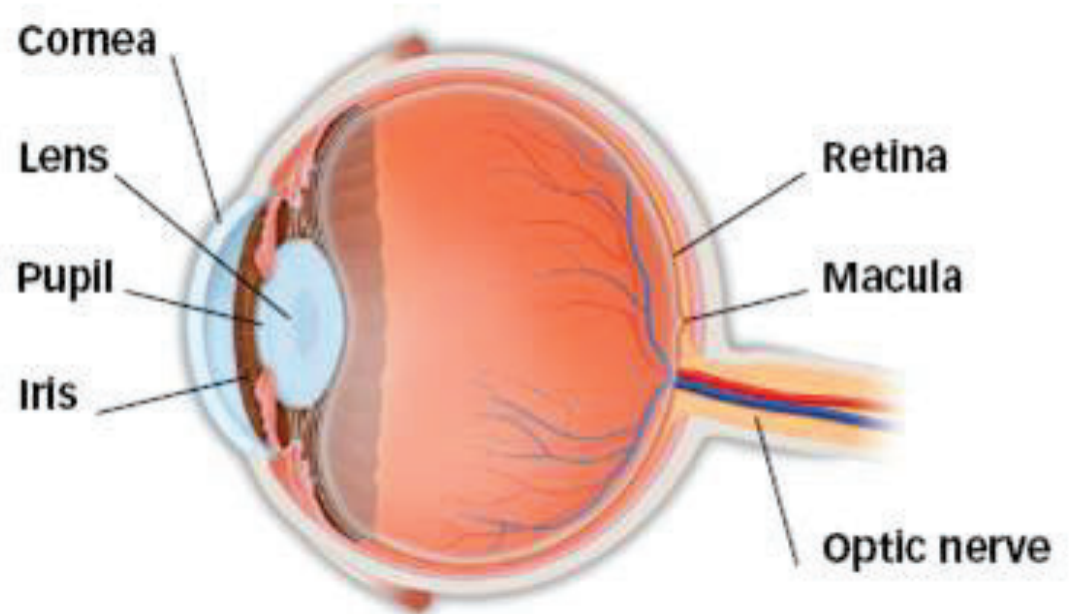
Avastin and ROP

## 2. ***Front of the EYE***

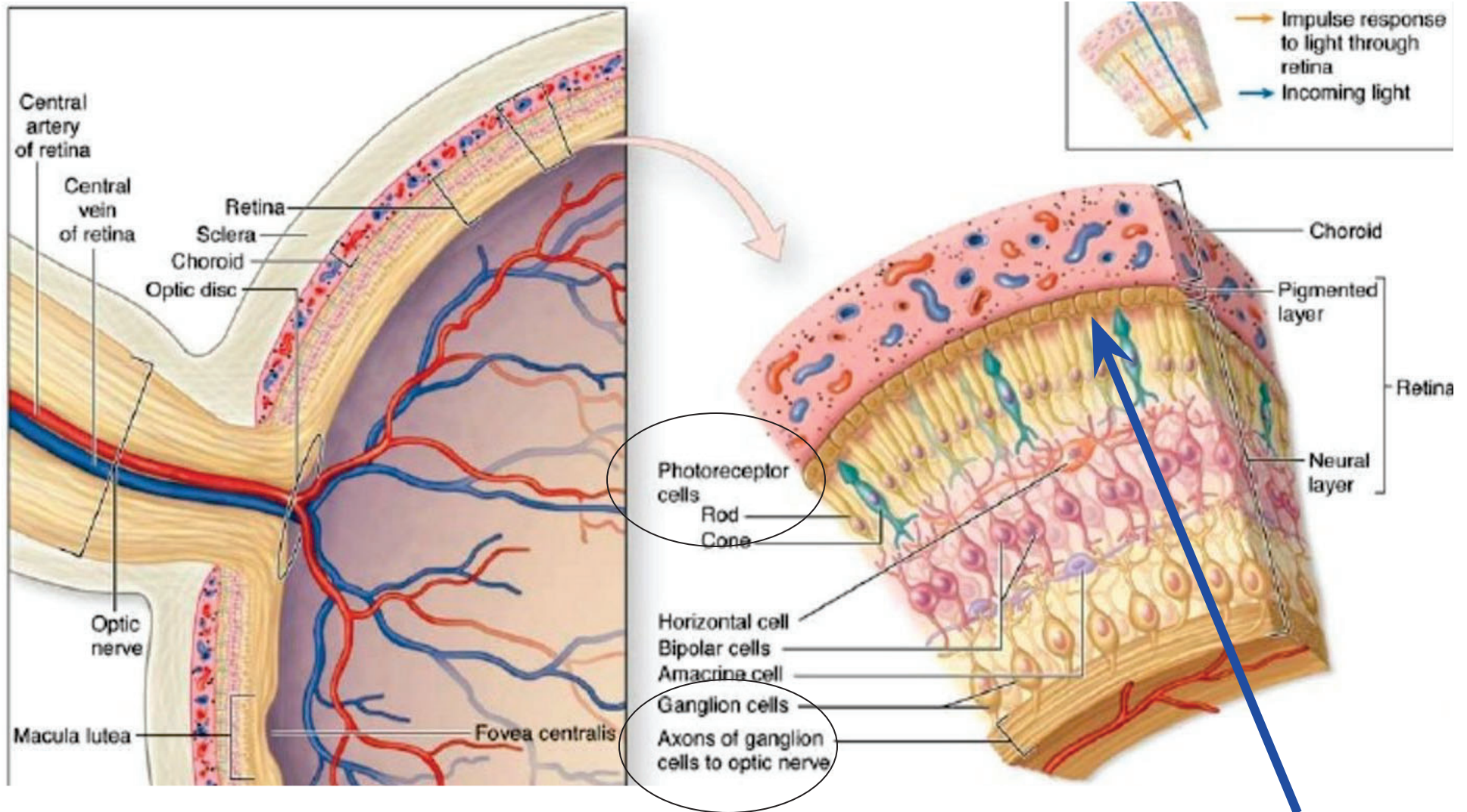
Corneal crosslinking

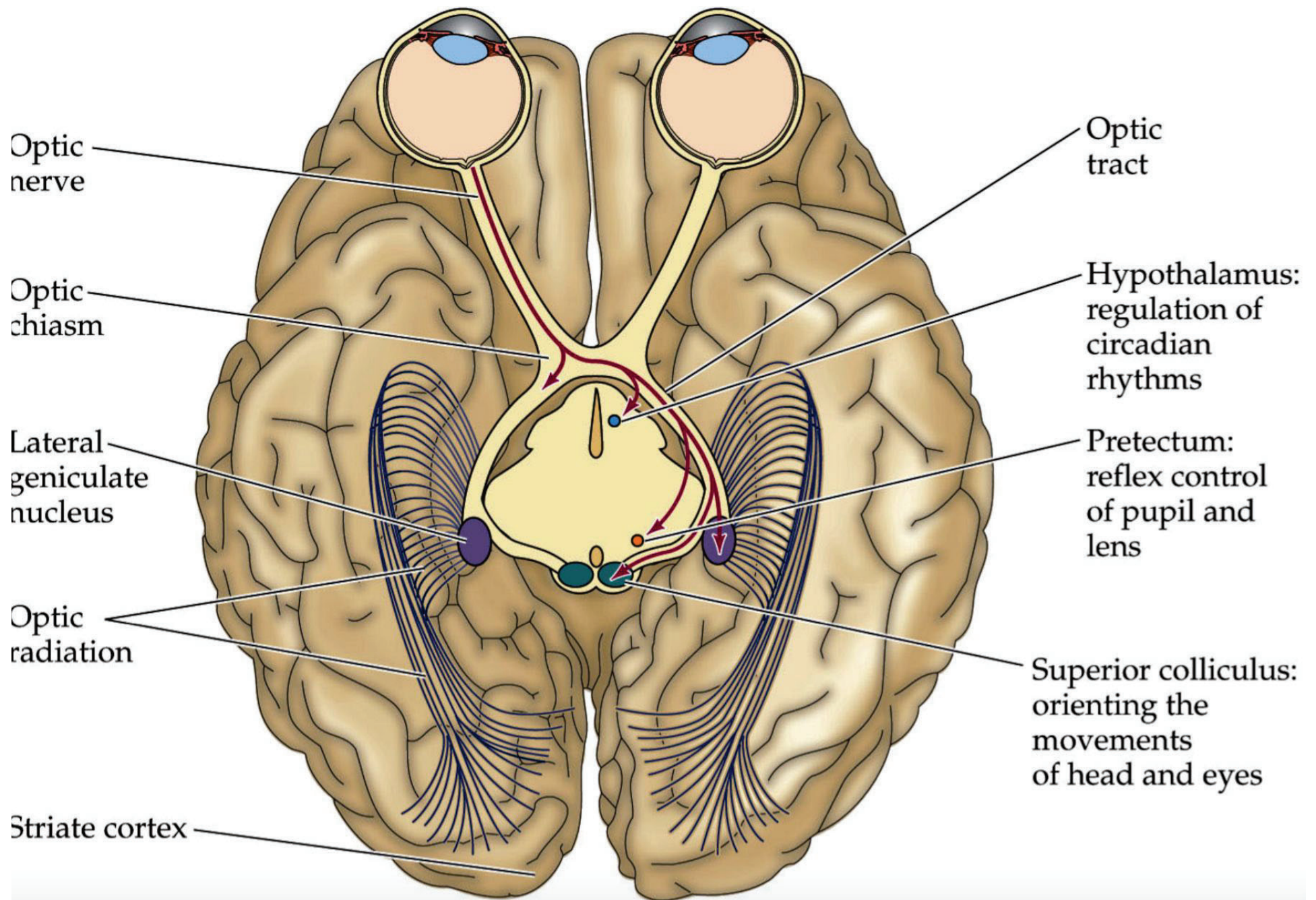
Refractive surgery for children

Glasses for infants( new little book)

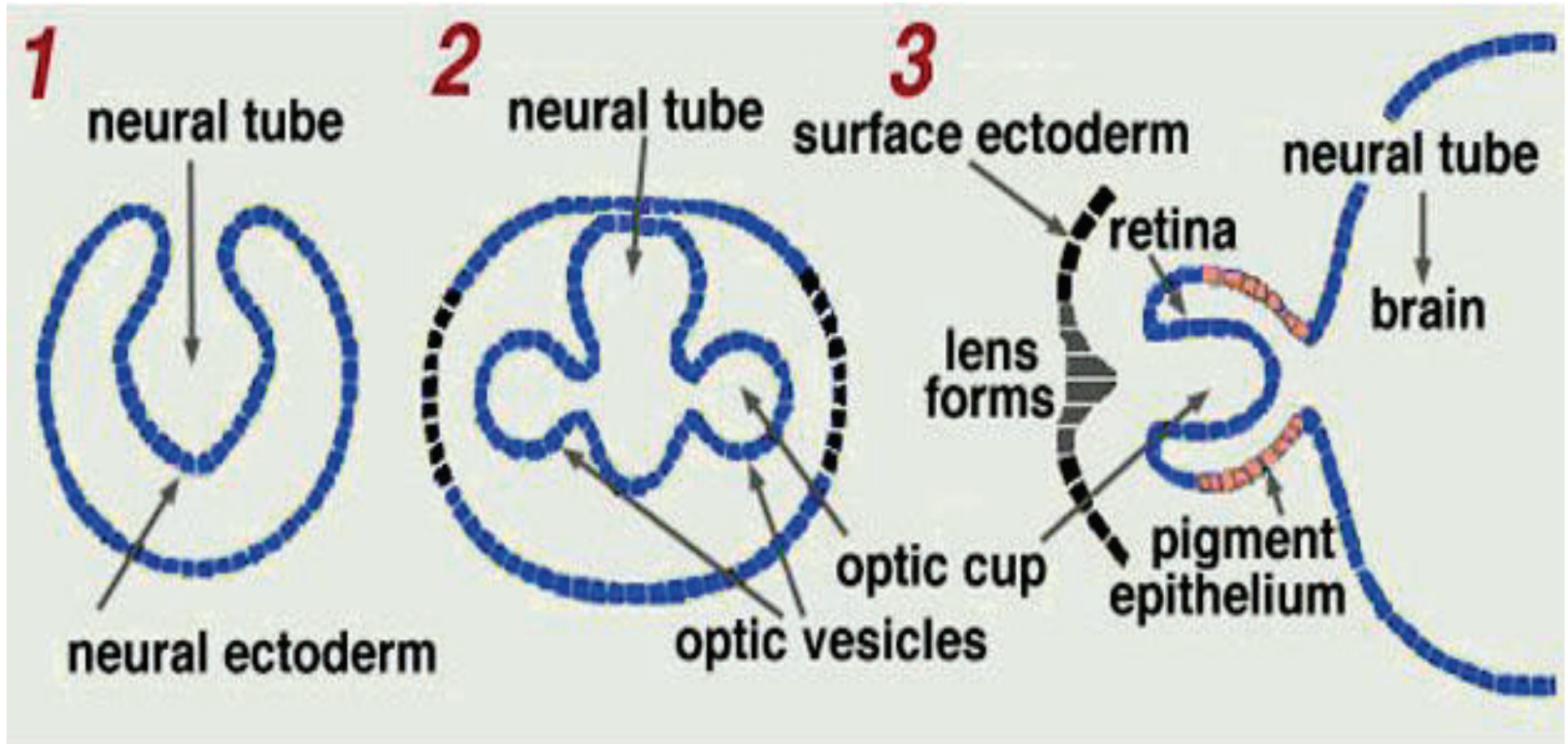


# Normal Retinal and Optic Nerve Anatomy



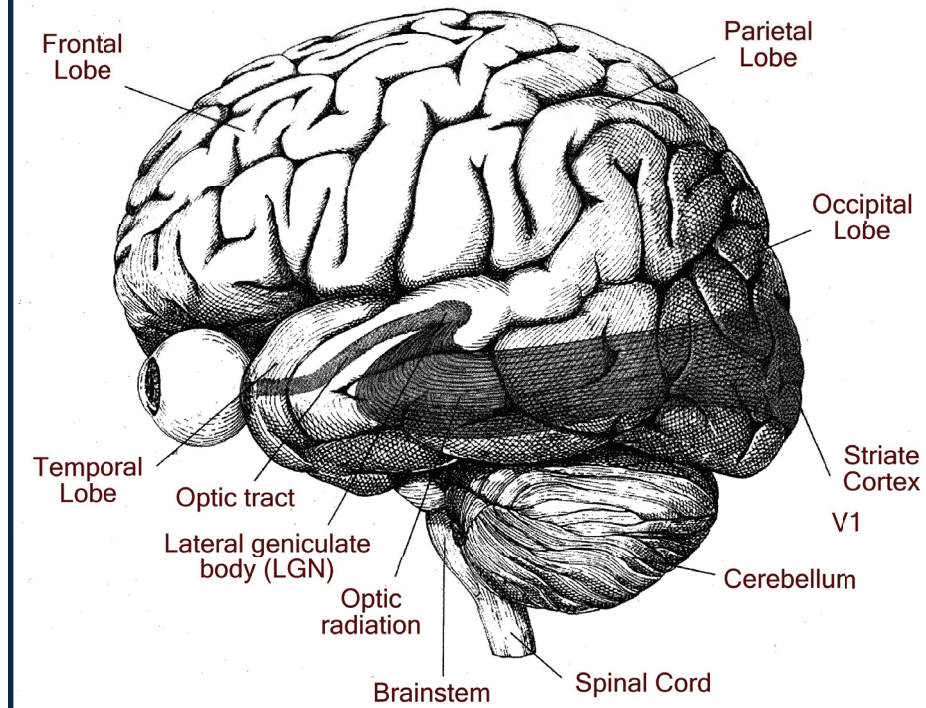


# Very Basic Embryology



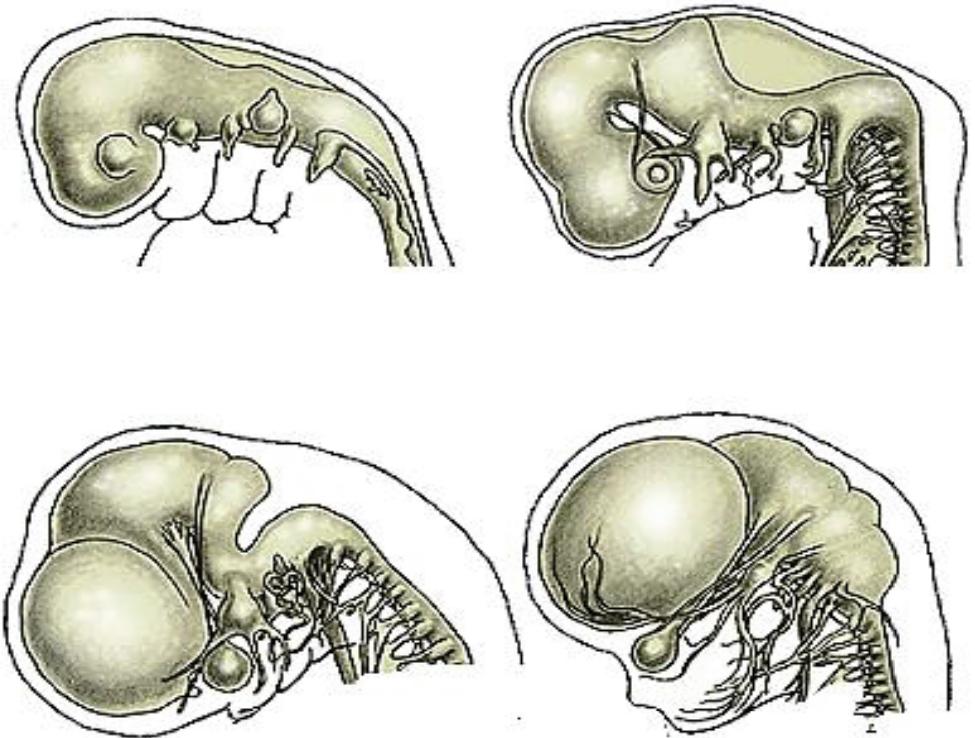
*Fig. 4. Development of the eye from the neural tube through the optic vesicles and the inverted optic cup forming the retina.*

## THE BRAIN

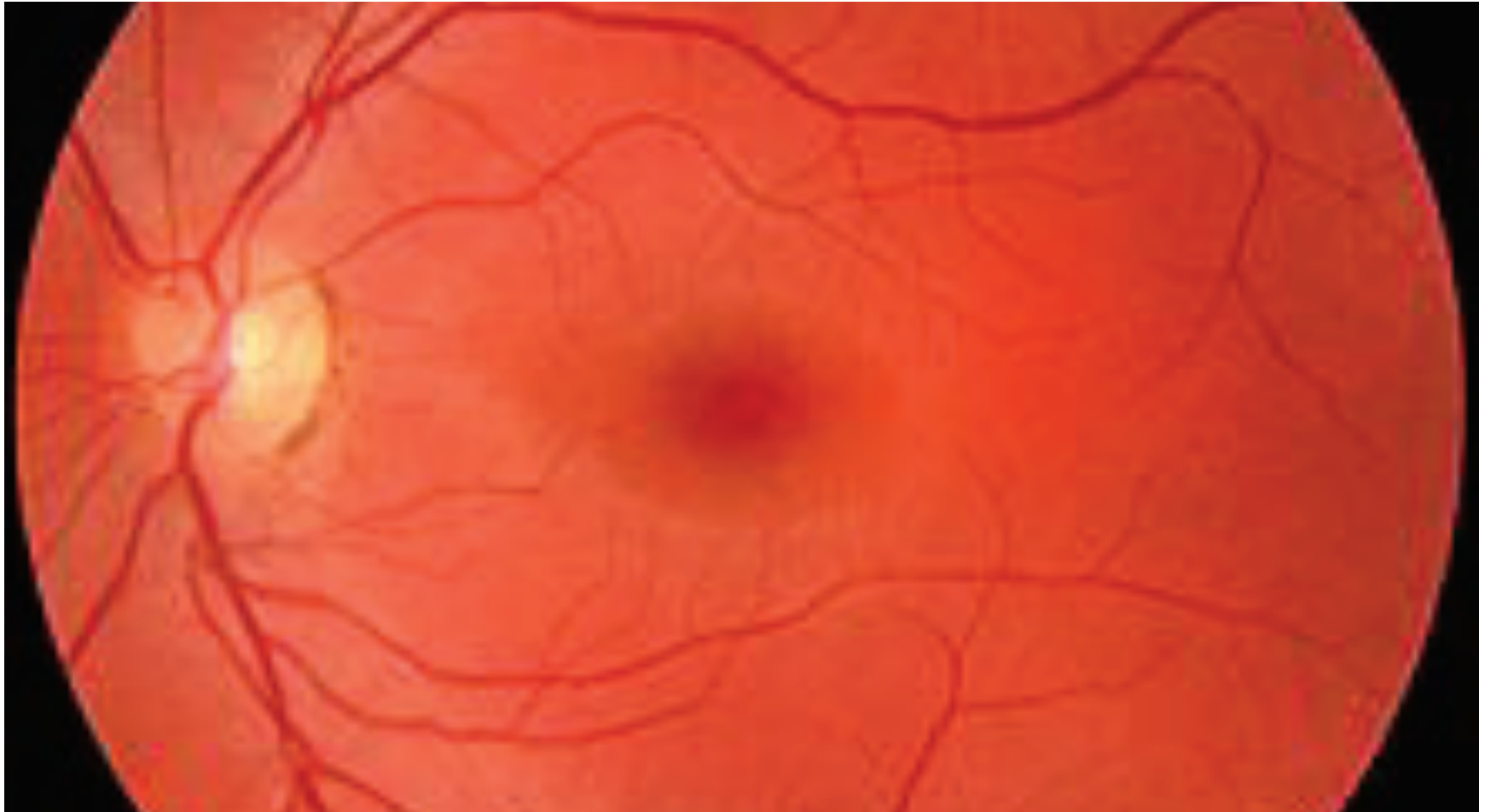


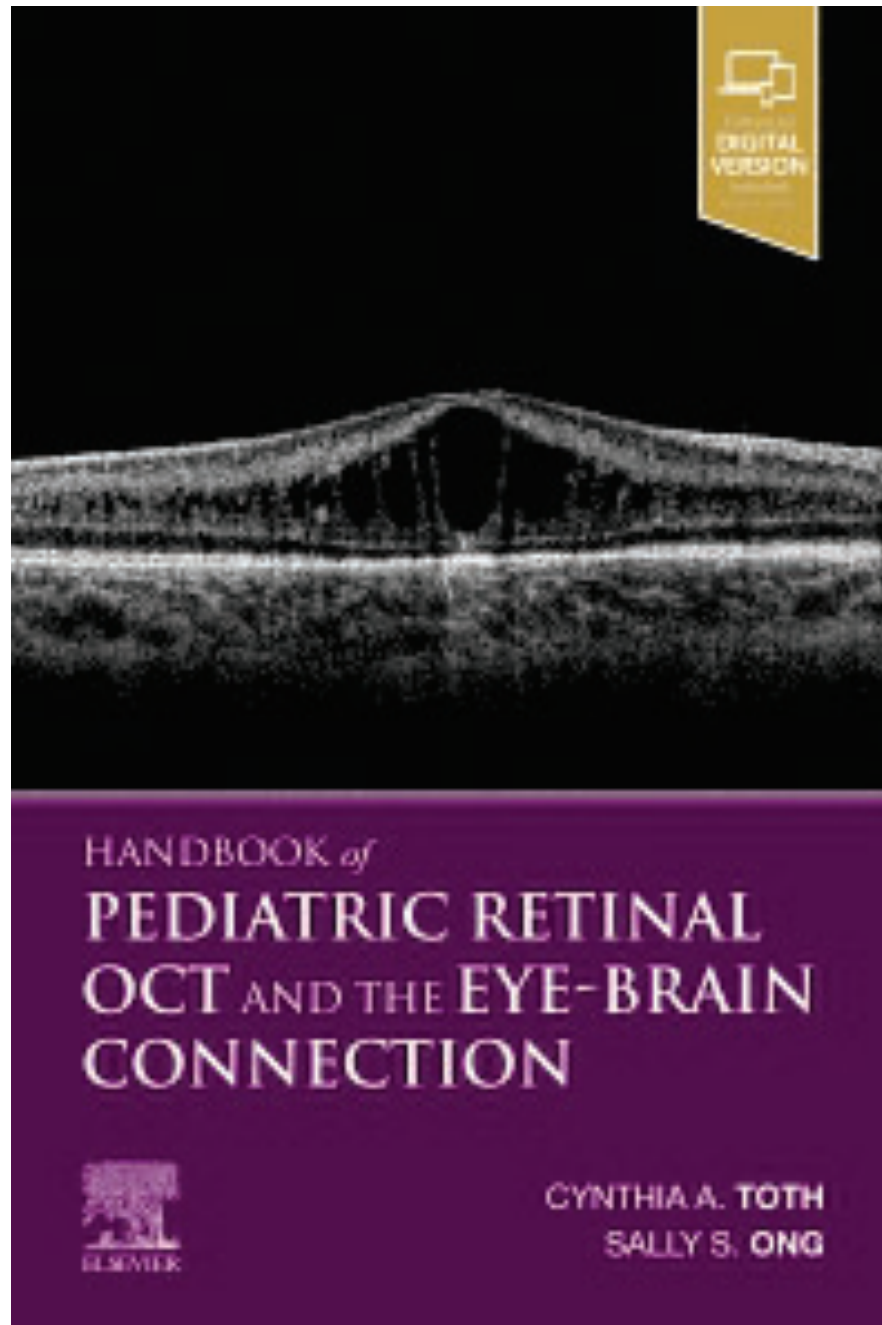
# Embryology

## Development of the Brain and Cranial Nerves

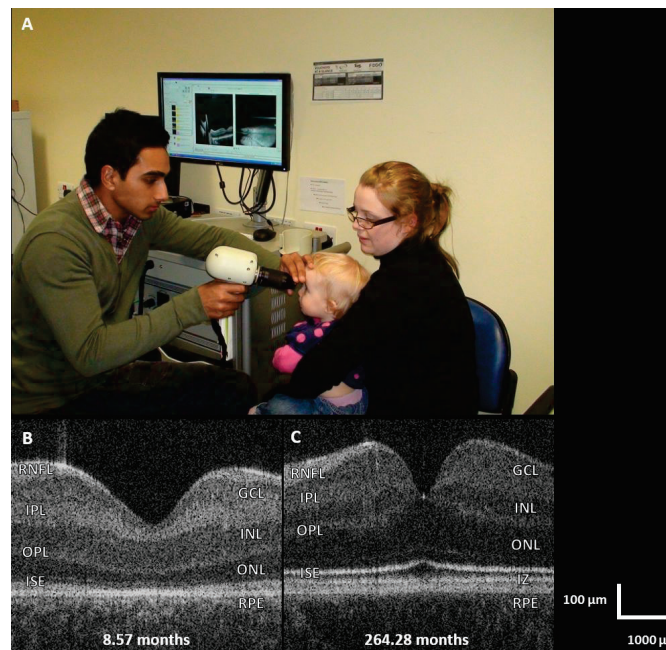


# Back of the Eye





## New Book on Pediatric OCT



### Figure Legend:

(A) Example of using HH-SDOCT to acquire a retinal tomogram in a child and two foveal tomograms taken at the foveal center illustrating normal retinal anatomy and the morphologic differences between the neonatal (B) and adult retina (C). Both participants were born at term, and the ages of the participants are given in months postmenstrual age. During normal foveal development, there is migration of the IRLs (GCL, IPL, INL, and OPL) away from the central fovea, migration of the cone photoreceptors into the central fovea, and elongation of the ORLs (ONL, IS, and OS) with increasing age. This explains the presence of the IRLs and absence of cone photoreceptors at the central fovea on the neonatal OCT (B). In contrast, the IRLs are absent and the cone photoreceptors are present at the central fovea on the adult OCT (C). The presence of the interdigitation zone in (C) is an additional marker of retinal maturity.

- The use of OCT (optical coherence tomography) is now becoming instrumental in the diagnosis and management of many pediatric conditions.
- Uses infrared light to provide micron-scale resolution of in vivo tissue
- OCT angiography (OCTA)  
Images retinal microvasculature



# How can we use? Optic Nerve

- Glaucoma vs. physiologic cupping
- Optic atrophy post trauma
- Optic nerve hypoplasia
- Progression of nerve fiber loss (optic nerve gliomas)
- Optic neuritis/papilledema
- Optic nerve drusen/pseudopapilledema
- Track increase ICP from VP shunt



# How can we use? Retina

- Foveal Hypoplasia
- Cystoid macular edema
- Macular holes/trauma
- Structural causes of amblyopia
- Retinal dystrophies
- Hereditary retinal dystrophies
- Toxicity (plaquenil, ?vigabatrin)
- tumors

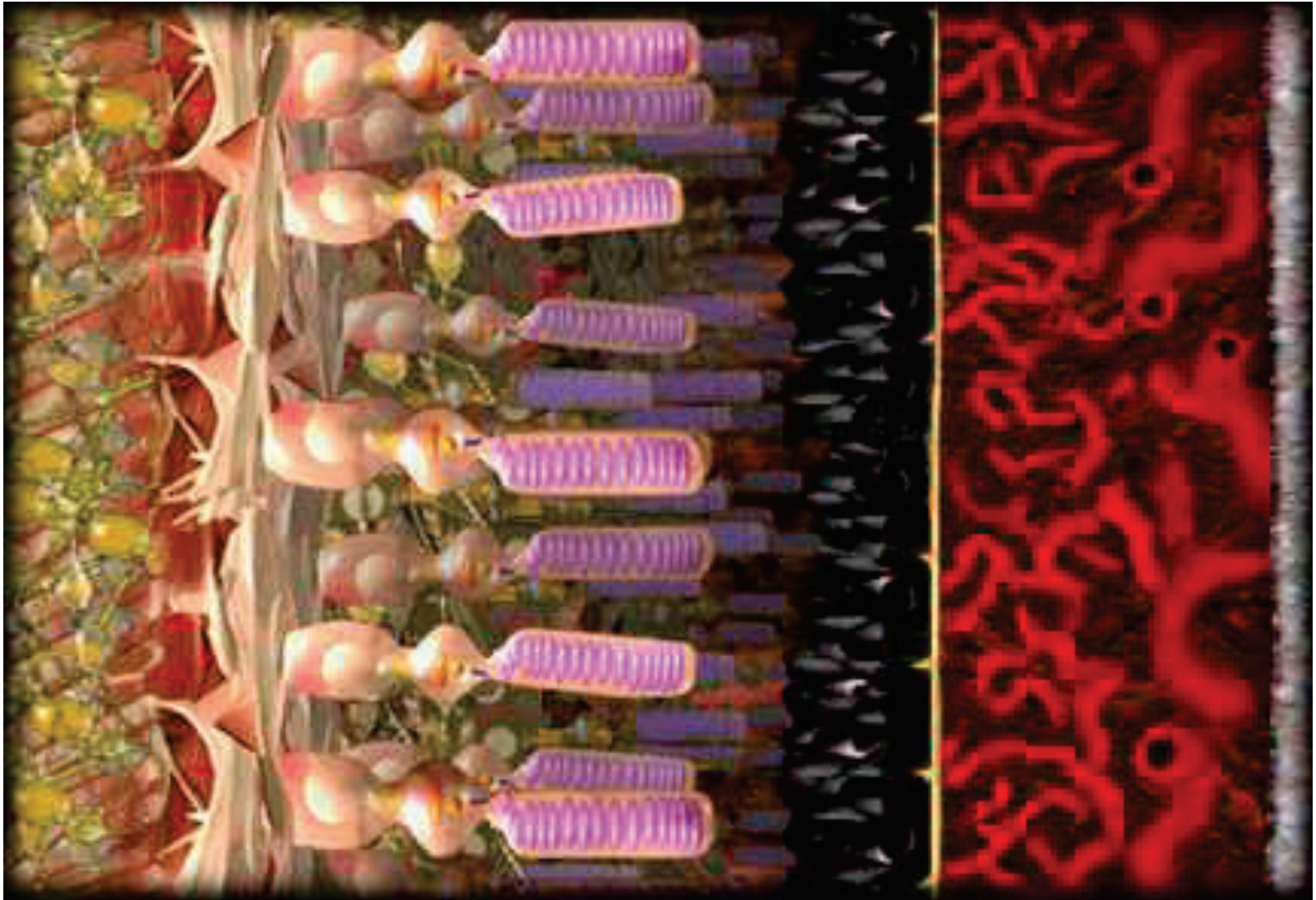


# Technical challenges in Kids

- No official norms for kids: soon
- Difficult technically in kids, nystagmus, fixation
- Hand held expensive
- Built for adults



# ANATOMY OF THE RETINA



# Normal Retina

Vitreous

Inner retina

- Internal limiting membrane

- Nerve fiber

- Ganglion cell

Central retina

- inner plexiform

- inner nuclear

- outer plexiform

- outer nuclear

Outer Retina

- external limiting membrane

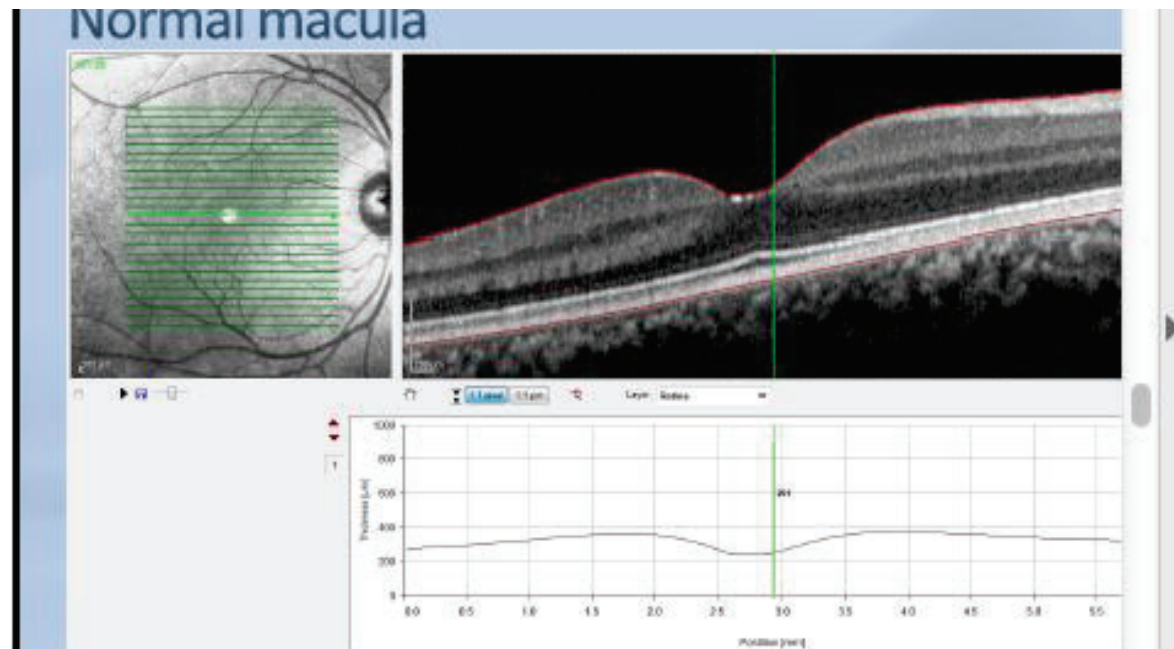
- rods and cones

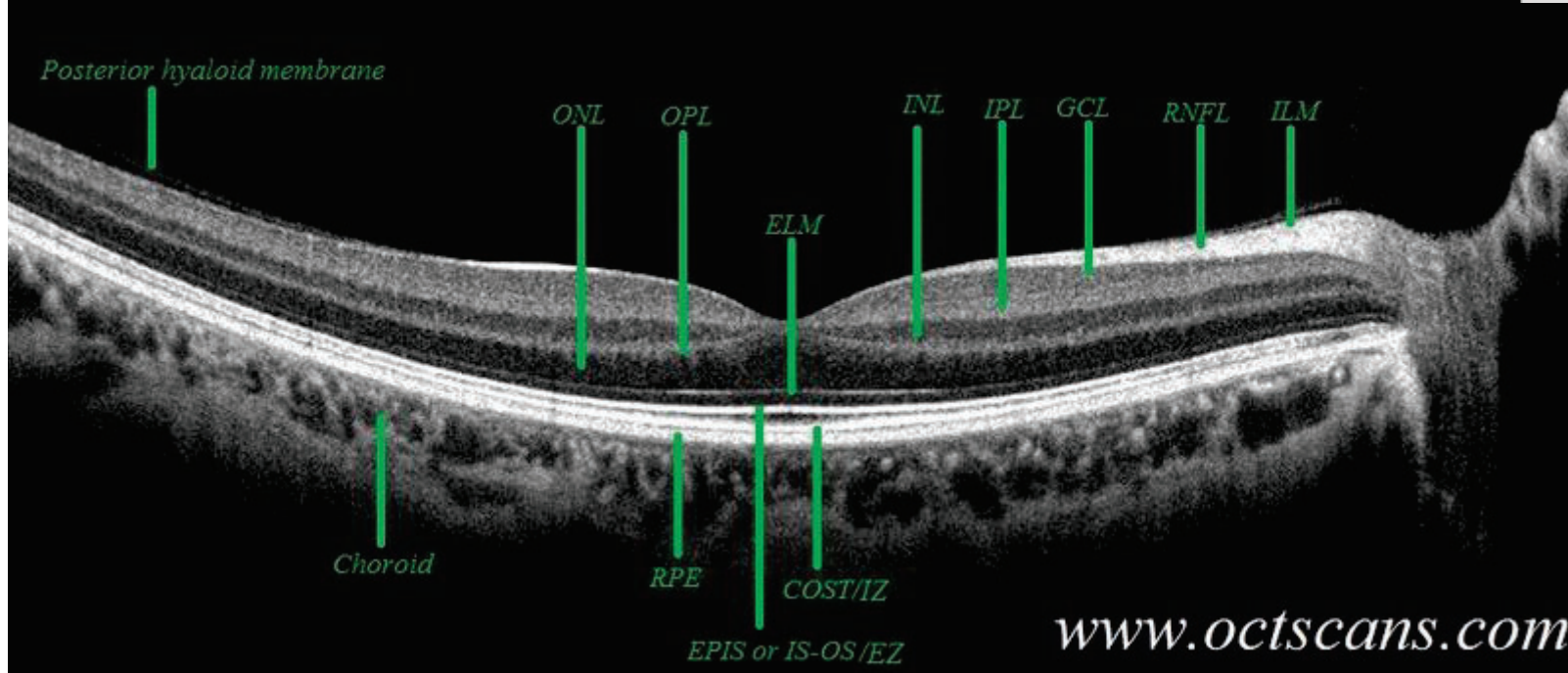
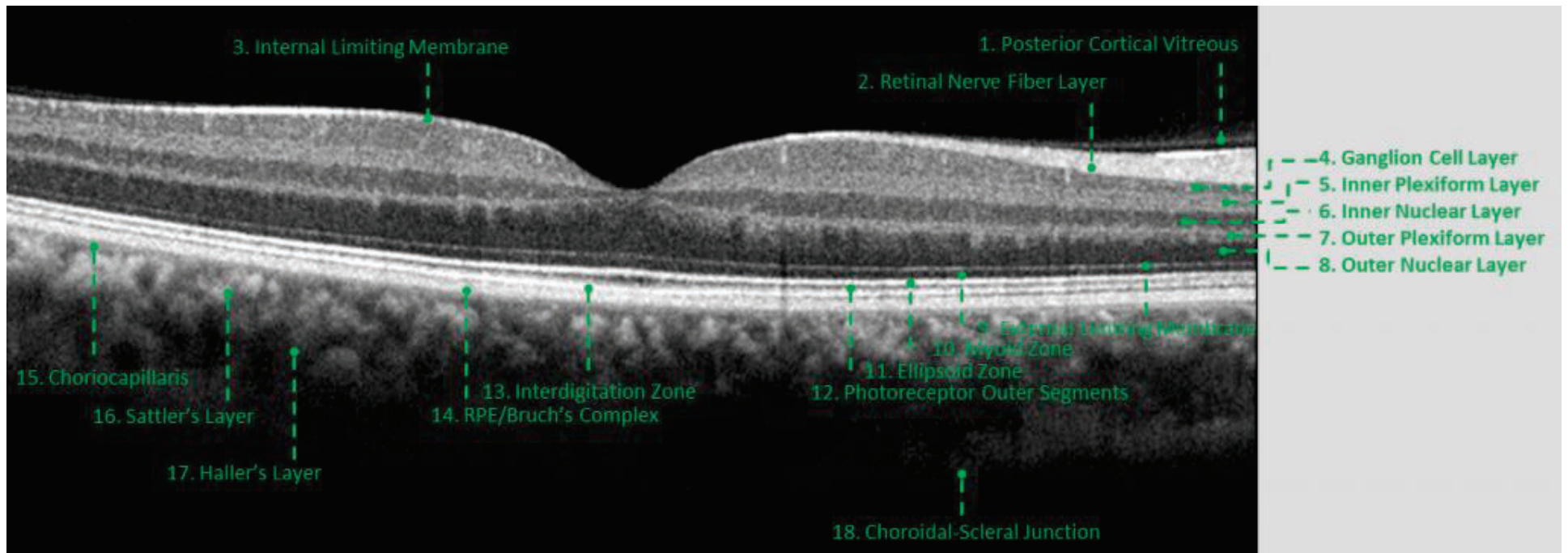
- retinal pigment epithelial

- Bruch's membrane

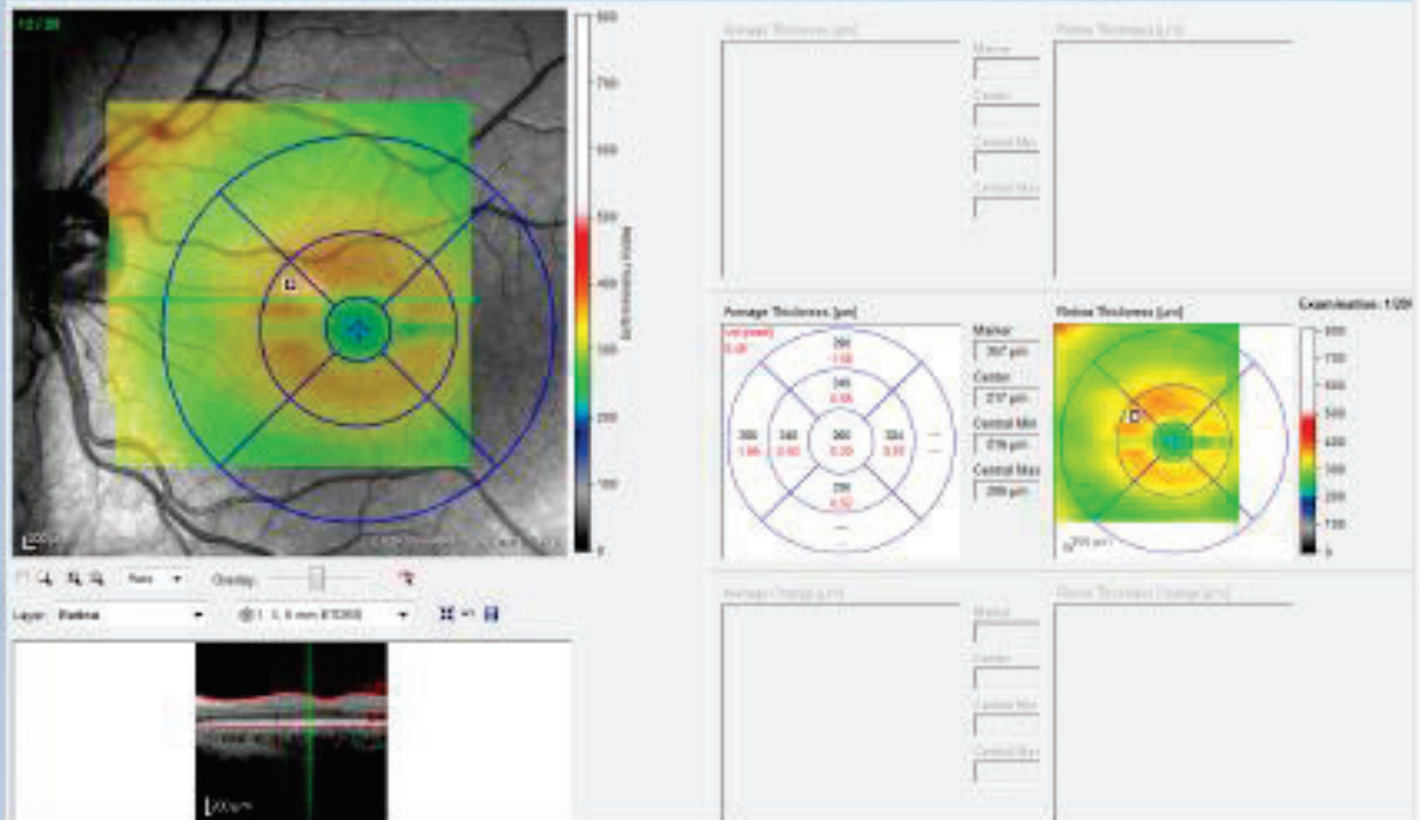
Choroid

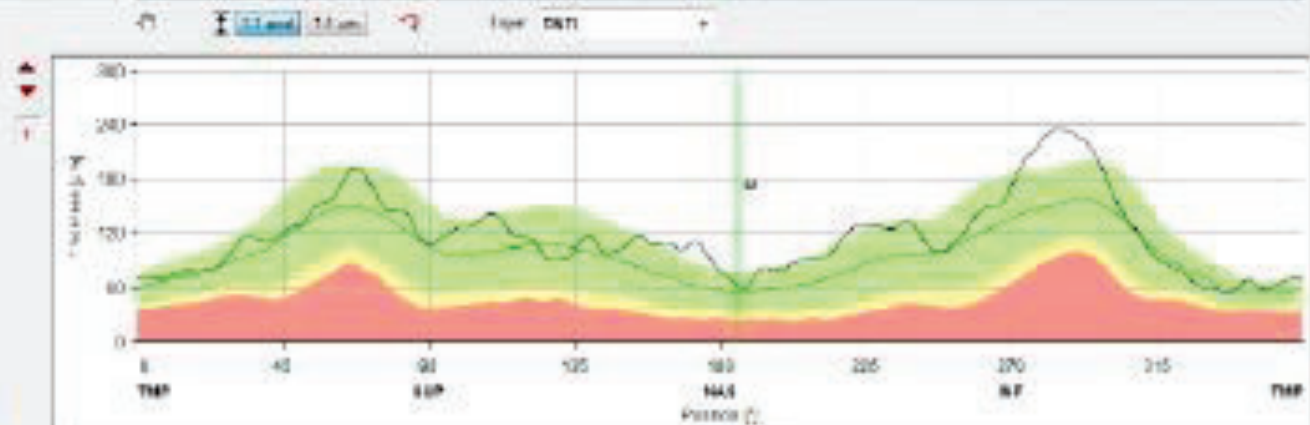
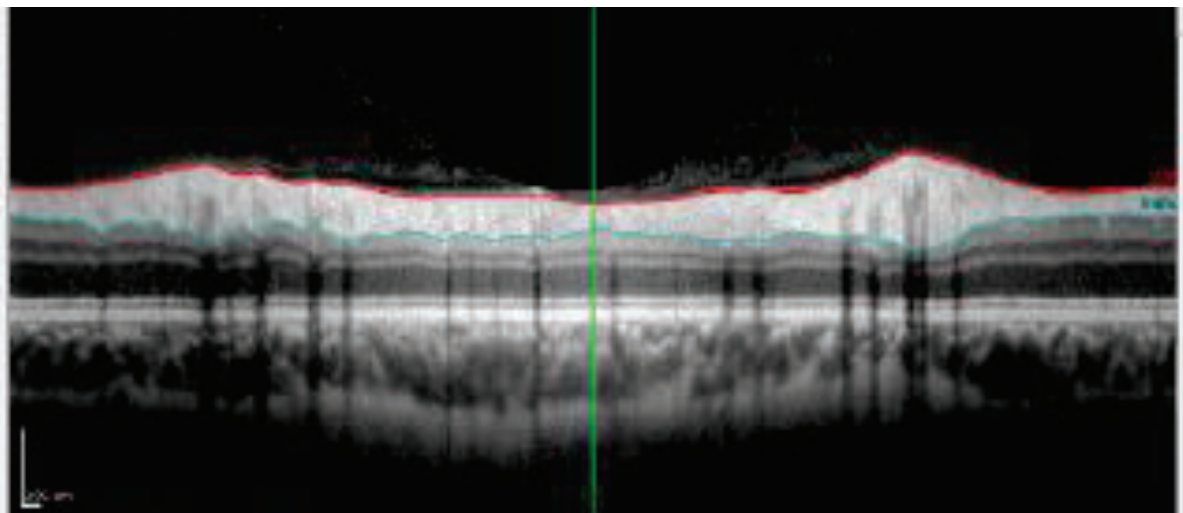
- choriocapillaris/choroid





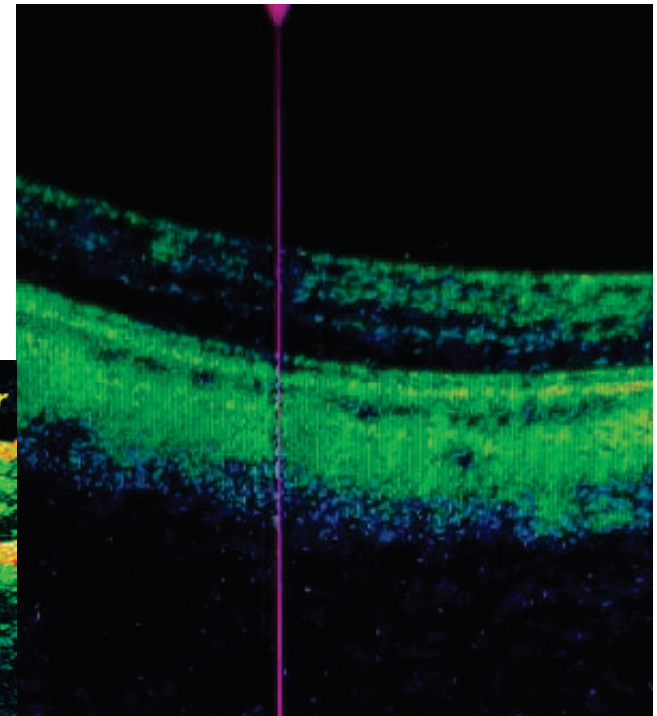
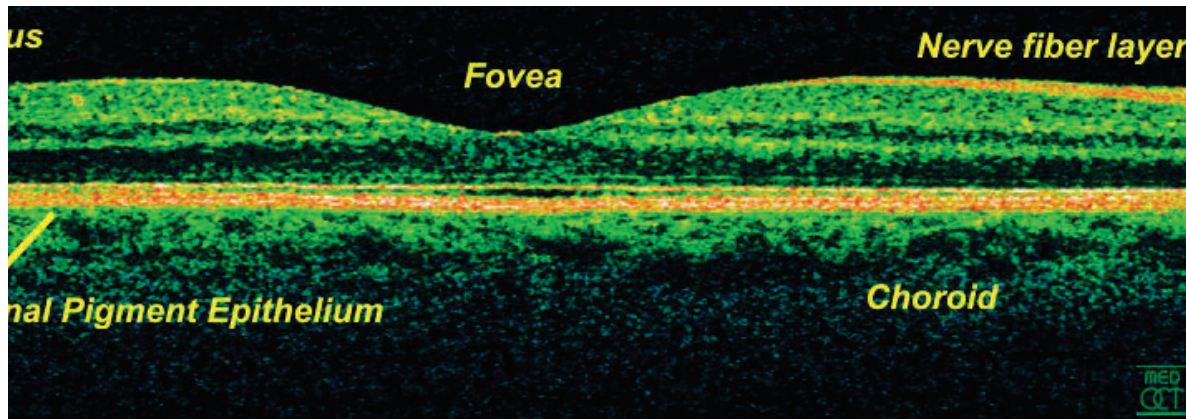
# Normal retinal NFL



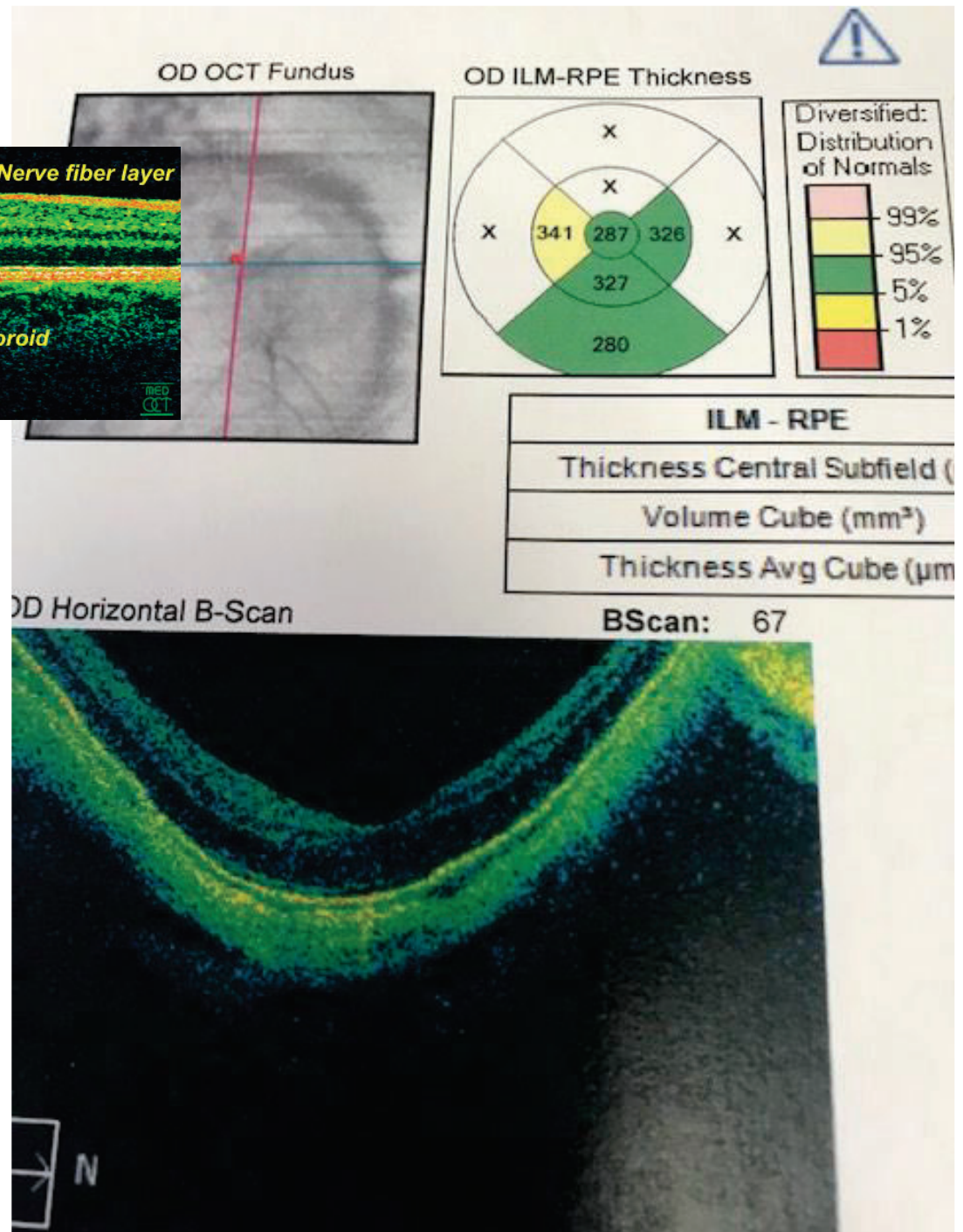


Warning: Classification results valid for Caucasian eyes only.

# Retinopathy of Prematurity

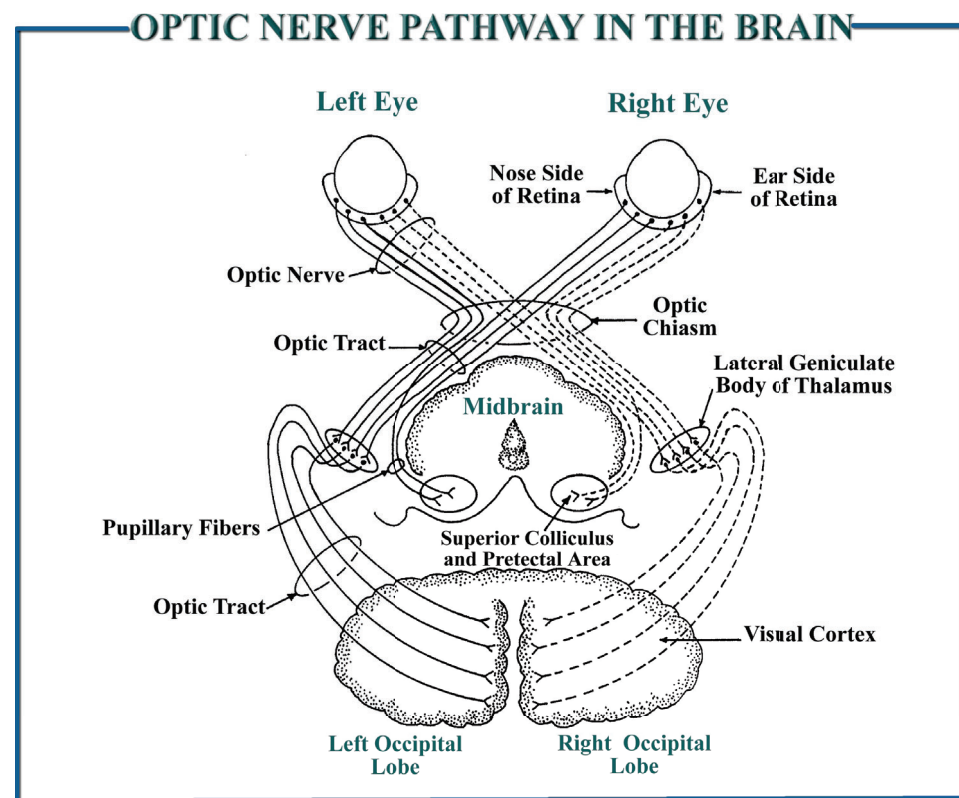


Macula OCT age 12 you



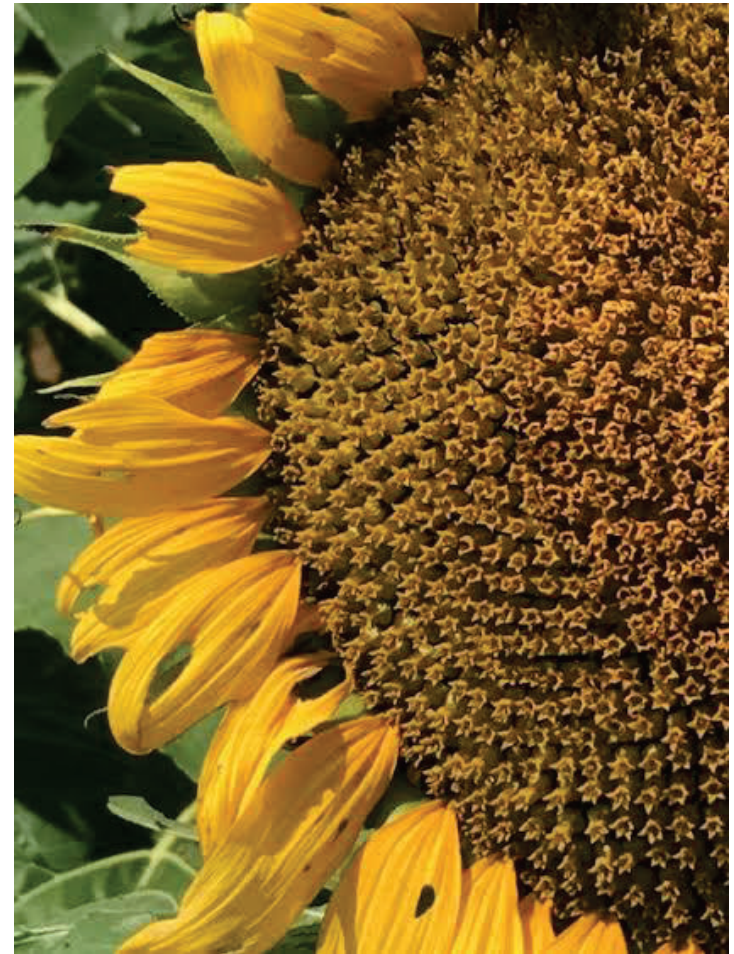
# Retinotopic Organization

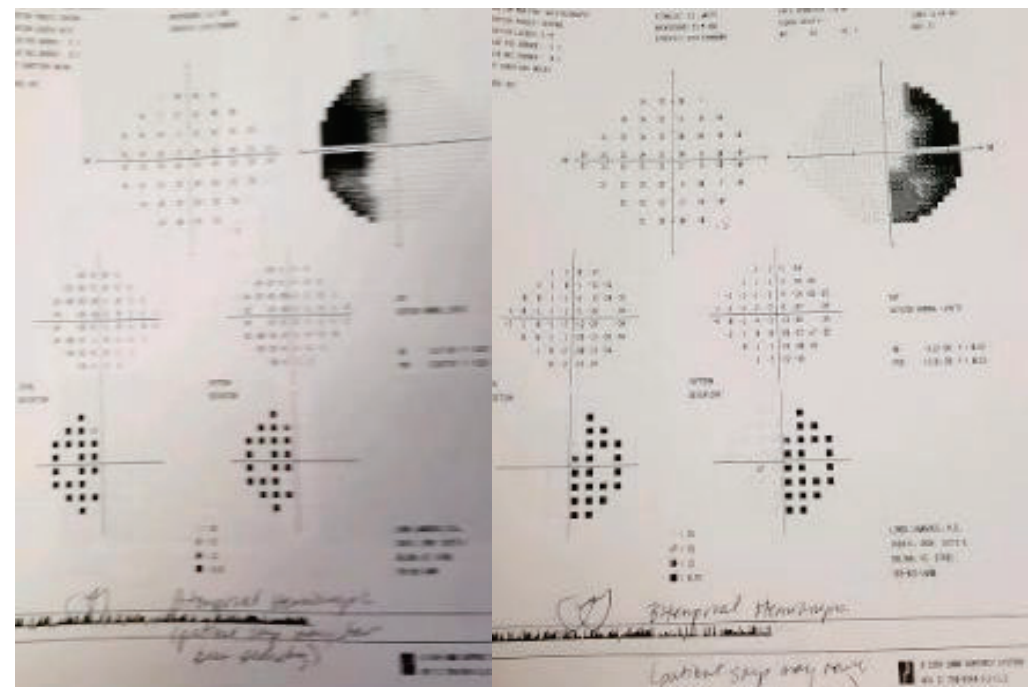
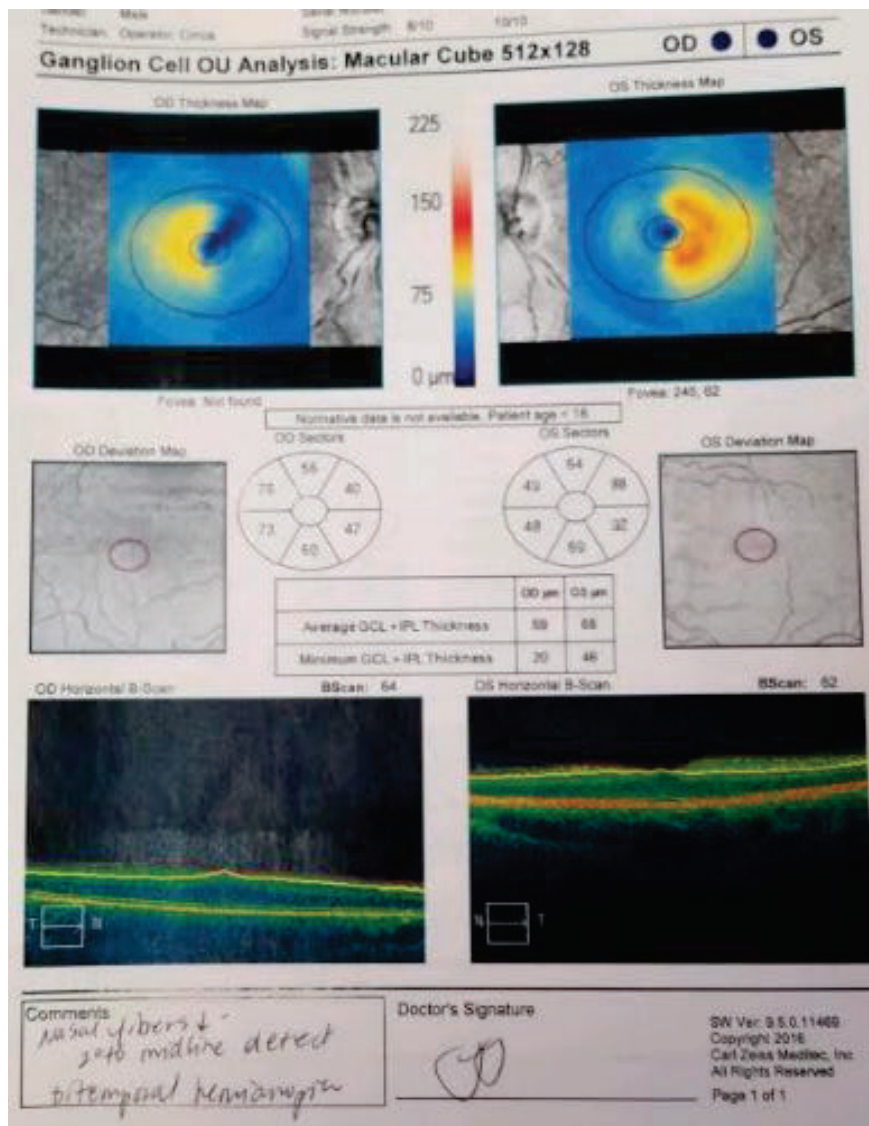
- Anatomy and Function go together
- Retinotopic organization maintained to occipital cortex



# Clinical applications in small office in Kansas

- 18yo boy
- Craniopharyngioma age 4yo
- Did fine until 4<sup>th</sup> grade difficulty reading





Nerve fiber layer loss correlates with visual field defect

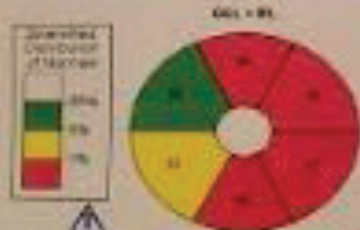
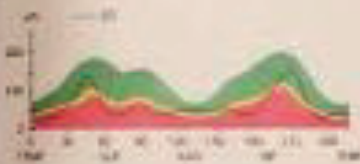
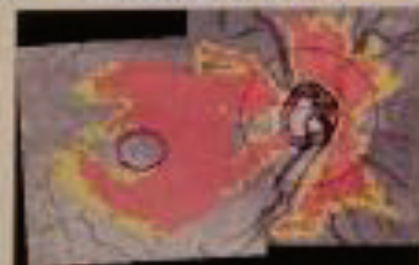
Eye: Left Eye      Exam Date: 04/20/10      04/20/10      04/20/10  
 Gender: Male      Serial Number: 500-33372      500-33372  
 Technician: Operator, Cirrus      Signal Strength: 10/10      10/10

### PanoMap Analysis: Right Eye

OD ☒ OS ☐



|                         |                       |
|-------------------------|-----------------------|
| Disc Area               | 1.51 mm <sup>2</sup>  |
| Para Area               | 1.34 mm <sup>2</sup>  |
| Average C/D Ratio       | 0.56                  |
| Vertical C/D Ratio      | 0.55                  |
| Cup Volume              | 0.129 mm <sup>3</sup> |
| Average RNFL Thickness  | 87 µm                 |
| Superior RNFL Thickness | 82 µm                 |
| Inferior RNFL Thickness | 95 µm                 |



|                             |    |
|-----------------------------|----|
| Average GCL + IPL Thickness | 78 |
| Minimum GCL + IPL Thickness | 61 |

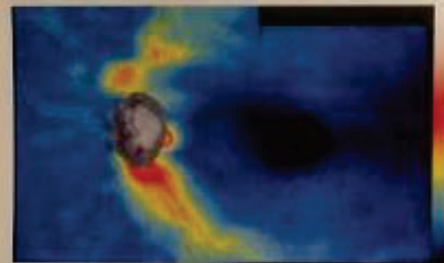


Comments:      Operator's Signature:

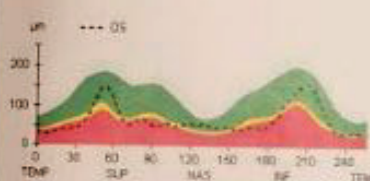
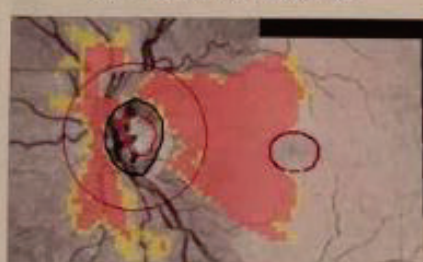
ID: 8001      Exam Date: 04/20/10      04/20/10      04/20/10  
 DOB: 9/2/1998      Exam Time: 3:52 PM      3:53 PM  
 Gender: Male      Serial Number: 500-33372      500-33372  
 Technician: Operator, Cirrus      Signal Strength: 10/10      10/10

### PanoMap Analysis: Left Eye

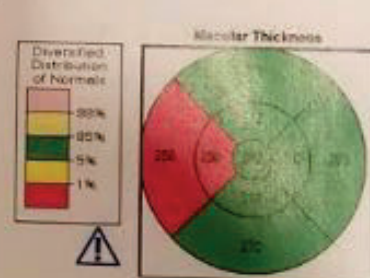
OD ☐ OS ☒



|                         |                       |
|-------------------------|-----------------------|
| Disc Area               | 1.51 mm <sup>2</sup>  |
| Para Area               | 1.34 mm <sup>2</sup>  |
| Average C/D Ratio       | 0.56                  |
| Vertical C/D Ratio      | 0.55                  |
| Cup Volume              | 0.129 mm <sup>3</sup> |
| Average RNFL Thickness  | 87 µm                 |
| Superior RNFL Thickness | 82 µm                 |
| Inferior RNFL Thickness | 95 µm                 |



|                             |    |
|-----------------------------|----|
| Average GCL + IPL Thickness | 68 |
| Minimum GCL + IPL Thickness | 46 |



Comments:      Operator's Signature:

# Genetic conditions



# Ways to think through Inherited eye disease

1. Congenital (present at birth)
2. Very early onset
3. Early onset and stable
4. Later onset and progressive

# What is the pattern of expression of a genetic disorder?

- Does it mainly affect the eye?
- Progressive or non-progressive?
- Early onset or late onset?
- Multisystem expression that happens to include the eye?
  - Ocular with hearing impairment
  - Ocular with other associated disorders
  - Cerebral visual impairment associated with genetic disorders

# Leber Congenital Amaurosis (LCA)

- Group of heterogeneous disorders characterized by early onset rod-cone dystrophy and severe visual loss.
- Most without associated findings
- Sporadic and inherited
- Appears normal at birth
- Total blindness develops
- Severe visual impairment, LP to NLP

# LCA

- Early age
- Severe
- Nystagmus, sluggish pupils, poor acuity, photophobia, high hyperopia
- Described by Theodor Karl Gustav von Leber in 1869
- AR, 17 phenotypes with 22 genotypes identified (about 50% identified)
- RPE65 4<sup>th</sup> most frequent (8%)

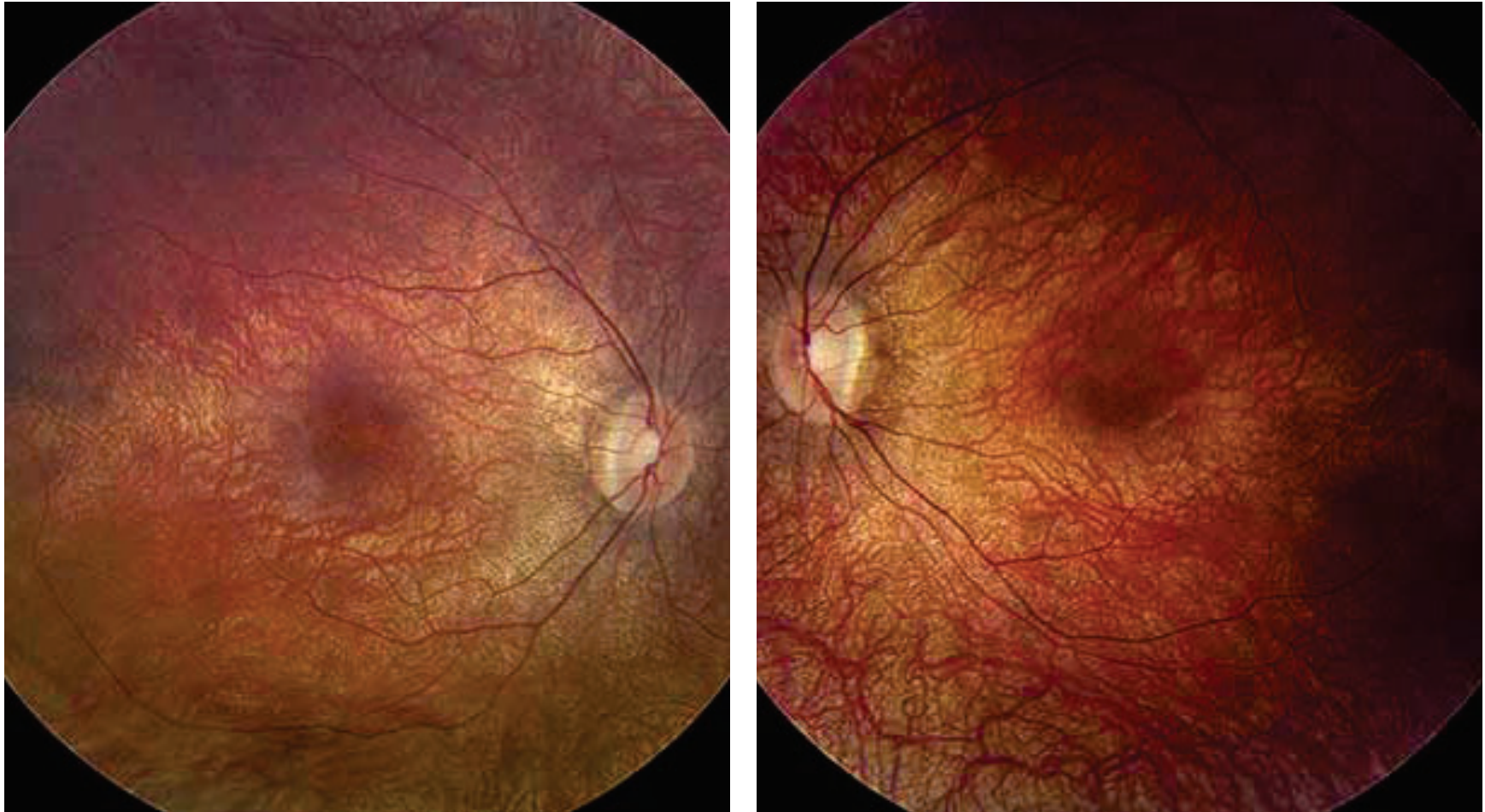
# LCA

- Inability of eye to undergo phototransduction due to disruption of visual cycle between RPE and neurosensory retina to metabolize dietary vit A into *11-cis retinal* to generate photopigment
- 2-3/100,000
- Most common inherited blindness in children
- 5% of all retinal dystrophies



Myopic-looking fundus with slight attenuation of the vasculature in this young child with RPE65 mutations. Pigmentary changes develop with age in this type of LCA

# RP65-associated Leber Congenital Amaurosis



Fundus photos with punctuate yellow dots and pigment mottling of the retina pigment epithelium.

# Clinical Findings and diagnostic testing

- OCT: relatively preserved central macula surrounded by retina thinning/atrophy
- FAF: reduced/absent autofluorescence signal, likely due to decreased levels of lipofuscin in the RPE layer.<sup>22</sup>

# LCA Hallmarks

Early:

- Severe, early vision loss
- Sluggish pupils
- Severely abnormal ERG
- Retina may look normal!
- Mild nystagmus
- Fundus exam is characteristic for a blond translucent appearance and whitish drusen-like deposits in about 90% of cases. Later in life, patients develop chorioretinal atrophy peripheral patches in 64% of cases

Late: oculo-digital sign,, chorio-retinal degeneration, keratoconus

# Pathology

Retinoid isomerohydrolase enzyme  
(Retinoid visual cycle)

This enzyme normally isomerizes and hydrolyzes all-trans retinyl ester to 11-cis retinol each time a photon hits 11-cis retinal.

Relatively good vision early in life (due to good residual cone function and alternative supply of 11-cis-retinal<sup>18</sup>) with a possible mild improvement in visual function temporarily.

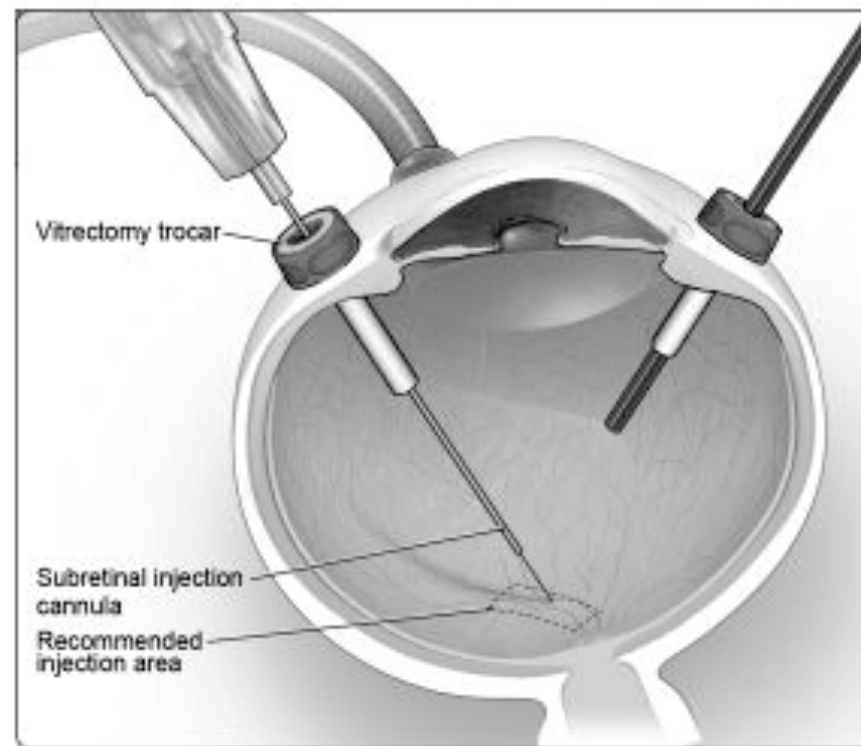
Specifically, patients have significant nyctalopia (poor rod function)

# Leber Congenital Amaurosis

## RPE65

- Luxturna®
- Adeno-associated viral vector
- Carries a normal copy of the human RPE65 gene
- Injected into subretinal space
- General anesthesia
- Only at specific centers

**Figure 5a. Subretinal injection cannula introduced via pars plana**



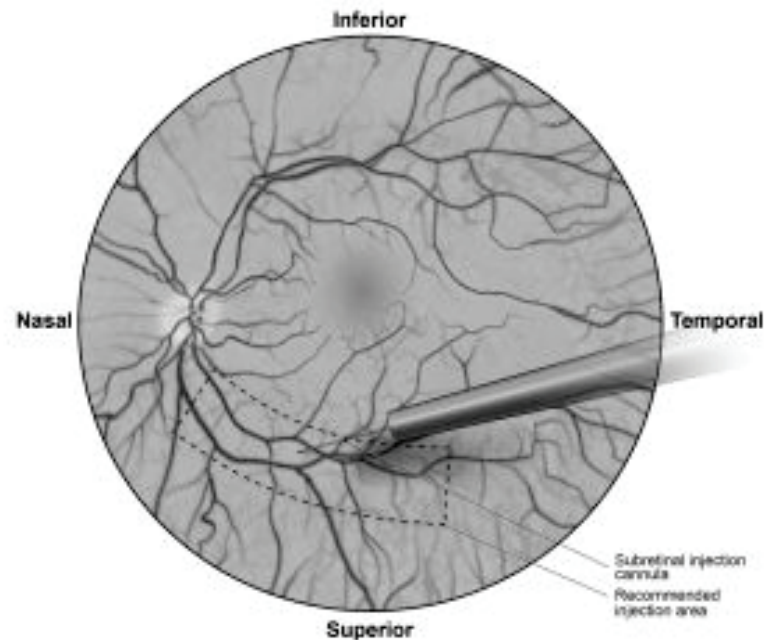
# Leber Congenital Amaurosis

- Requires genetic testing to ensure have the appropriate condition for treatment
- ERG, OCT

Who pays?

- Insurance?
- Compassionate care?
- \$450,000 per injection for medication

**Figure 5b. Tip of the subretinal injection cannula placed within the recommended site of injection (surgeon's point of view)**



# Leber Congenital Amaurosis

## RPE65

- Approved Dec. 19, 2017 by FDA
- Approved for children 12 months and older
- 5 medical centers in USA doing the treatment

## Current Gene Therapy Trials

| Disease                                   | Gene    | Status             | Intervention          | Age Limit                              | Contact                                          | Comment           |
|-------------------------------------------|---------|--------------------|-----------------------|----------------------------------------|--------------------------------------------------|-------------------|
| Leber Congenital Amaurosis (LCA)          | RPE65   | FDA Approved       | Voretigene (Luxturna) | 1 y.o (though only studied in > 3 y.o) | Spark Therapeutics<br>1-833-772-7577             | Phase 3 completed |
| LCA                                       | CEP290  | Recruiting         | QR-110                | 6 y.o.                                 | clinical@proqr.com                               | Phase 1/2         |
| Stargardt                                 | ABCA4   | Recruiting         | SAR422459             | 6 y.o.                                 | Contact-Us@sanfoni.com                           | Phase 1/2         |
| Stargardt                                 | ABCA4   | Recruiting         | ALK-001               | 12 y.o.                                | Leonide Saad, PhD<br>trials@alkeus.com           | Phase 2           |
| Achromatopsia                             | CNGB3   | Recruiting         | AAV-CNGB3             | 6 y.o.                                 | ocularinfo@meiragtx.com                          | UK: Phase 1/2     |
| Achromatopsia                             | CNGA3   | Recruiting         | AGTC-402              | 6 y.o.                                 | Jill Dolgin, Pharm D<br>advocacy@agtc.com        | Phase 1/2         |
| X-Linked Retinoschisis                    | RS1     | Recruiting         | AAV2/RYF-CB-hRS1      | 6 y.o.                                 | Jill Dolgin, Pharm D<br>advocacy@agtc.com        | Phase 1/2         |
| Leber Hereditary Optic Neuroopathy (LHON) | G11778A | Recruiting         | AAV2-P1ND4v2          | 15 y.o.                                | John Guy, MD<br>jguy@med.miami.gov               | Phase 1           |
| LHON                                      | ND4     | Not yet recruiting | GS010                 | 15 y.o.                                | Barrett Katz, MD<br>bkatz@gensight-biologics.com | Phase 3           |

# Questions

1. What is the effect of preexisting deprivational amblyopia? Do we need to look at the occipital lobe function with FMRI?
2. Can there be immunity against the vector (adenovirus)
3. How do you measure functional improvement  
light sensitivity, visual field, navigation, visual acuity. Each study is developing their own functional measurements, there is no standard

# Will the newly FDA approved gene therapy help my child?

- On December 19, 2017, the FDA approved for the first time a gene therapy product for a type of congenital retinal blindness,
- Leber Congenital Amaurosis caused by mutations in both copies of the RPE65 gene.
- Most patients with RPE65-related inherited retinal disease have poor vision from birth, but some patients lose vision at older ages.
- Luxturna<sup>®</sup>, is an adeno-associated viral vector carrying a normal copy of the human RPE65 gene. It is injected under the retina into the subretinal space following a vitrectomy (surgical removal of the vitreous).
- This procedure is performed under general anesthesia.
- This treatment will be available at several sites across the country. Because this is a brand new therapy, insurance coverage issues currently are not known.

# Retinopathy of Prematurity and Cerebral/Cortical Visual Impairment

*Extremely premature infants and  
ANTIVEGF*

**Visual Function** – describes how the **EYE** functions: VA, contrast sensitivity, VF, color vision

- **Functional Vision** – describes how the **PERSON** functions in vision-related activities (in baby)
- **ETROP** 14.3% with favorable structural retinal outcome but unfavorable functional vision outcome

Good, WV. Final results of the ETROP randomized trial.  
Trans Amer Ophth Soc. 2004; 102:233-48

***Impact of CVI on Four Areas***



# Impact of Visual Impairment Starts at Birth

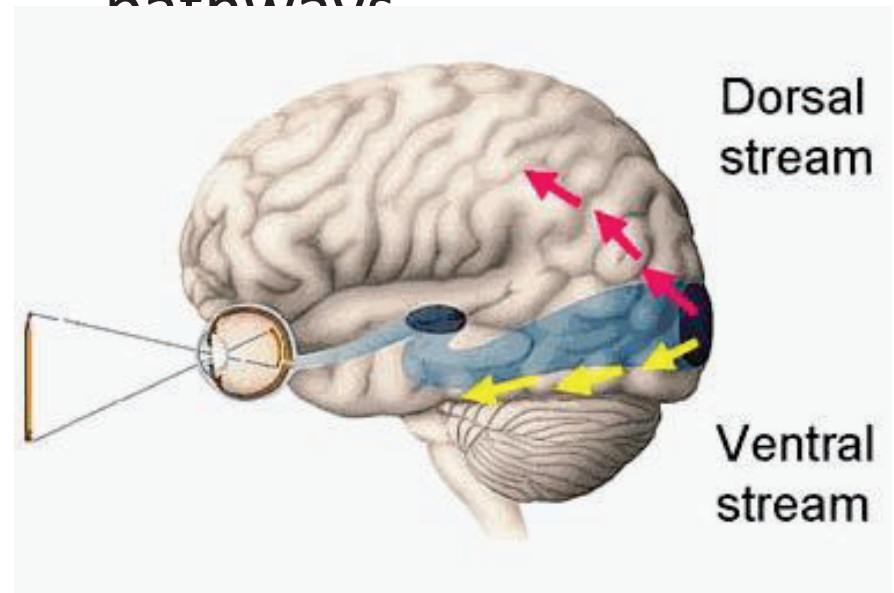
- Mutual eye gaze between the infant and families facilitates attachment.
- When vision is impaired, attachment and communication between parent and infant is challenged.

**Each child will be unique**

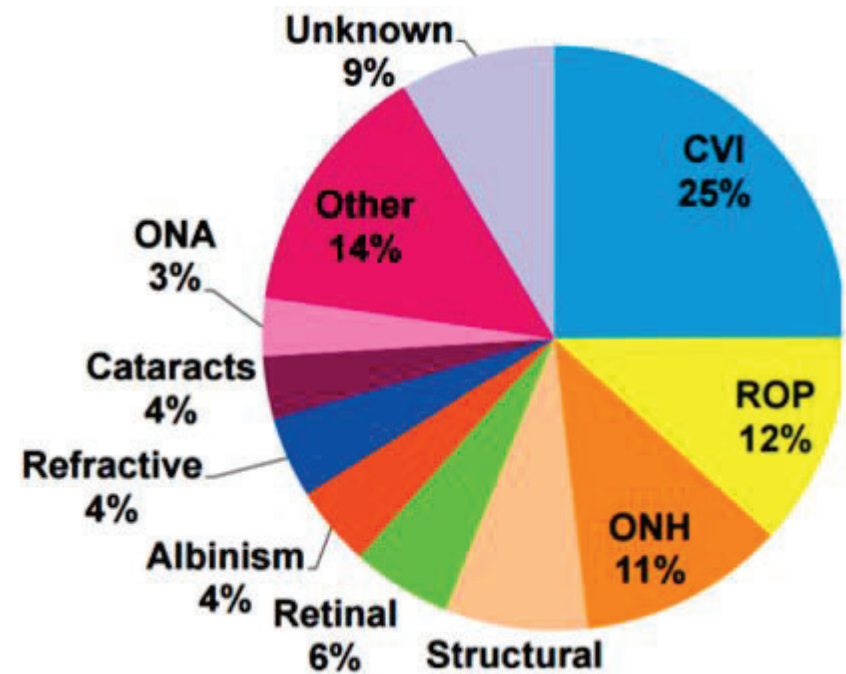
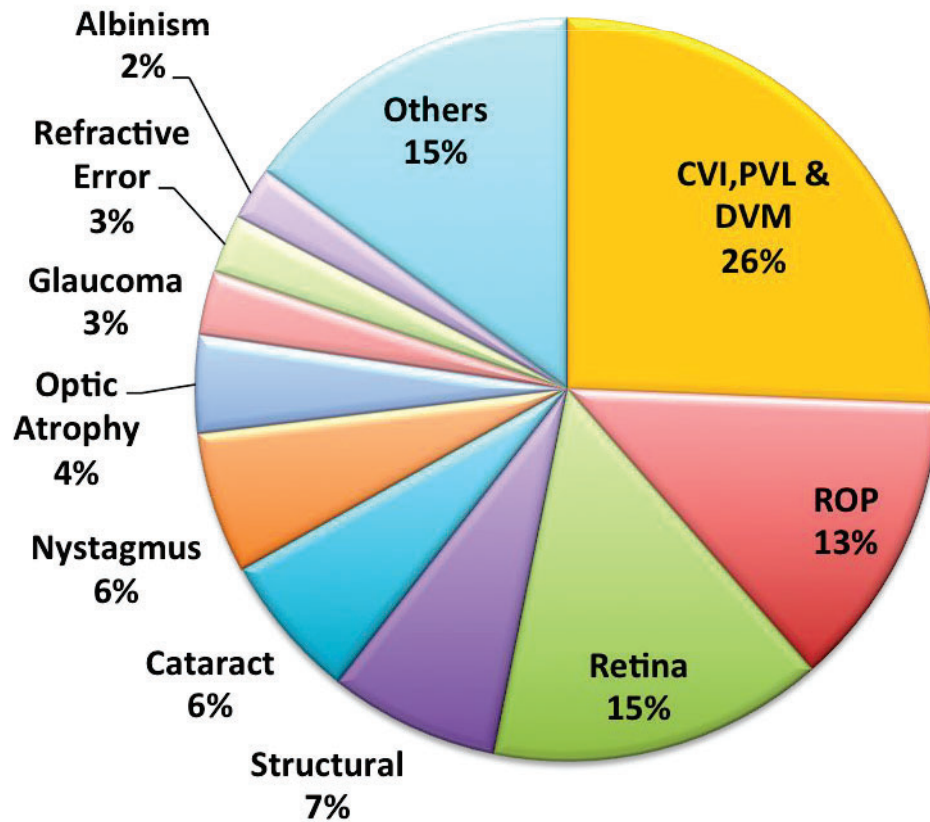


# What is CVI?

- Cerebral or Cortical or Neurological?
- Dysfunction, anomaly, or injury to retro-geniculate pathways
- Ocular impairment does not explain VI.



# CVI



Most common cause of visual impairment in developed countries, but also increasing in developing countries as there is improved intensive care for neonates

**Babies Count**  
*The National Registry  
 for Children With  
 Visual Impairments,  
 Birth to 3 years*

Deborah Hatton, Ph.D., & Sarah Ivy, M.Ed.  
 Vanderbilt University

Burt Boyer, M.A.  
 American Printing House for the Blind



September 2012  
 National Data

# Additional Risks of the infant born premature for brain damage

- Perinatal asphyxia
- Intracranial hemorrhage (IVH)
- Intrauterine exposure to toxins, drugs
- Intrauterine infection (TORCH), Zika
- **Prematurity (especially <2000 g)**
- **Very low birth weight (<1500 g)**
- Kernicterus
- **Hypoglycemia**
- Syndromes/genetic disorders
- Seizure disorder

# ROP: A CNS neurovascular disease?

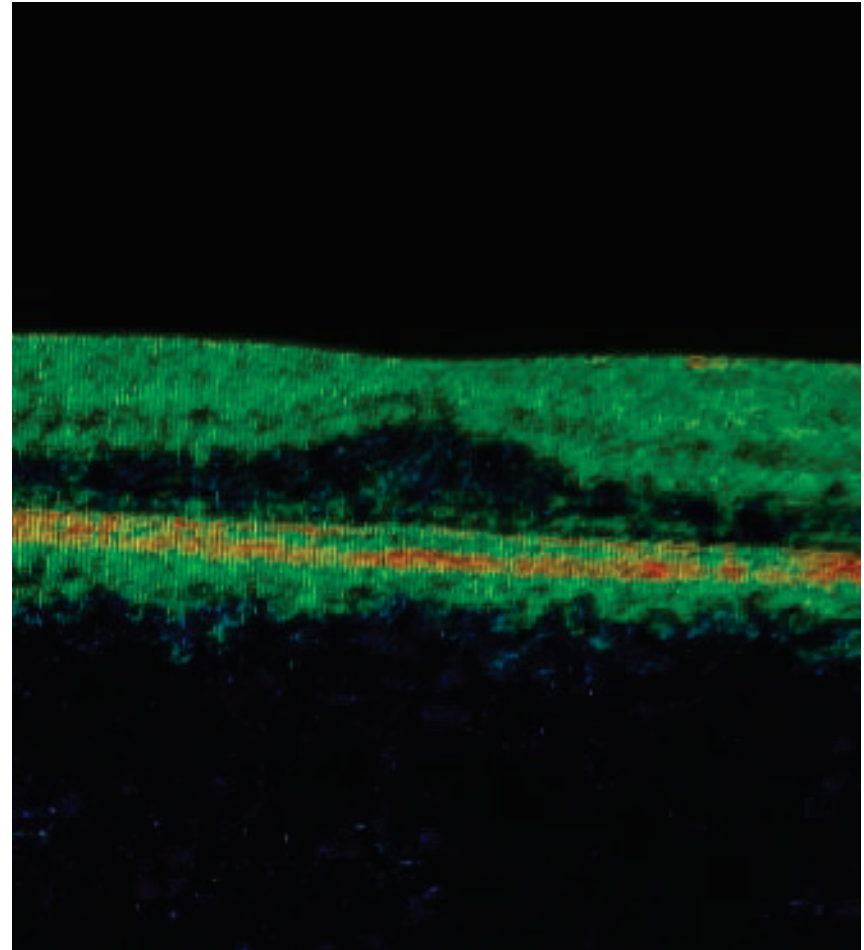
- Retina is part of the Central nervous system
- ROP is associated with other cerebral lesions
- Neurodevelopmental disorders in 50-70% of very preterm infants
- Is ROP a risk factor, or can it be associated or a predictor of NVI?

IGF-1 in retinopathy of prematurity, a CNS neurovascular disease, Liefel et al, *Early Hum Dev.* 2016 November; 102: 13-19

# OCT

- Pathological persistence of inner retinal layers in fovea and increased foveal thickness
- ROP with anatomical and visual classification does not correlate with VA outcomes later

IGF-1 in retinopathy of prematurity, a CNS neurovascular disease, Liefel et al, *Early Hum Dev.* 2016 November; 102: 13-19



Macula OCT of 10 yo with ROP treated and CVI

Is the visual impairment ocular,  
brain based, or combined?

And how do we measure it?



available at [www.sciencedirect.com](http://www.sciencedirect.com)



[www.elsevier.com/locate/earlhumdev](http://www.elsevier.com/locate/earlhumdev)



## Application of a neonatal assessment of visual function in a population of low risk full-term newborn

Daniela Ricci <sup>a,b,\*</sup>, Domenico M.M. Romeo <sup>c,1</sup>, Francesca Serrao <sup>d</sup>,  
Laura Cesarini <sup>a</sup>, Francesca Gallini <sup>d</sup>, Francesco Cota <sup>d</sup>, Daniela Leone <sup>a</sup>,  
Antonio A. Zuppa <sup>d</sup>, Costantino Romagnoli <sup>d</sup>,  
Frances Cowan <sup>b</sup>, Eugenio Mercuri <sup>a,b</sup>

- 124 low risk term babies
- 38-41 weeks gestational age
- $48 \pm 8$  hours
- 50 infants examined also at  $72 \pm 8$  hours
- 110 (89%) babies completed the assessment

# How early is early?

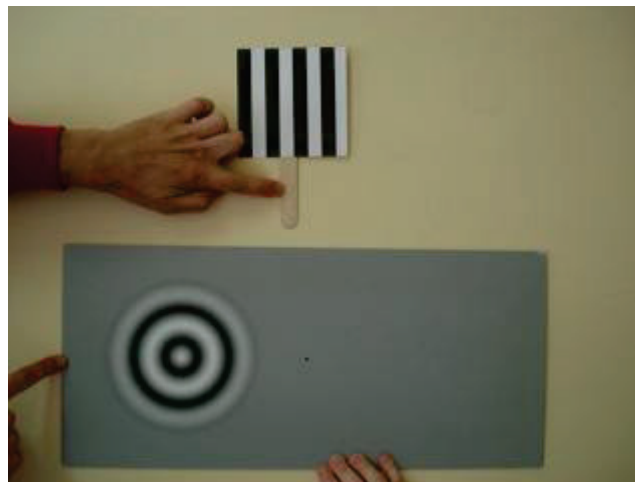
Daniela Ricci MD.

- Fixing and tracking

Already present in preterm babies at 30-32 weeks of gestational age

## Maturation:

- 30-32 : fix and track for a brief arc
- 35-36: track for a horizontal and a vertical arc
- 38: track in a circle



Early Hum Dev. 2010 Jan;86(1):29-33. Epub 2010 Jan 6, Ricci, D et al  
***Early assessment of visual function in preterm infants: how early is early?***

# **Neonatal** assessment of visual function: ideally

## **MARIANI FOUNDATION PROJECT**

- Structured protocol
- Assessing several aspects of visual function
- Short
- Easy even for people not used to visual function
- Requiring small equipment
- Easy to use in difficult settings (NICU-incubator) – easy to clean
- Reliable

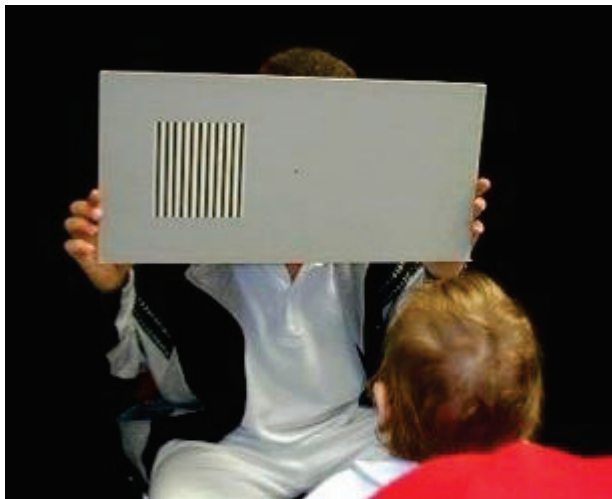
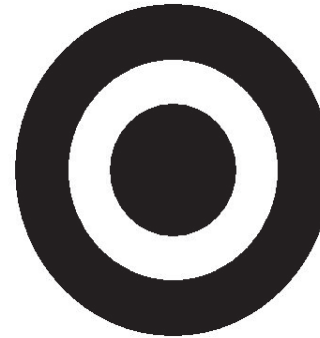
# MARIANI FOUNDATION PROJECT

Development of an Italian network for early visual function:  
diagnosis, follow up and research

Aim of this project is to create an Italian pediatric visual function network in order to:

- agree on a library of protocols to be used according to the different etiology or involvement of visual function, for diagnosis, follow up and plans of intervention in infants with isolated CVI or with concomitant ocular involvement
- provide training for large maternity centers with excellent standards of neonatal care but less experienced in visual assessment
- establish common elements for the creation of a dataset that will facilitate data collection and sharing
- identify normal and abnormal development of visual function in relation to specific patterns of brain lesions

# Neonatal visual assessment: targets





## Early assessment of visual function in full term newborns

Daniela Ricci <sup>a,b</sup>, Laura Cesarini <sup>a</sup>, Michela Groppo <sup>c</sup>, Agnese De Carli <sup>c</sup>,  
Francesca Gallini <sup>d</sup>, Francesca Serrao <sup>d</sup>, Monica Fumagalli <sup>c</sup>, Frances Cowan <sup>b</sup>,  
Luca A. Ramenghi <sup>c</sup>, Shirley Anker <sup>e</sup>, Eugenio Mercuri <sup>a,b,\*</sup>, Fabio Mosca <sup>c</sup>

Table 2 Final proforma with instruction

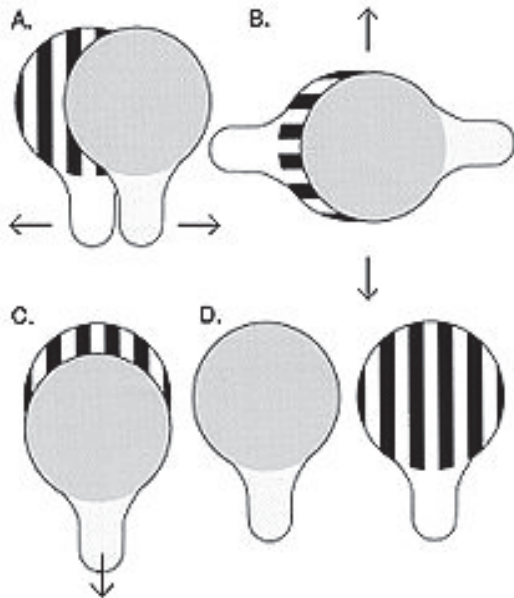
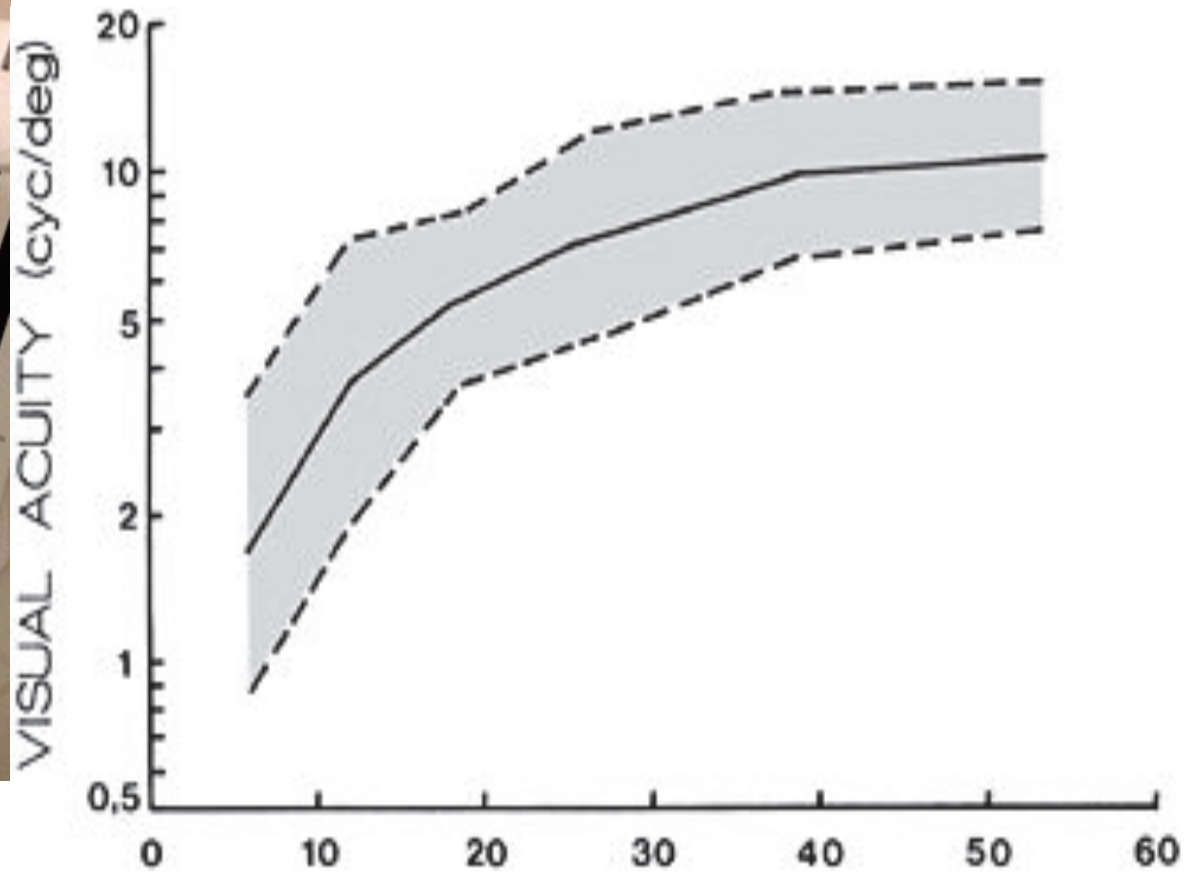
|   |                                                                                                                                                                                                                                         |   | Mainly conjugated         | Occasional strabismus | Occasional/lateral nystagmus | Intermittent Strabismus | Nystagmus | Continuous Strabismus | Nystagmus |
|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------|-----------------------|------------------------------|-------------------------|-----------|-----------------------|-----------|
|   |                                                                                                                                                                                                                                         |   |                           |                       |                              |                         |           |                       |           |
| 1 | Spontaneous ocular motility: note spontaneous ocular movements before presenting a target                                                                                                                                               |   |                           | R                     | L R                          | L R                     | L R       | L R                   | L         |
| 2 | Ocular movements with a target: note ocular movements while presenting the target                                                                                                                                                       |   | Mainly conjugated         | Occasional strabismus | Occasional/lateral nystagmus | Intermittent Strabismus | Nystagmus | Continuous Strabismus | Nystagmus |
| 3 | Fixation: with the target in front of the infant at 25 cm, note the ability of the infant to fix on the target<br>Tracking — black/white target                                                                                         |   | Stable (>3 s)             | Unstable (<3 s)       |                              | Absent                  |           |                       |           |
|   | Tracking: note the infant's eye movement in response to the target movements                                                                                                                                                            |   |                           |                       |                              |                         |           |                       |           |
| 4 | Horizontal: with the target at 25 cm and starting in the midline move it slowly to both left and right                                                                                                                                  | → | Complete                  | Incomplete            |                              | Brief                   |           | Absent                |           |
| 5 | Vertical: with the target at 25 cm, and starting in the midline move it slowly upwards and downwards                                                                                                                                    | ↑ | Complete                  | Incomplete            |                              | Brief                   |           | Absent                |           |
| 6 | Arc: with the target at 25 cm, move it slowly tracing an arc                                                                                                                                                                            |   | Complete                  | Incomplete            |                              | Brief                   |           | Absent                |           |
|   | Colour/discrimination/attention                                                                                                                                                                                                         |   |                           |                       |                              |                         |           |                       |           |
| 7 | Tracking coloured stimulus: note the infant's eye movement in response to the target movements, starting from the midline towards lateral                                                                                               |   | Present                   | Absent                |                              |                         |           |                       |           |
| 8 | Stripes discrimination: note the infant's ability to fixate on a series of targets of decreasing stripe widths held at a distance of 38 cm starting with the widest stripe; note the narrowest stripe width on which the infant fixates |   | Last card identified..... |                       |                              |                         |           |                       |           |
| 9 | Attention at distance: after eliciting central fixation move the target slowly away and a few cm laterally from the infant and note the maximal distance at which focusing is maintained                                                |   | Cm.....                   |                       |                              |                         |           |                       |           |

# Response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome

Liana O. Ventura, MD, PhD,<sup>a,b</sup> Linda Lawrence, MD,<sup>c</sup> Camila V. Ventura, MD,<sup>a,b</sup> Gordon N. Dutton, MD, FRCOphth,<sup>d</sup> Polyana Marinho, MD,<sup>a</sup> Priscila F. Ferro, MD,<sup>a</sup> Adriana L. Gois, MD,<sup>a,b</sup> Natalia C. Dias, MD,<sup>a</sup> Larissa Ventura, MD,<sup>a</sup> Cynthia A. Moore, MD,<sup>e</sup> and Lea Hyvärinen, MD<sup>f</sup>  
(J AAPOS 2017;21:480-484)

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|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PURPOSE</b>     | To describe the immediate response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome (CZS).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>METHODS</b>     | Children born between May and December 2015 with a confirmed diagnosis of CZS and enrolled in a multidisciplinary early intervention program were included in this study. All children received a comprehensive ophthalmic examination, including dynamic retinoscopy and cycloplegic refraction. Children were prescribed their full correction if they met the criteria for refractive error, and additional plus 3.00 overcorrection for strabismus, accommodative dysfunction, and/or low vision. Monocular and binocular visual responses to Lea Grating Test at 30 cm, with and without eyeglasses, were measured on day 1 of glasses wear.                                                                                                                                                                                                                                   |
| <b>RESULTS</b>     | A total of 60 children were evaluated (mean age at evaluation, $11.5 \pm 1.1$ months; range, 9.0-16.0 months). Lea Grating Test responses were abnormal in all children prior to spectacle correction. Hypoaccommodation was present in 17 of 21 children (81%). Overcorrection was prescribed for all children. Visual responses were subnormal even with glasses use; however, immediate improvement in binocular vision was found in 37 children (62%) and in 74 of 119 eyes (62.2%). For the monocular visual improvement, 27 of 115 eyes (23.5%) had structural abnormalities, and 44 of 115 eyes (38.3%) were structurally normal. There was a statistical difference between the cycloplegic refraction of the children in August and in November, including emmetropia ( $P = 0.001$ ), hyperopia ( $P = 0.000$ ), myopia ( $P = 0.007$ ), and astigmatism ( $P = 0.004$ ). |
| <b>CONCLUSIONS</b> | Eyeglasses can improve visual acuity in children with CZS. Significant changes in their refractive status over time requires periodic updates. (J AAPOS 2017;21:480-484)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |



# Evaluation: Visual Developmental Milestones

Table 1. Visual development milestone of children with congenital Zika syndrome (n = 119) and healthy controls (n = 85)

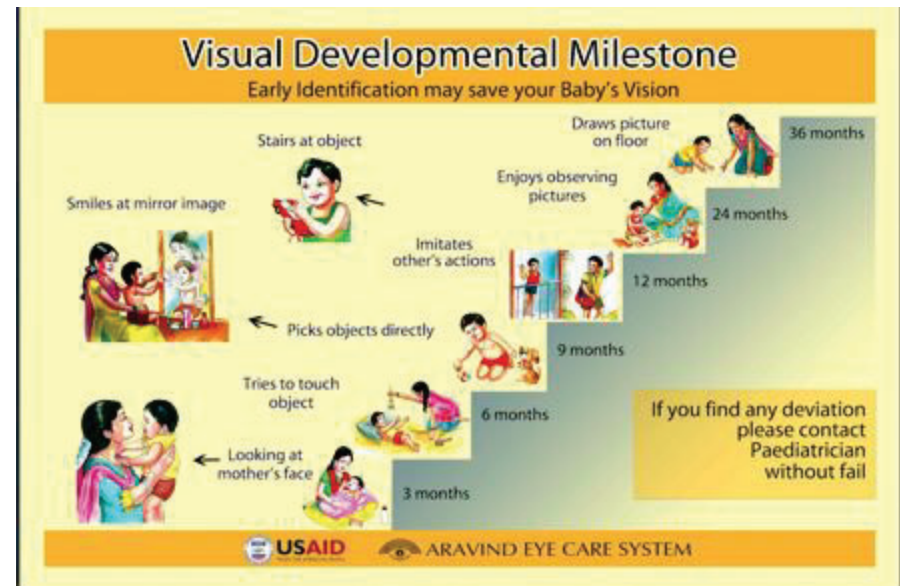
| Visual milestone                          | CZS group<br>(n = 119) | Control group<br>(n = 85) | P value <sup>a</sup> |
|-------------------------------------------|------------------------|---------------------------|----------------------|
| 8 Weeks: eye contact,<br>n (%)            | 91/104 (87.5)          | 79/79 (100.0)             | <0.001               |
| 3 months                                  |                        |                           |                      |
| Social smile                              | 57/106 (53.8)          | 78/80 (97.5)              | <0.001               |
| Regards hands                             | 27/107 (25.2)          | 79/80 (98.8)              | <0.001               |
| 5-6 months                                |                        |                           |                      |
| Goal directed reach                       | 29/107 (27.1)          | 79/80 (98.8)              | <0.001               |
| Moves to reach                            | 27/107 (25.2)          | 78/79 (98.7)              | <0.001               |
| Hands to the midline                      | 15/107 (14.0)          | 78/79 (98.7)              | <0.001               |
| 7-10 months                               |                        |                           |                      |
| Regard to facial<br>features <sup>b</sup> | 26/96 (27.1)           | 64/68 (94.1)              | <0.001               |
| 11-12 months <sup>c</sup>                 |                        |                           |                      |
| Reach for a dangling<br>object            | 1/2 (50.0)             | 3/3 (100.0)               | NA                   |

CZS, congenital Zika syndrome; NA, not applicable.

<sup>a</sup>Pearson's  $\chi^2$  test.

<sup>b</sup>Does not apply to age for 6 patients in study group and 9 patients in control group.

<sup>c</sup>Does not apply to age for 116 patients in study group and 73 in control group.



- From Deborah Chen PhD  
kanlovkids.org and  
Dr. Lea personal  
correspondence, AAO.org

# Case Studies

BW 540, 23 wk. GA  
post bevacizumab, age 1year old



Delayed visual  
maturation, expected  
because of extreme  
prematurity

High risk for CVI

Close developmental  
follow-up

# Treatment Options: Primary Prevention

- Decrease preterm birth
- Modify or treat risk factors



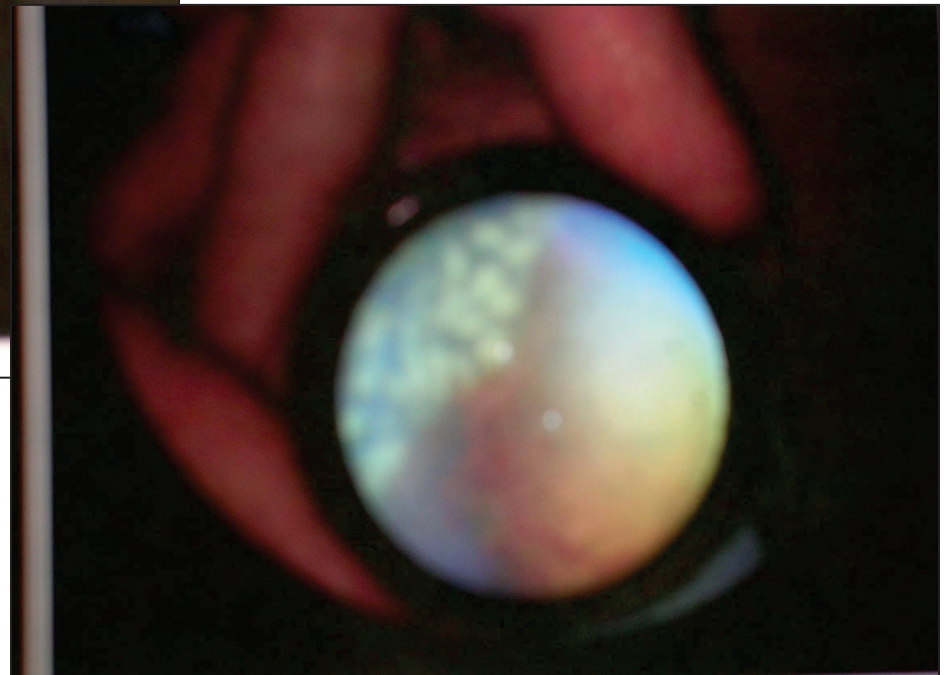
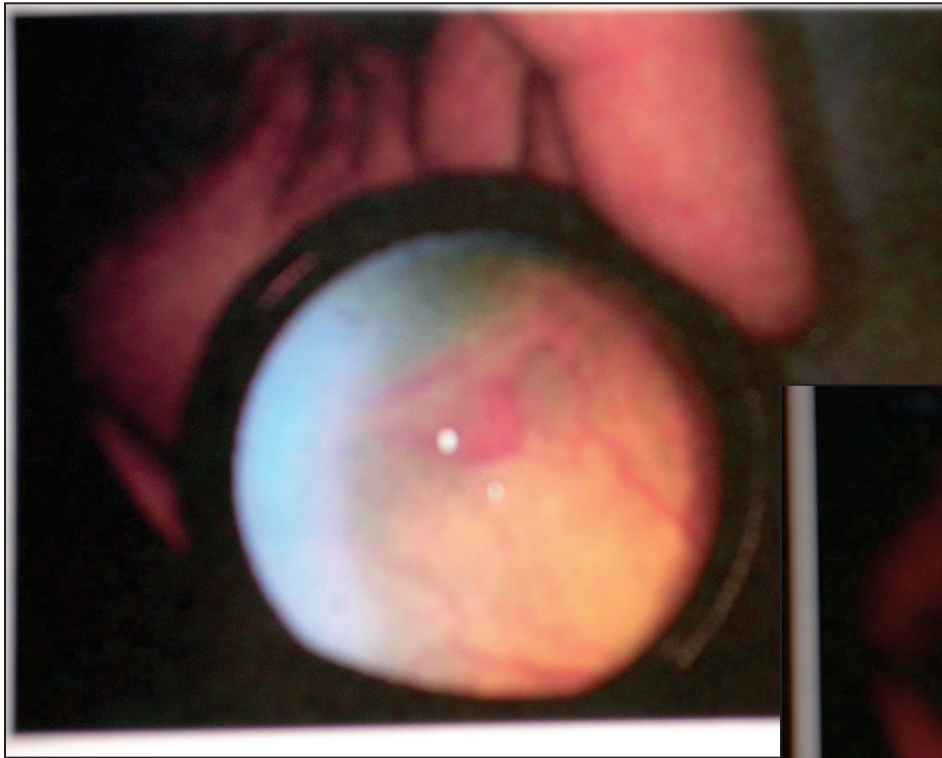
# Current Treatment Options

- Retinal ablation
  - Laser photocoagulation of retina
  - Cryotherapy
- Intravitreal Anti-VEGF injections
  - Avastin
  - Lucentis

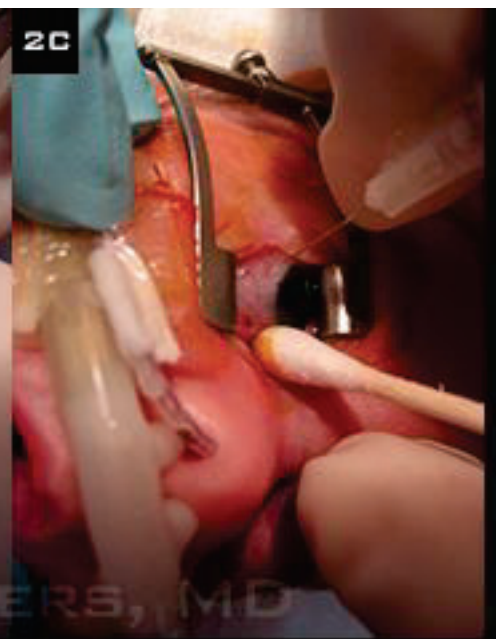
# When a baby needs treatment for ROP

- Consider treating in OR or neonatal ICU
- Arrange Pediatric anesthesiologist/neonatologist for sedation
- Presence of treating physician (pediatric ophthalmologist or retina specialist)
- Informed Consent from parents
- Treatments: diode laser machine or intravitreal injection Avastin/Lucentis

# Treatment: ROP laser photocoagulation







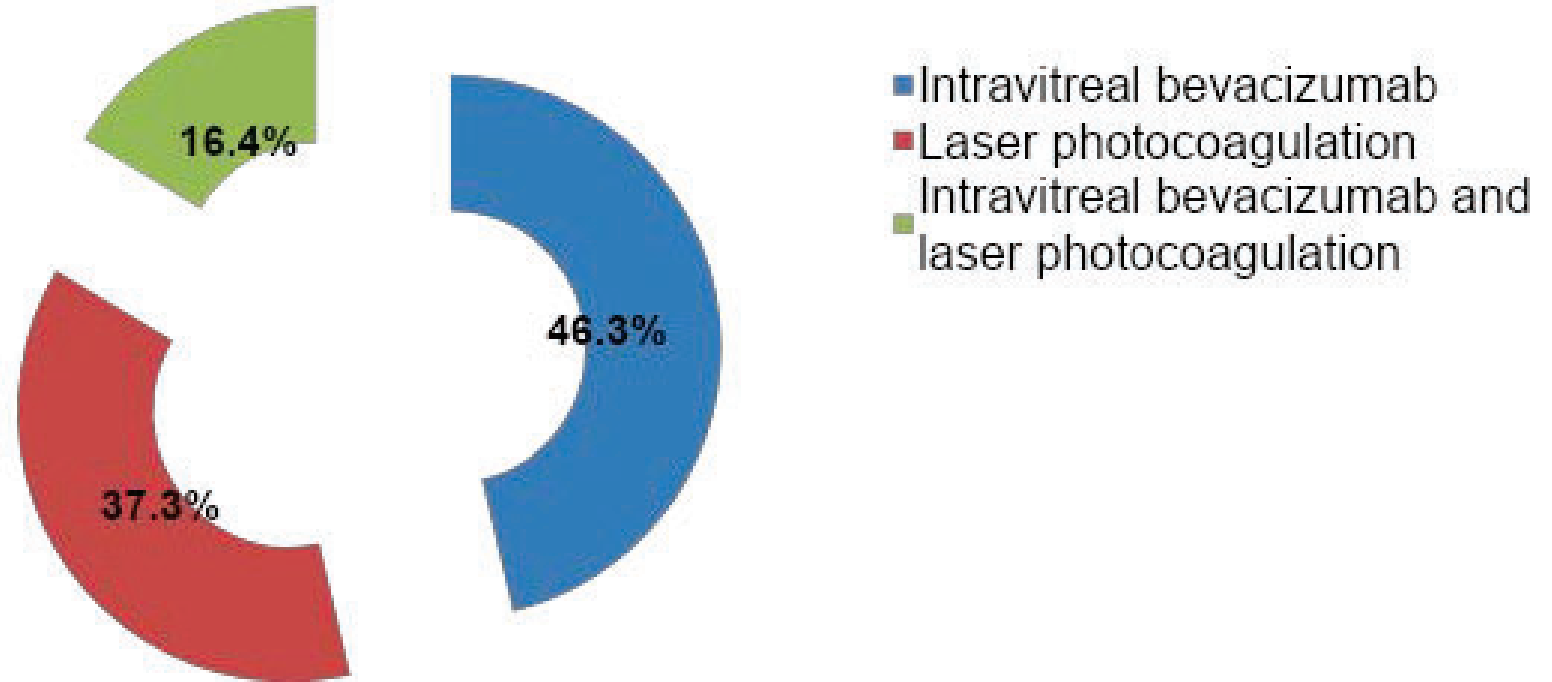
# Treatment: Intravitreal anti-VEGF injection

- Anti-VEGF medicines have not been approved by the FDA to treat children, so its use is called **off-label**
- Current recommendations (2013):
  - Consideration may be given to treatment of infants with zone I, stage 3+ ROP with intravitreal injection of Avastin (bevacizumab)
  - Detailed informed consent as there remains unanswered questions involving dosage, timing, safety, visual outcomes and other long-term effects
  - Monitor weekly until the retina is fully vascularized

# Clinical Trials: Intravitreal anti-VEGF Injection

- **Beat ROP Study**: Established the role of anti-VEGF (Avastin) in the treatment of ROP
- Pediatric Eye Disease Investigators Group (PEDIG) has an ongoing clinical trials with Avastin to study the least dose required in treating ROP
- Novartis pharmaceutical has an ongoing clinical trial with Lucentis in treating ROP

# Web-Survey: For infants with type 1 ROP, nearly 50% physicians prefers Avastin as primary monotherapy

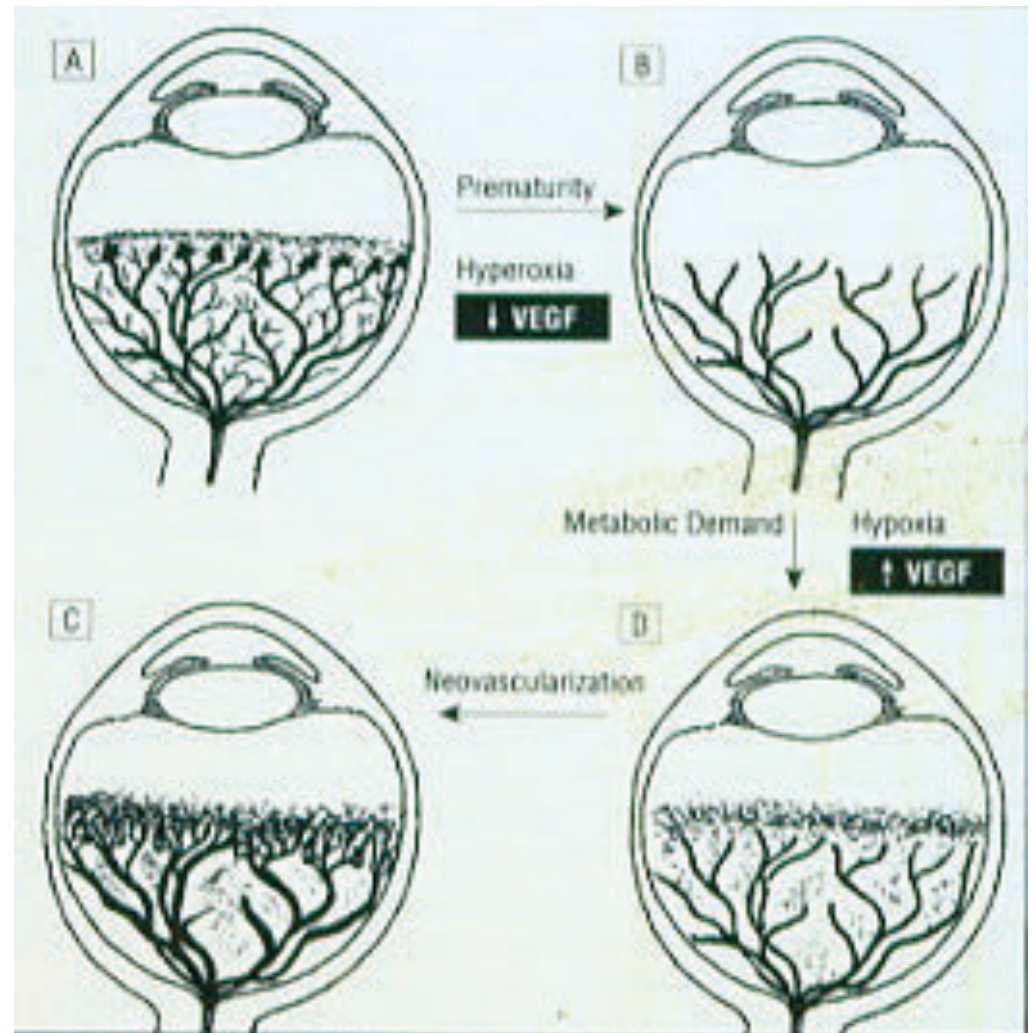


Courtesy: Swati Agarwal-Sinha, MD

# Anti-VEGF treatment for ROP

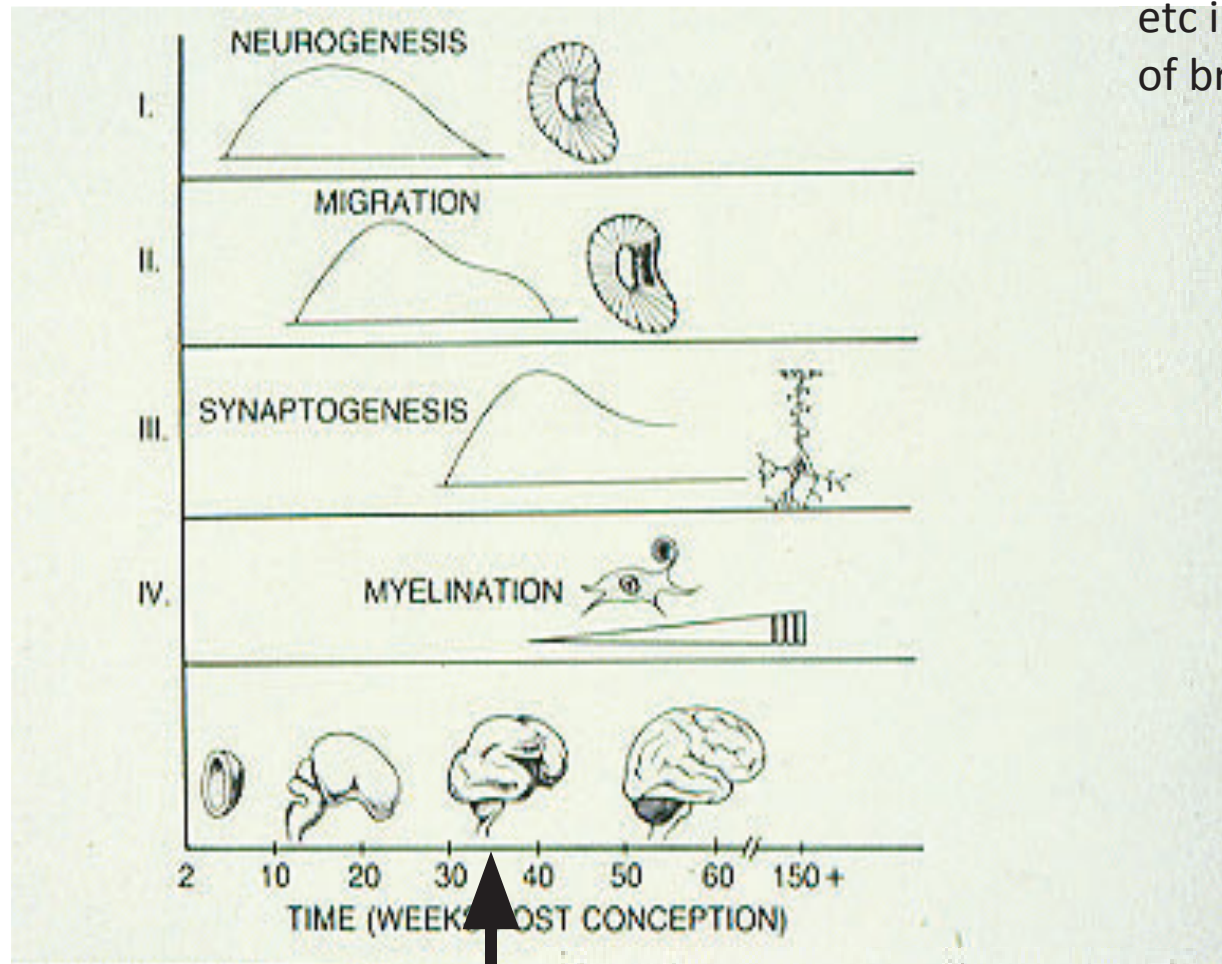
- There are a number of angiogenic factors reported to be involved in mouse oxygen induced retinopathy (OIR) models
- Vascular endothelial growth factor (VEGF) is one of the factors involved in the pathogenesis of ROP

Courtesy G Gole



# Angiogenesis

Angiogenesis is also involved in neurogenesis, synaptogenesis, etc involved in the development of brain, besides ROP

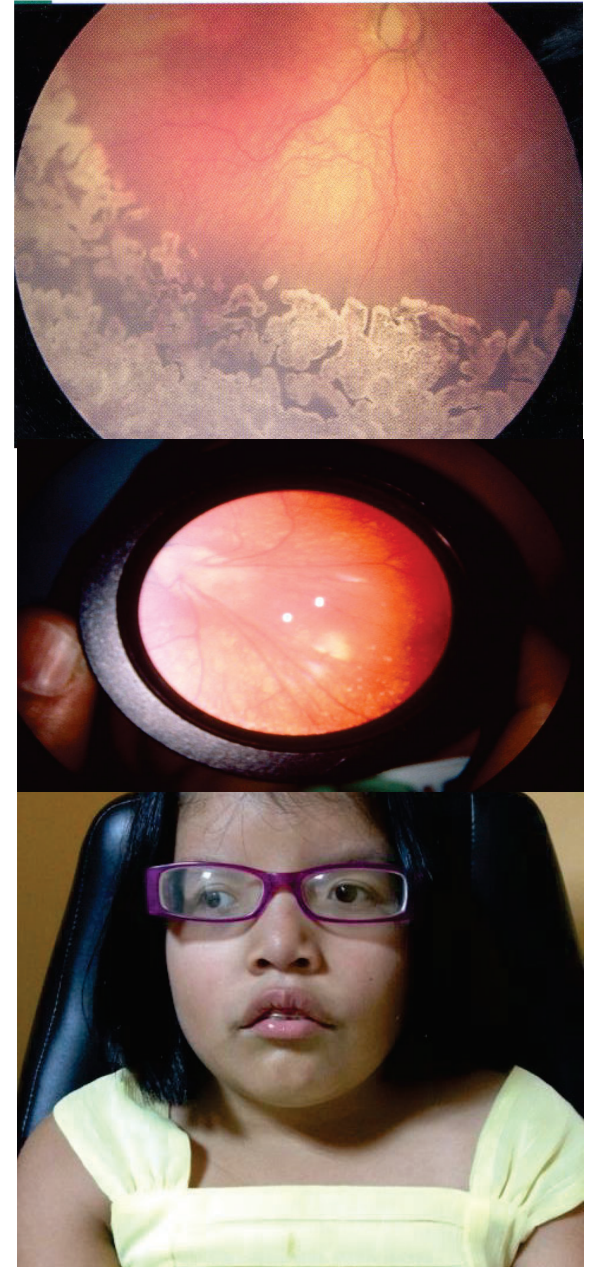


ROP most severe

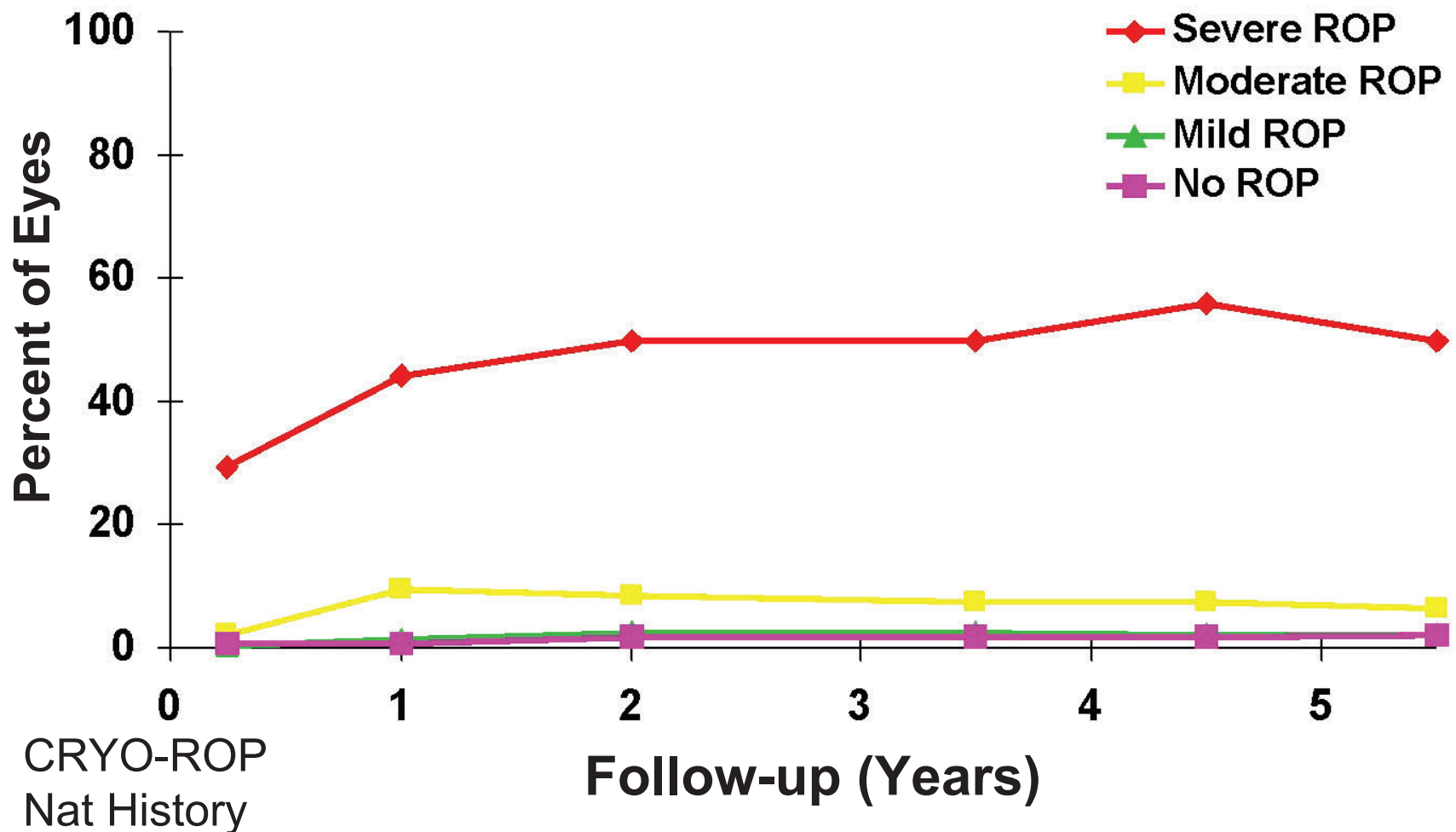
Courtesy G Gole

# Long term sequelae of ROP

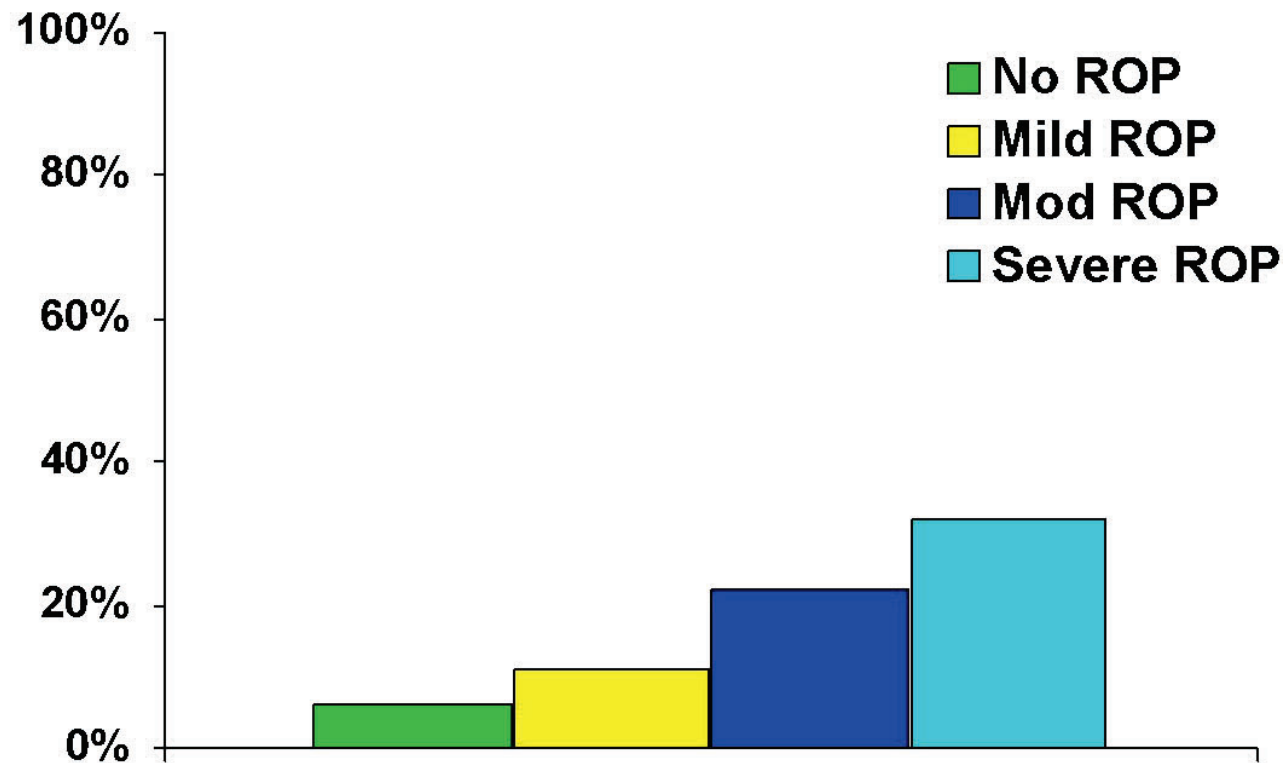
- Myopia (near-sightedness)- need for full time glasses to see at distance
  - Risk higher with Laser photocoagulation
- Anisometropia- leading to risk of lazy eye (amblyopia)
  - Risk higher with Laser photocoagulation
- Restriction of peripheral visual fields
  - Risk higher with Laser photocoagulation
- Macular dragging (compromising the central reading/ writing vision)
- Eccentric fixation causing misalignment of eyes (strabismus)
- Astigmatism (needing glasses full time)



# Prevalence of high myopia in preterm Children ( $\geq 5.0D$ )



# Strabismus in preterm children with BW <1251g



AT 1 YEAR EXAM

CRYO-ROP  
Nat History

# Retinopathy of prematurity

## School age



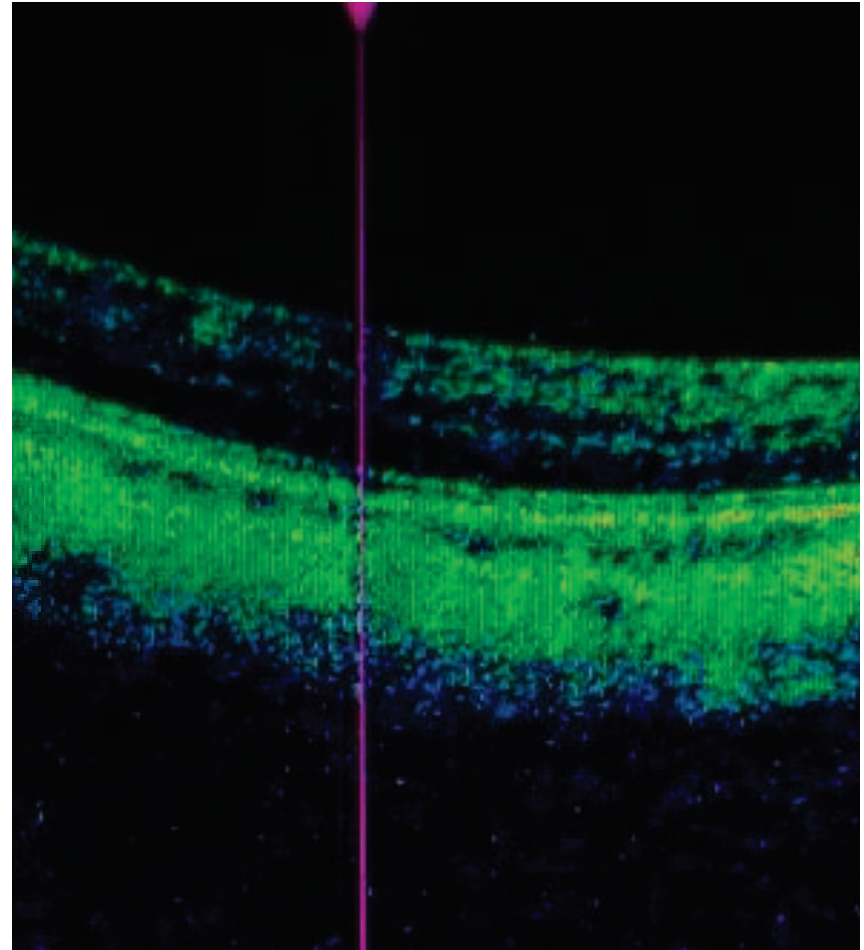
- Delightful young lady
- 13 years
- Birth weight 520 gms, 1lb 2 oz, 24 weeks
- NICU course difficult, chest tube
- ROP diode laser ou
- Stage 5 OD NLP
- Stage 3 OS, threshold with extensive diode laser -15.50, macular dragging
- In regular classroom
- Parents have elected no contact sports

# Retinopathy of Prematurity

## School age

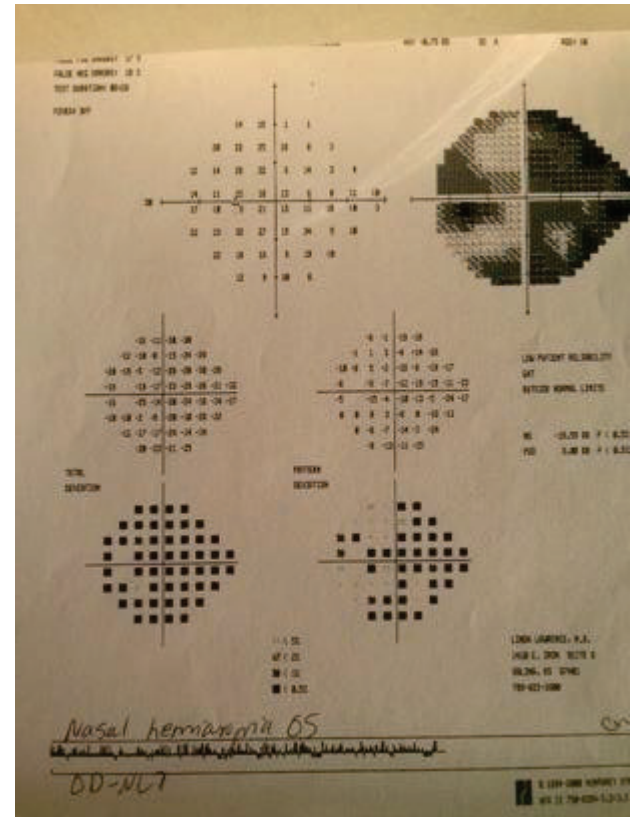


**Interventions**  
**Orientation and Mobility!!**  
**Educational plan by TVI with IEP team**



Macula OCT age 12 you

- Able to do visual field !



# Front of the Eye



# Retinopathy of prematurity

## School age challenges



- **Poor self esteem: teach to advocate for self**
- **Thick glasses further distorted vision**
- **Participated in refractive surgery trial**
- **Now -4.00, can read without glasses and functional vision and social interactions with peers improved**

# Refractive Surgery in Children

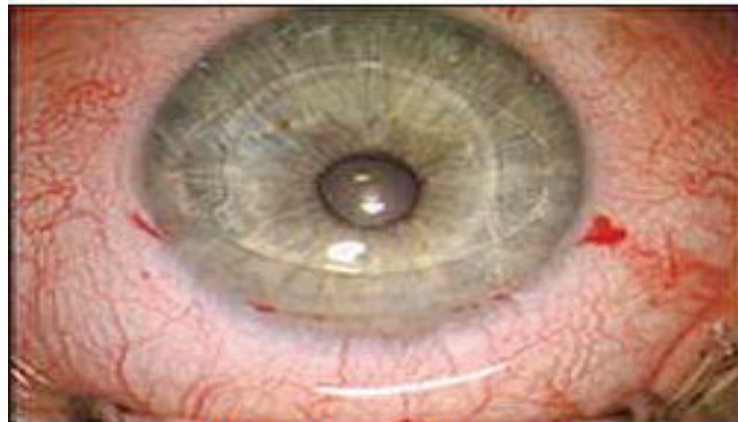
- Ethical considerations
- Possibilities

## Past treatments

- Glasses
- Contact lenses
- Bifocals!
- Phakic lens implant
- Lasik
- Secondary lens implants in aphakes

# Pediatric Refractive Surgery

Lasik, PRK

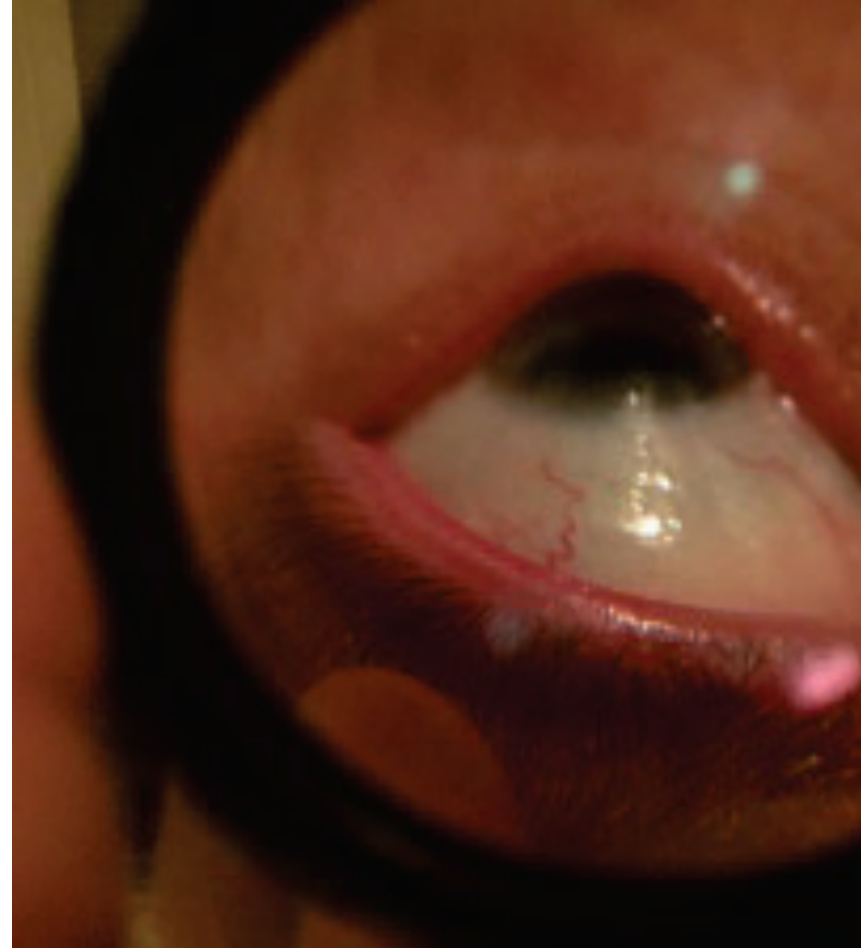


**Artisan IOL** implanted in pediatric eye.

Phakic lens implants



# Keratoconus



# What is keratoconus?

- A condition in which the cornea begins to thin and bulge in a cone shape
  - Symptoms develop around puberty
  - More common in Down syndrome (71%)
- Past treatments
- Glasses
  - Contact lenses
  - Corneal transplant

# Keratoconus

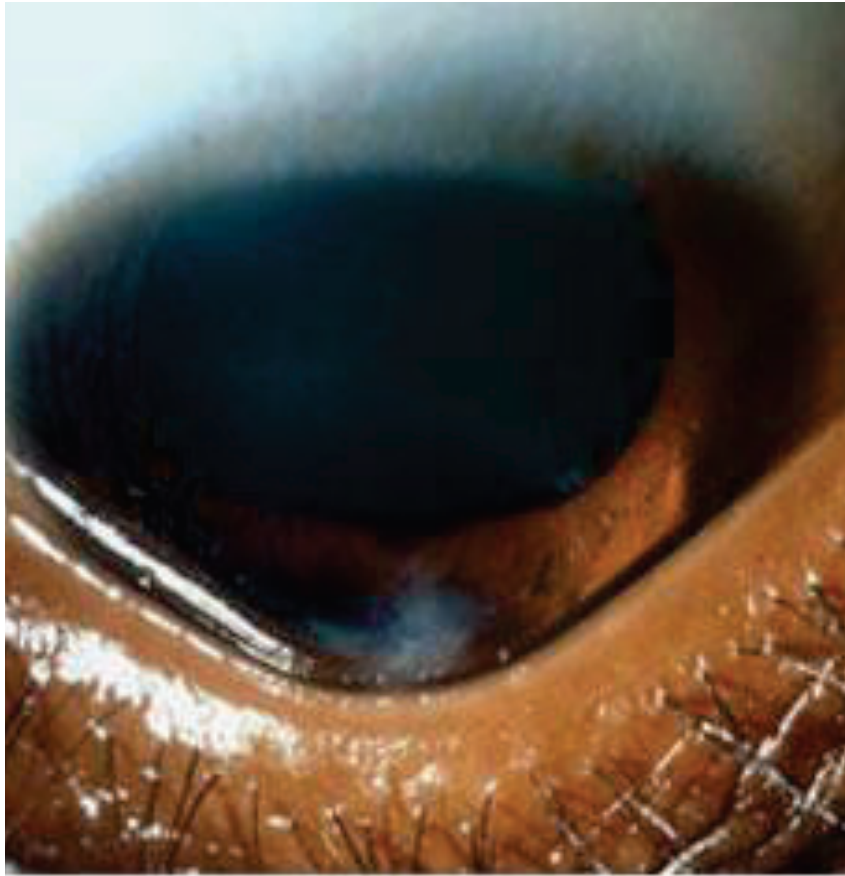
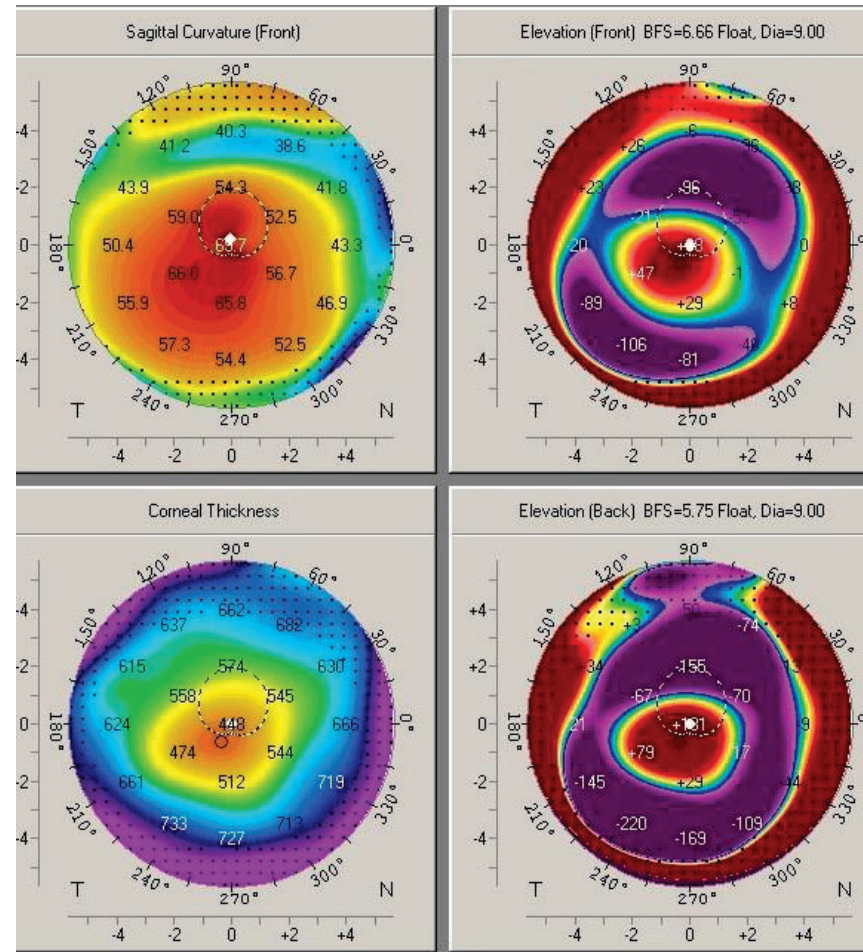
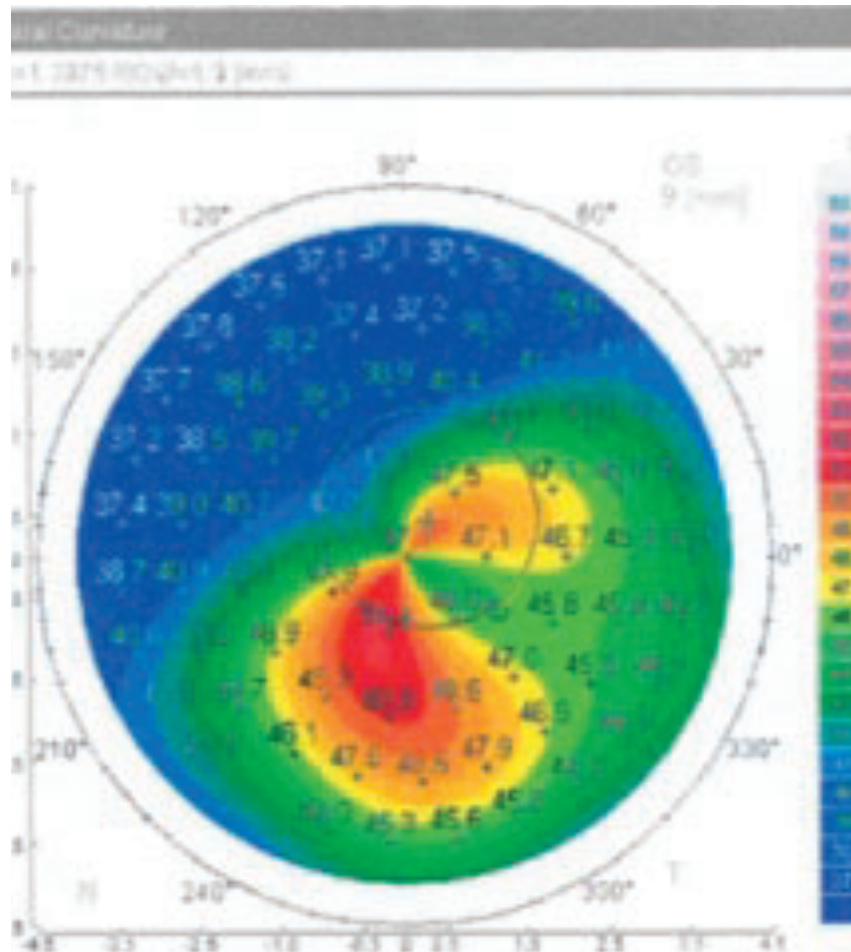


fig. 1 keratoconus

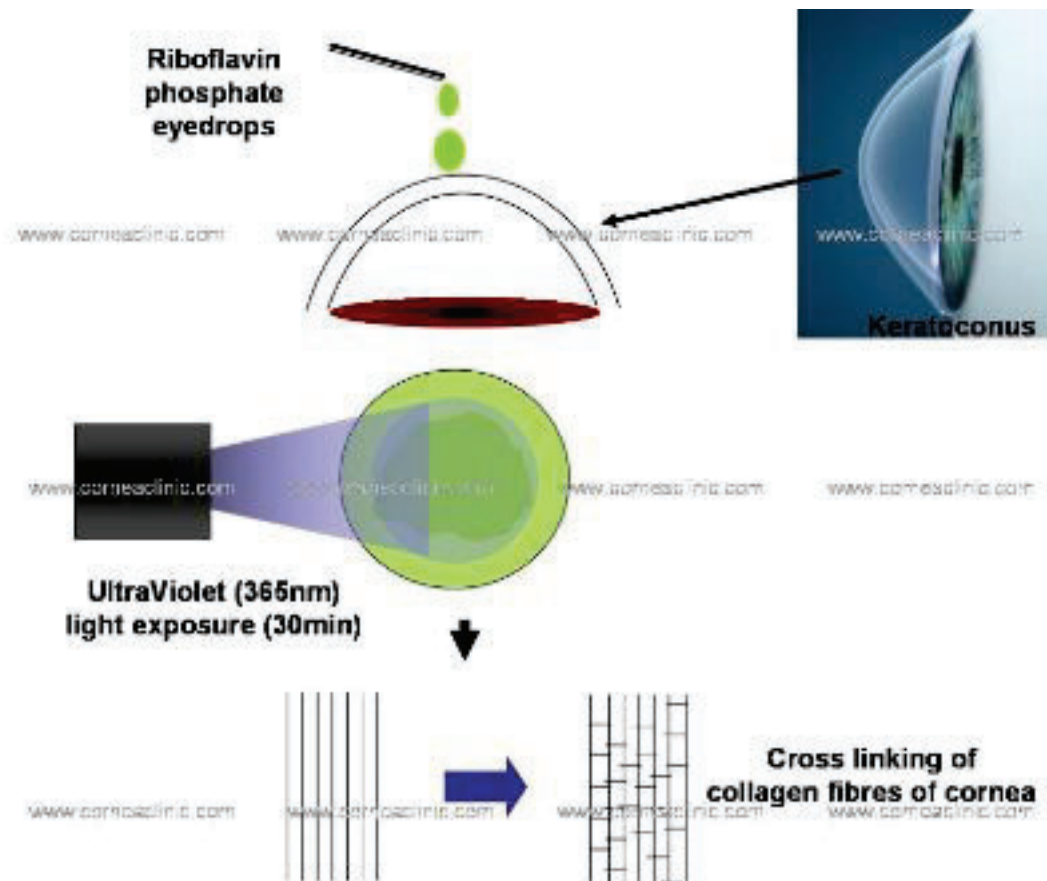
- Degenerative
- Type of corneal ectasia or dystrophy
- 1/2000
- Sporadic or inherited (10%) AD or AR
- Comorbidities: Down syndrome, atopy, Marfan's, Lebers congenital amaurosis



# Corneal cross linking (CXL)

- Combination of vit B2 drops and ultraviolet light applied to corneal over controlled length of time
- Procedure takes about an hour
- In children general anesthesia





# Corneal Crosslinking

- Now FDA approved
- Careful evaluation
- Doesn't cure, stabilizes

Why do infants wear glasses and  
how to talk to parents.

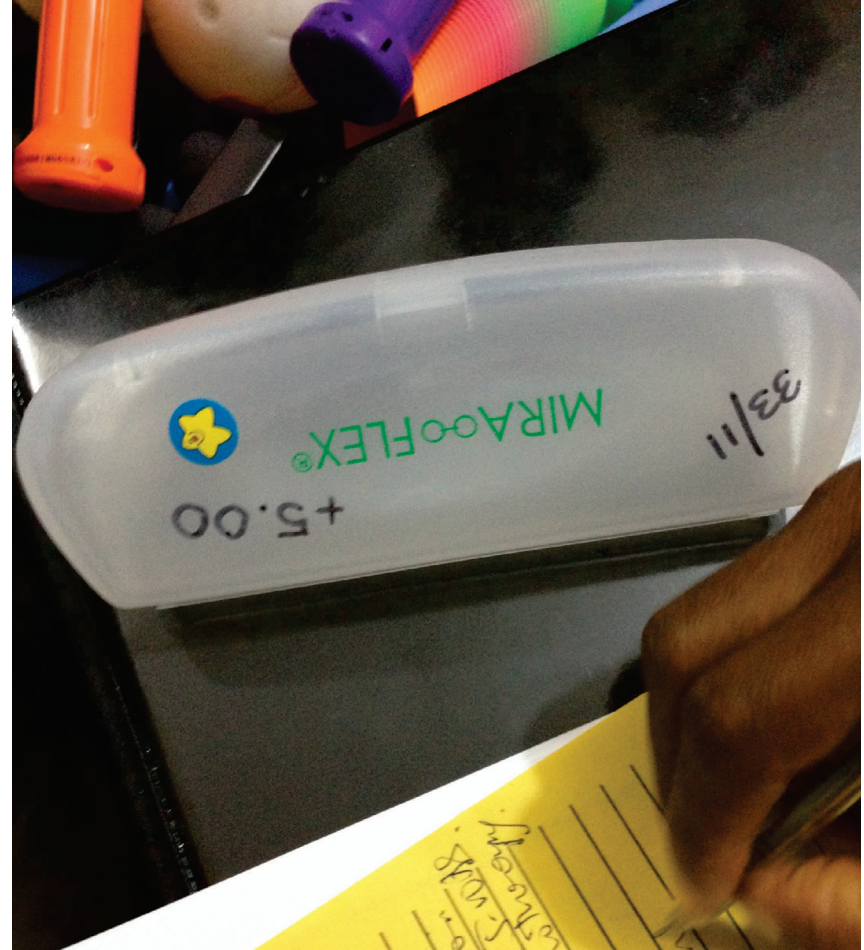
# Response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome

Liana O. Ventura, MD, PhD,<sup>a,b</sup> Linda Lawrence, MD,<sup>c</sup> Camila V. Ventura, MD,<sup>a,b</sup> Gordon N. Dutton, MD, FRCOphth,<sup>d</sup> Polyana Marinho, MD,<sup>a</sup> Priscila F. Ferro, MD,<sup>a</sup> Adriana L. Gois, MD,<sup>a,b</sup> Natalia C. Dias, MD,<sup>a</sup> Larissa Ventura, MD,<sup>a</sup> Cynthia A. Moore, MD,<sup>e</sup> and Lea Hyvärinen, MD<sup>f</sup>  
(J AAPOS 2017;21:480-484)

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|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <b>PURPOSE</b>     | To describe the immediate response to correction of refractive errors and hypoaccommodation in children with congenital Zika syndrome (CZS).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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# Lack of Accommodation measure it!



# Glasses??

- Do a refraction and think about it!
- Dynamic retinoscopy....

Prior to dilation with correction

- Cycloplegic refraction
- Children with Low Vision deserve it!



## Cycloplegic refraction with appropriate prescription of glasses



- Make sure child is comfortable and supported
- Document difference in child's behaviors
- Trial set may be helpful
- Individualize for child's needs

# Significant refractive errors



What is a significant refractive error?

Who made the rules?

1998

## Consensus of AAPOS members but only 68% responded

Pediatric Eye Evaluations (page 9 of 49)

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Refractive correction should be prescribed for children according to the following guidelines.  
*(discretionary recommendation, insufficient evidence)*

**Guidelines for Refractive Correction in Infants and Young Children**

| Condition                                                      | Refractive Errors (diopters) |               |               |
|----------------------------------------------------------------|------------------------------|---------------|---------------|
|                                                                | Age <1 year                  | Age 1-2 years | Age 2-3 years |
| <b>Isoametropia</b><br>(similar refractive error in both eyes) |                              |               |               |
| Myopia                                                         | -5.00 or more                | -4.00 or more | -3.00 or more |
| Hyperopia (no manifest deviation)                              | +6.00 or more                | +5.00 or more | +4.50 or more |
| Hyperopia with esotropia                                       | +2.50 or more                | +2.00 or more | +1.50 or more |
| Astigmatism                                                    | 3.00 or more                 | 2.50 or more  | 2.00 or more  |
| <b>Anisometropia (without strabismus)*</b>                     |                              |               |               |
| Myopia                                                         | -4.00 or more                | -3.00 or more | -3.00 or more |
| Hyperopia                                                      | +2.50 or more                | +2.00 or more | +1.50 or more |
| Astigmatism                                                    | 2.50 or more                 | 2.00 or more  | 2.00 or more  |

NOTE: These values were generated by consensus and are based solely on professional experience and clinical impressions because there are no scientifically rigorous published data for guidance. The exact values are unknown and may differ among age groups; they are presented as general guidelines that should be tailored to the individual child. Specific guidelines for older children are not provided because refractive correction is determined by the severity of the refractive error, visual acuity, and visual symptoms.

\* Threshold for correction of anisometropia should be lower if the child has strabismus. The values represent the minimum difference in the magnitude of refractive error between eyes that would prompt refractive correction.

# Refraction



- Based on 1% cyclopentolate refraction • Full: anisometropia, astigmatism, myopia
- Hyperopia – Fully correct (primarily for ET)
- OR – Under-correct symmetrically\*
- \*no more than 1.50 D for most PEDIG studies

# Proper fitting

**Wrap around**



poorly fitting cable temples on left and well fitting cables on right.

# Proper fitting

**Smashes eye closed**



**Proper fitting**



# Accommodative Esotropia



- including prescription of bifocals as indicated

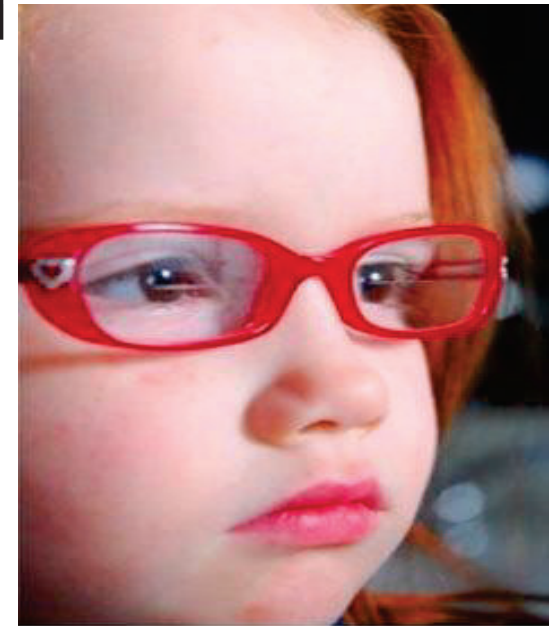


Figure 3: Well fitting bifocal.

# Anisometropia/amblyopia



Bifocals in children with Down syndrome (BiDS) – visual acuity, accommodation and early literacy skills Krithika Nandakumar and Susan J. Leat School of Optometry, University of Waterloo, Ontario, Canada Acta Ophthalmol. 2010; 88: e196–e204

Although preliminary and longitudinal in nature, the current study gives evidence of **superior focusing, better near VA, improved literacy skills** over time and enhanced school performance as a result of bifocal prescription in children with DS.

The children adapt well to bifocal wear.

**Bifocals** should be considered in the clinical management of children and teenagers with DS.

More long-term studies are required to demonstrate whether long-term bifocal wear would improve absolute VA.

Dev Med Child Neurol. 2000 Oct;42(10):701-3.

Reduced accommodative function in dyskinetic cerebral palsy: a novel management strategy.

[Ross LM](#)<sup>1</sup>, [Heron G](#), [Mackie R](#), [McWilliam R](#), [Dutton GN](#)

A 9-year-old boy with **dyskinetic cerebral palsy** secondary to neonatal encephalopathy is described. He presented with **blurring of near vision** which had begun to impact on his school work. Objective assessment of accommodation showed that very little was present, although convergence was almost normal. The near-vision symptoms were completely removed and reading dramatically improved with the provision of varifocal spectacles. **Varifocal** lenses provide an optimal correction for far, intermediate (i.e. for computer screens), and near distances (i.e. for reading). Managing this type of patient with varifocal spectacles has not been previously reported. It is clearly very important to prescribe an optimal spectacle correction to provide clear vision to optimize learning.

# Other uses for glasses in children with low vision

1. magnification for low vision
2. “blinder” effect of thick frames for those with attention deficits
3. Protection from injury
4. Transition lenses or tints for photophobia
5. Individualize!

# Questions the families need answers to :

1. What are the glasses for?
2. Does the family and educational team understand when the glasses are to be worn?
3. What is the expected outcome of the glasses?
4. Do they promote visual, social, motor, communication skills?
5. How do we assess this outcome?
6. What are the family QOL issues?
7. What is the role for refractive surgery?



## Basic Principles of eyeglass wear

Each child is unique.

The visual pathways are the sensory channel responsible for much of the information the infant/toddler receives.

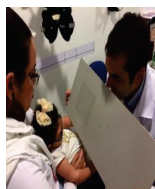
Glasses are prescribed for a variety of optical, medical, and functional reasons. Proper fitting of glasses enhances wear.

The reasons for the glasses prescription and wearing should be understood by parents, educators, and therapists to help facilitate their proper use and enhance development of vision as well as overall development.



## Common Questions about Infant/ Toddler Glasses

1. What are the glasses for?
2. Do the glasses promote social, motor, communication, or adaptive skill development?
3. What is the expected outcome and who accesses the outcome?  
(What can the child do better with the glasses wear that could not do before?)
4. When are the glasses to be worn and do parent's and team understand?
5. What are the hardships for the family and child and how do we overcome these?



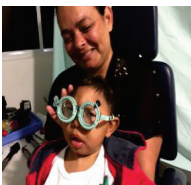
Teller cards for acuity



Cycloplegic refraction



LEA GRATINGS



Trial Lenses

## Why are glasses prescribed?

Rarely is vision considered as a contributing factor when developmental delay is suspected.

There is little consensus as to the best method of assessing vision in young children with neurological delay or disability, or the prescribing of eyeglasses.

I continue to be amazed at how refractive correction can improve function in children with developmental delay.

**1. Significant refractive error**, with evaluation not only according to published consensus standards for typically developing babies, but for the individual baby's needs.

Myopia (nearsighted), Hyperopia (farsighted), anisometropia (different prescriptions in each eye) and astigmatism are common eye conditions that require glasses to help with prevention of amblyopia, and proper development of the visual system, as well as enhance the overall development of the child.

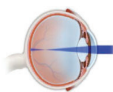
Aphakia may occur after lens removal for congenital cataracts in a baby.

**2. Prevent amblyopia from optical errors in eyes** (very high myopia, high hyperopia, astigmatism that is significant or amblyogenic anisometropia)

### Refractive errors: myopia

In myopia (nearsightedness), there is too much optical power in the eye.

– The distance between the cornea and the retina may be too long or the power of the cornea and the lens may be too strong.  
Light rays focus in front of the retina instead of on it.  
Close objects will look clear, but distant objects will appear blurred.

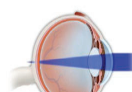


- Myopia, or nearsightedness

### Refractive errors: hyperopia

In hyperopia (farsightedness), there is too little optical power.

– The distance between the cornea and the retina may be too short.  
Light rays are focused behind the retina instead of on it.  
In adults (but not necessarily children), distant objects will look clear, but close objects will appear blurred.

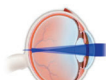


- Hyperopia, or farsightedness

### Refractive errors: astigmatism

• In astigmatism, the cornea is curved unevenly — shaped more like a football than a basketball.

• Light passing through the uneven cornea is focused in two or more locations.  
• Distant and close objects may appear blurry.

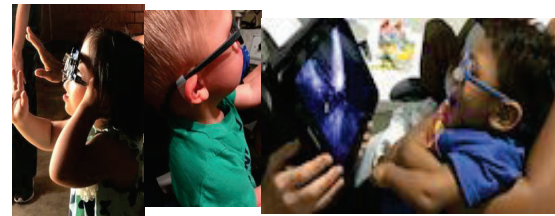


- Astigmatism occurs when light passes through football-shaped cornea and/or lens.

**3. Lack of accommodation (focusing)** measured by dynamic retinoscopy; The difficulty with accommodation may occur because of inadequate neurological direction, lack of motivation or attention to near target by child, seizure medication or medication (hyocine) used to decrease salivation can paralyze pupil and affect accommodation. This means that hyperopia which is typical in a child may not be compensated for: no focusing at near, no compensation for hyperopia, blurred or poor quality of image.



**4. Correction of strabismus (eye turning).** Typically would be accommodative esotropia, may occur earlier in children with neurodevelopmental disabilities, these are typically hyperopic children (plus prescription, or “farsighted”)



## Fitting Tips for glasses

Comfort is important as well as function.



Wrap around

### Proper fitting

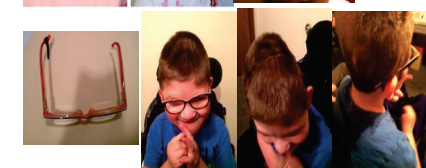


Temple Pieces

Smashes eye closed

Proper fitting

Built-up bridge

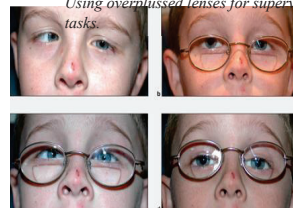


*Baby with congenital Zika virus syndrome and microcephaly. Much improved eye contact with overplussed glasses (+3.00 more than cycloplegic refraction) Worn for near, supervised tasks.*

*Toddler with myopia. Full time wear. Notice the lens minimizes the face.*



*Poor focusing in baby with microcephaly in Africa. Using overplussed lenses for supervised near tasks.*



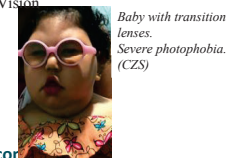
*Hyperopic glasses for strabismus with bifocal. Full time.*

*Notice how magnifies the face.*

*Mom and optician figured out best fit for this child with different ear placement and head shape!*

## OTHER USES FOR GLASSES

1. Protection for children with low vision/blindness
2. Transition or tints for photophobia
3. Magnification for Low Vision
4. “Blinder effect” ??
5. All children are unique.



*Baby with transition lenses. Severe photophobia. (CZS)*

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# ANTEOJOS Neonato a 3 años

Guía para padres de NMSBVI y Dra. Linda Lawrence