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Objectives

Retinopathy of prematurity (ROP) is a major cause of infant blindness worldwide. Therefore, it is essential to have an effective screening programme to identify, in a timely fashion, the infants most at risk for severe ROP.

This module examines **ROP screening** with a focus on which infants to screen, when to screen them, and how to screen them. Also explored are the benefits of a telemedicine approach to ROP screening.

Having completed this module, you will be able to:

- ✓ List the 3 key questions and the 3 fundamental challenges with respect to ROP screening.
- ✓ Identify the relationship between the level of economy in a country and the associated epidemiology of ROP in that country, when identifying infants at high risk for severe ROP.
- ✓ List the criteria types used by countries to define premature infants most at risk for severe ROP.
- ✓ Identify how the criteria, for defining and identifying which infants to screen, typically changes between developed and developing countries.
- ✓ Identify the typical onset of screening infants for ROP in both developed and developing countries, and describe why it is important to adjust the onset of screening according to each countries own demographics.
- ✓ State 4 instances where ROP screening should be typically terminated in infants.
- ✓ List 3 benefits of a telemedicine approach to ROP screening.

Click Next to begin

Module Progress:

Screening for Retinopathy of Prematurity

Introduction to ROP

This module examines **screening for retinopathy of prematurity** (ROP).

Retinopathy of prematurity:

- Is a vasoproliferative disease of the retina
- Affects prematurely-born babies that have typically received intensive neonatal care where oxygen therapy was used
- Is a major cause of infant blindness around the world

Click here to learn more about basic ROP pathophysiology

Example 1: ROP is a vasoproliferative disease of the retina

Use the arrows to scroll through examples

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Example 2: ROP is a vasoproliferative disease of the retina

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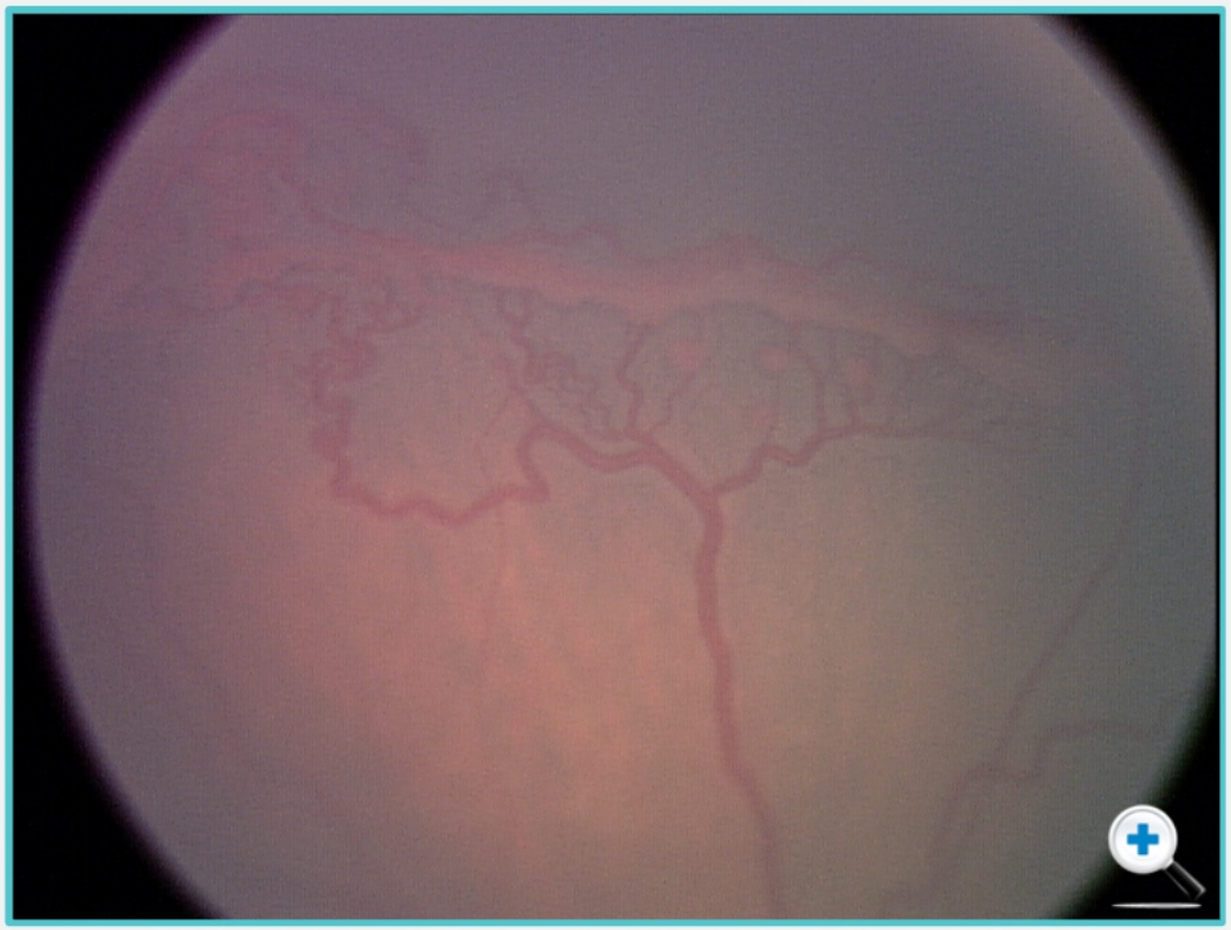
Example 3: ROP is a vasoproliferative disease of the retina



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Example 4: ROP is a vasoproliferative disease of the retina

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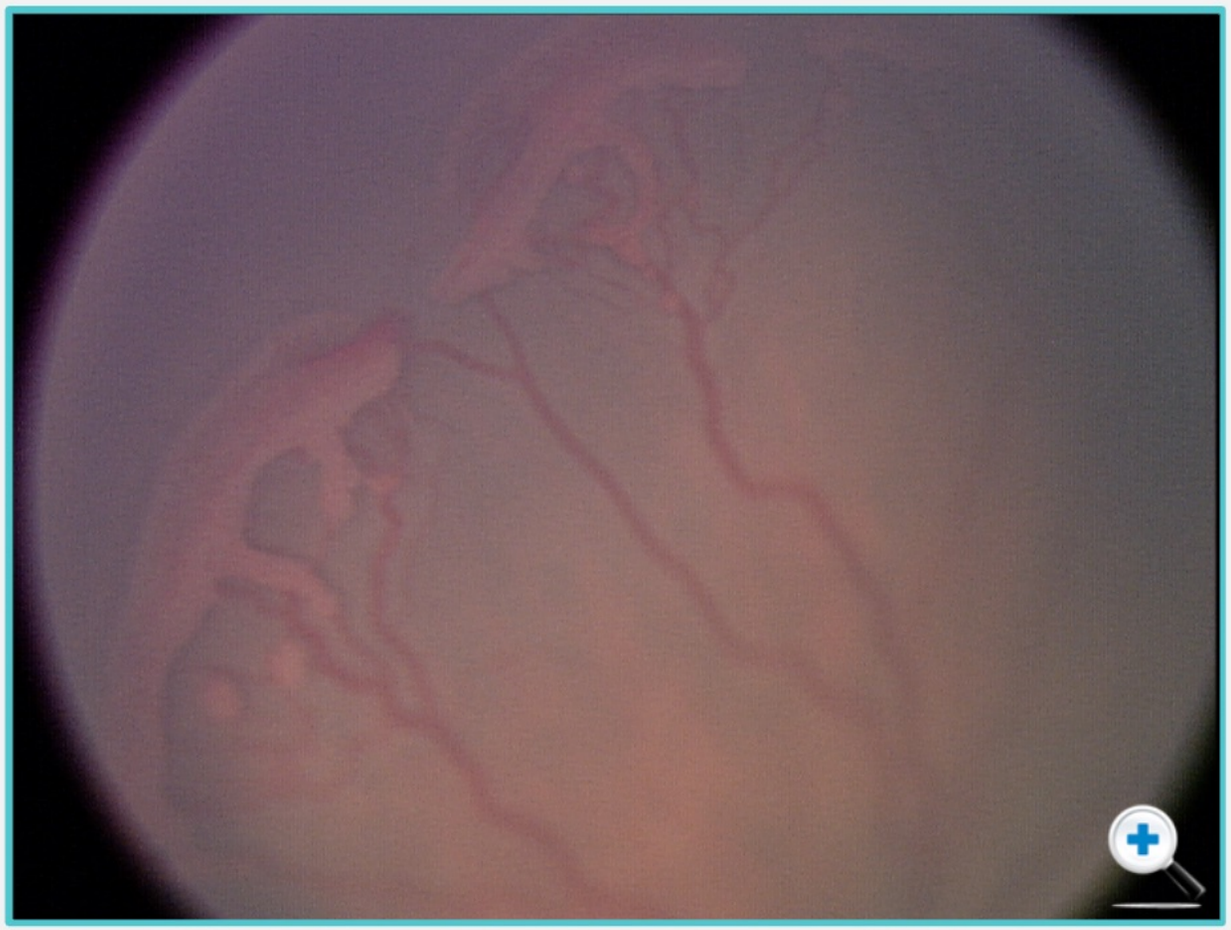
Example 5: ROP is a vasoproliferative disease of the retina



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Example 6: ROP is a vasoproliferative disease of the retina

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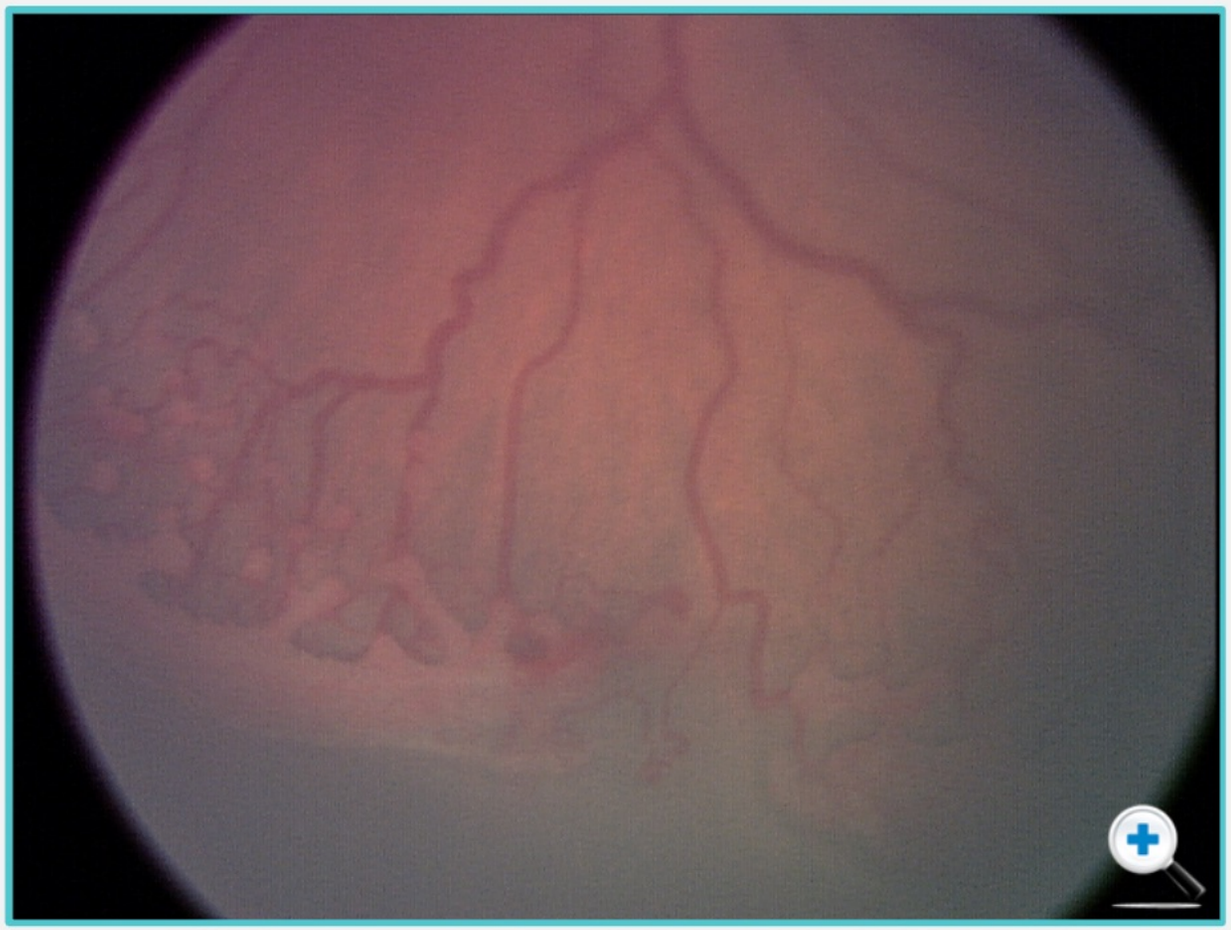
Example 7: ROP is a vasoproliferative disease of the retina



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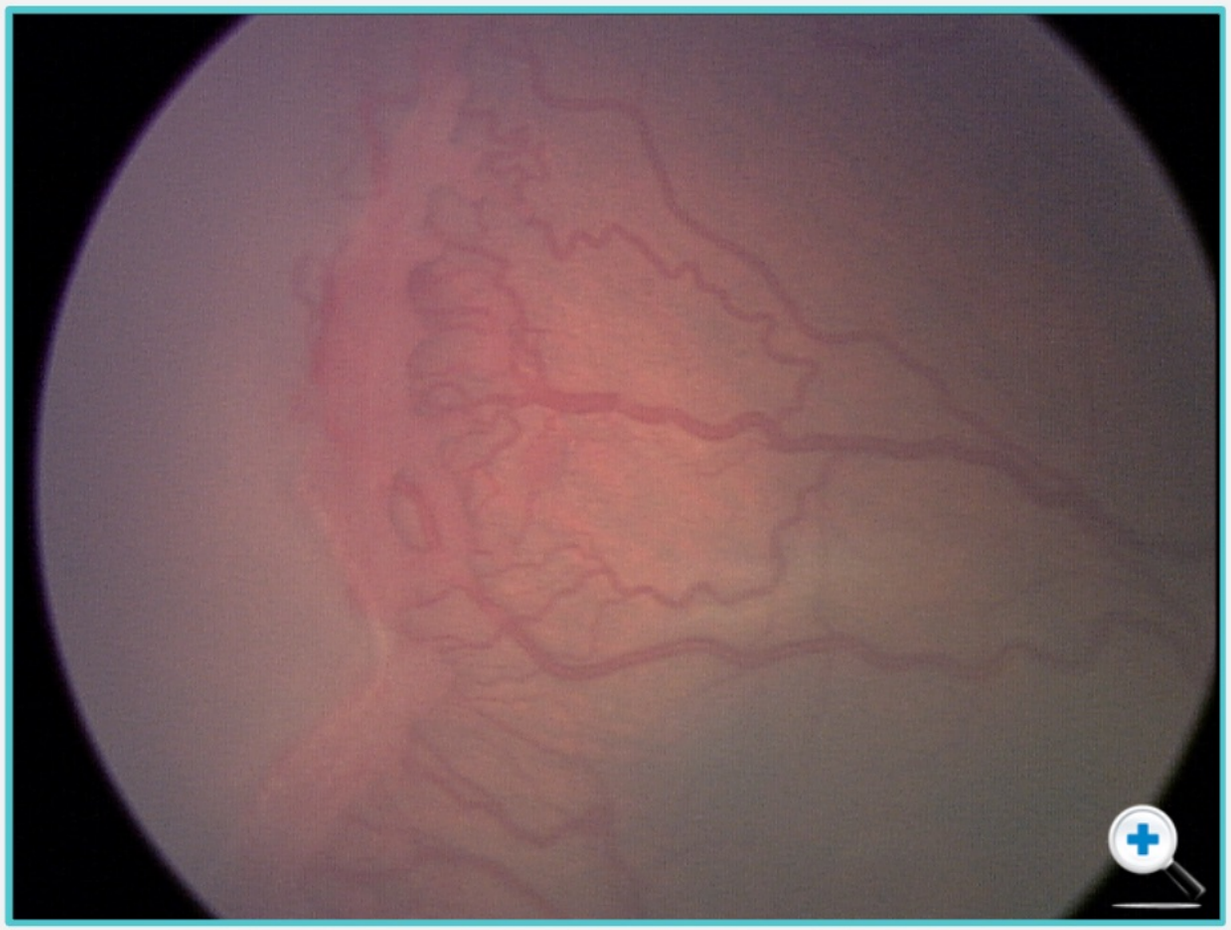
Example 8: ROP is a vasoproliferative disease of the retina



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Introduction to ROP

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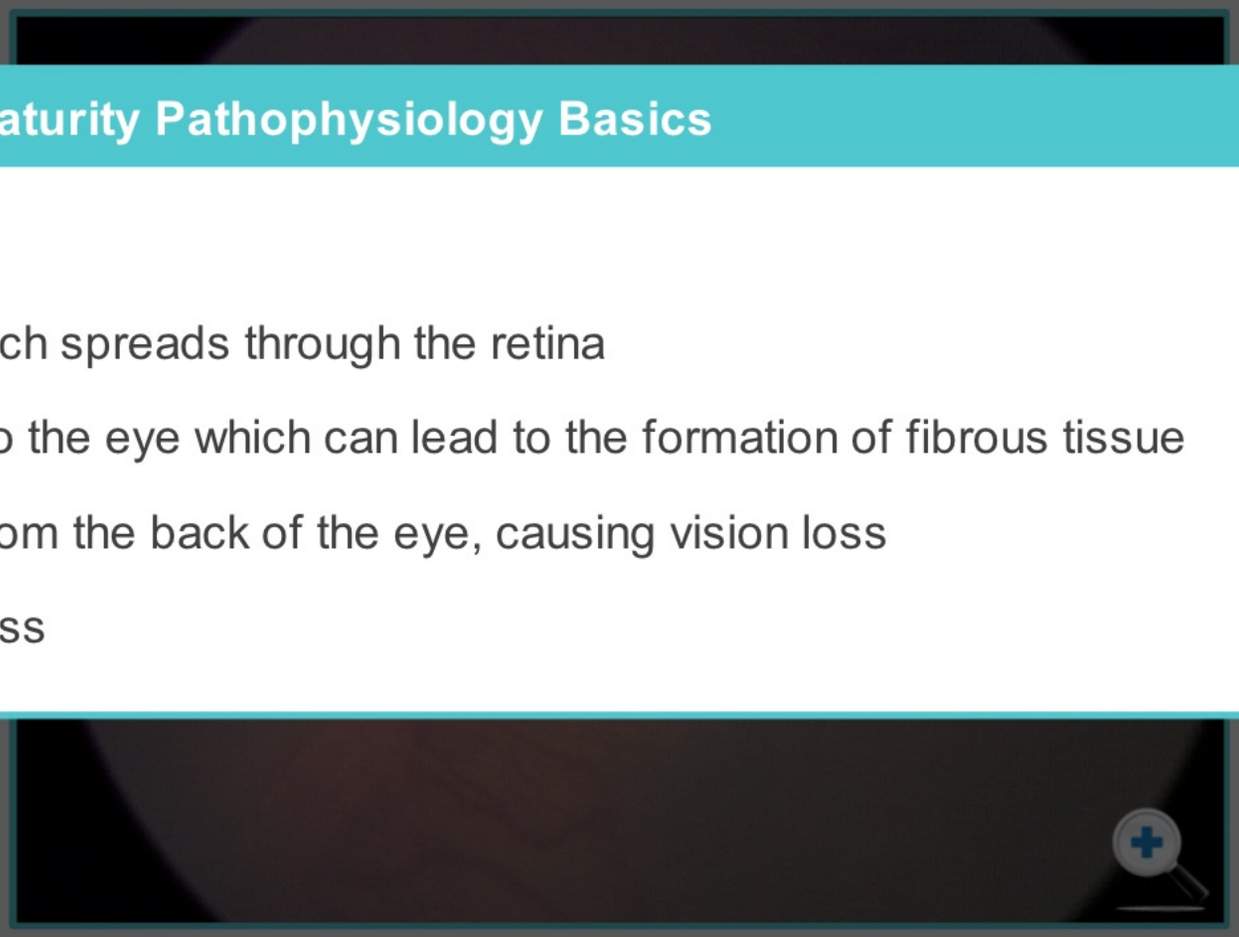
R

Example 8: ROP is a vasoproliferative disease of the retina



Use the arrows to scroll through examples

Retinopathy of Prematurity Pathophysiology Basics

Retinopathy of prematurity:

1. Causes abnormal blood vessel growth which spreads through the retina
2. These fragile blood vessels leak blood into the eye which can lead to the formation of fibrous tissue
3. This scar tissue can pull up on the retina from the back of the eye, causing vision loss
4. In serious cases, ROP can lead to blindness

Click here to learn more about basic ROP pathophysiology

Vision 2020: The Right to Sight

Vision 2020: The Right to Sight is a global programme for the **elimination of avoidable blindness**, launched in 1999 by the World Health Organisation (WHO) and the International Agency for the Prevention of Blindness (IAPB).

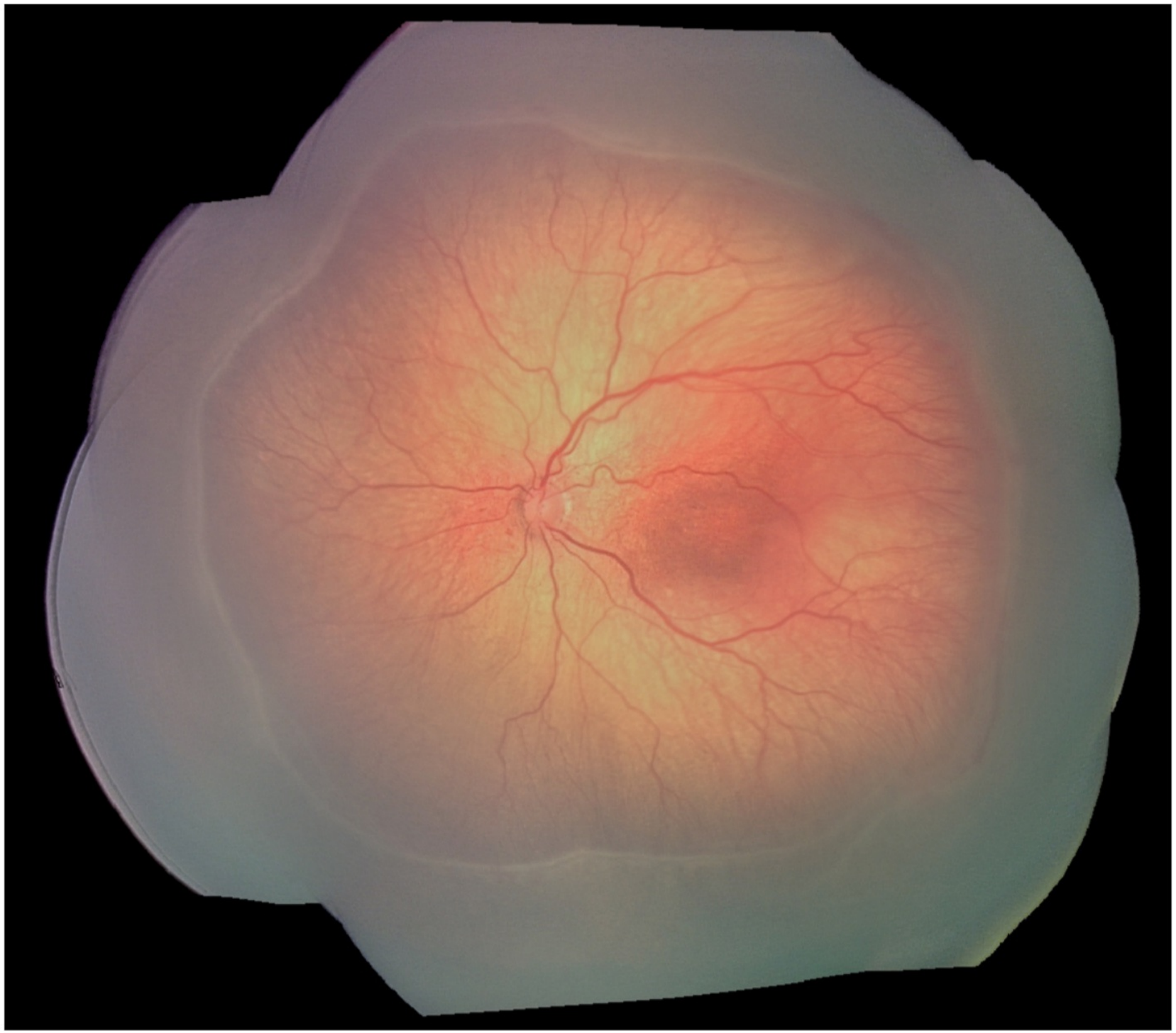
VISION 2020 THE RIGHT TO SIGHT

The overall aim of the programme is to provide treatment for infants with ROP, using the following **3 strategies**:

- Examine premature infants at risk for ROP
- Ensure available ophthalmologists with experience
- Ensure timely examination schedules

Retinopathy of Prematurity

Retinopathy of prematurity



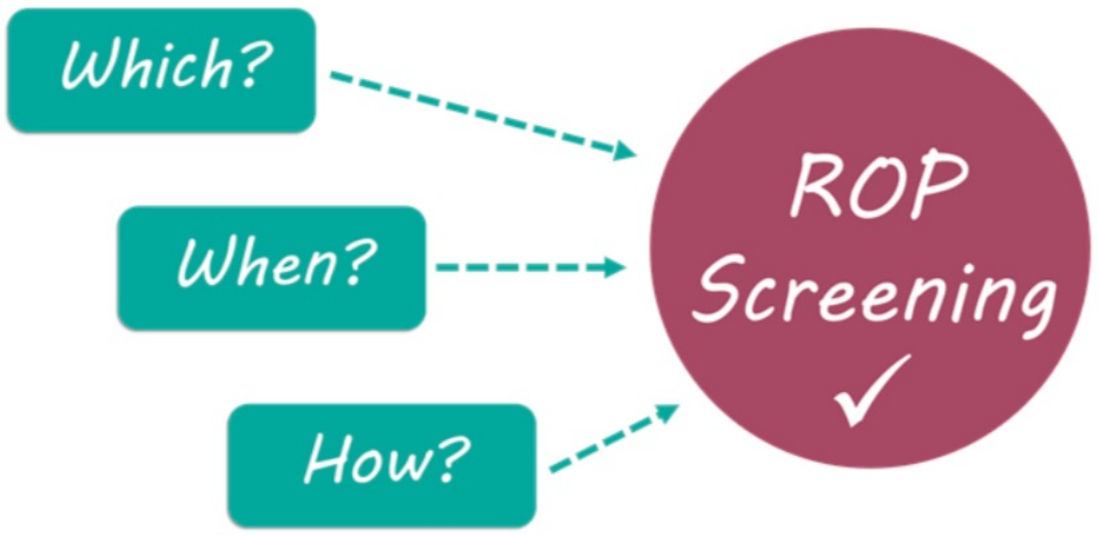
ROP Screening: Which, When and How

To support timely intervention, a system of screening is undertaken for **infants at risk** of developing ROP.

These **screening guidelines differ geographically** because the definition for high-risk infants is not consistently defined worldwide.

The **3 key questions** with respect to screening for infants at risk of severe ROP are:

- **Which** infants should be screened? (i.e. which infants are most at risk?)
- **When** should infants be screened? (i.e. when should screening start? When should screening finish?)
- **How** should infants be screened?



CHALLENGES

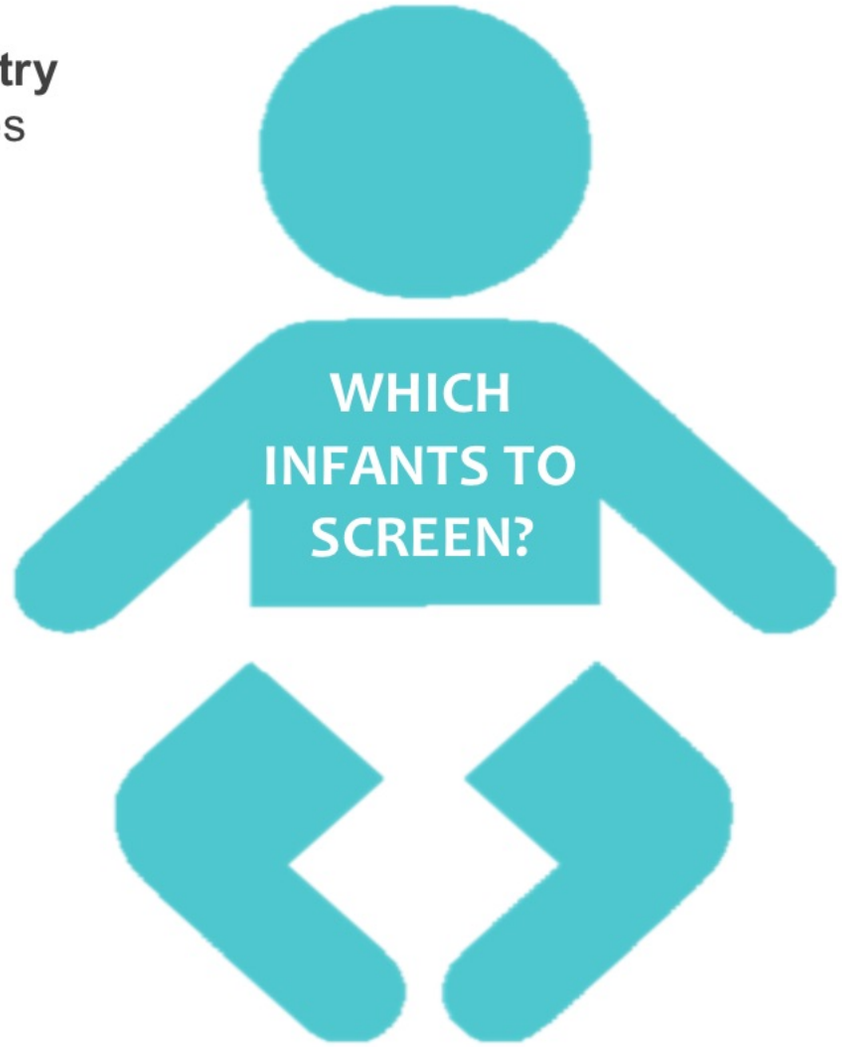
Challenges of ROP screening include:

- Understanding the population at risk
- Ensuring the required manpower is available
- Comprehensive knowledge of diagnosis and management of disease

Which Infants Should be Screened for ROP?

Infants at high risk for severe ROP **differ in their demographics** depending on the economic level of the particular country / region in which they are born.

Therefore, it is important to **study the epidemiology of ROP in each country in order to identify the infants at risk for severe disease**. Some countries do this very well, typically Scandinavian countries such as Denmark and Sweden, where long-term prospective databases are available.



HIGH RISK INFANTS

Developed Countries

Developing Countries

Click each bar to learn more about high risk infants in developed and developing countries

High Risk Infants in Developed Countries

Developed countries, with **uniform levels of high standard NICU** (neonatal intensive care unit) **care**, typically have the following approach to ROP screening:

- **GA and BW alone**
  Developed countries use **gestational age (GA)** and **birth weight (BW)** as the primary markers to define those infants most at risk and to determine which infants should be screened.

- **GA and BW, combined with sickness criteria**
  Some developed countries, in addition to **gestational age (GA)** and **birth weight (BW)**, also have a **sickness criteria** added to their screening guideline.
  Canada, for example, has a sickness criteria added to its screening guideline. If an infant falls outside the guideline - but has had, for example, sepsis, neonatal enterocolitis, or a significantly difficult course - then the infant will be screened.

- **Almost all ROP requiring treatment affects infants < 32 weeks GA or < 1500g BW**
  In developed countries, almost all ROP requiring treatment affects infants that are less than 32 weeks of gestational age and with a birth weight of less than 1500 grams.

AAP, AAPOS, AAO, et al. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013; 131(1): 189-95.

High Risk Infants in Developing Countries

In developing countries, the approach to ROP screening **differs** from high-income developed countries.

Developing countries:

- **Great variation in the standard of neonatal care**
  Developing countries can have considerable variations in the standard of neonatal care. Even within a developing country (i.e. within cities, from city to city, and within different territories), neonatal care and infant mortality rates can vary enormously.
- **Infants of greater GA and BW are at risk of developing sight-threatening ROP**
  In developing countries, infants at risk are typically **larger and older**. Therefore, infants of greater gestational age (GA) and birth weight (BW) are at risk for developing sight-threatening ROP.
- **Excessive and unblended oxygen support are believed to contribute**
  In developing countries, excessive and unblended oxygen support are believed to be primary contribution factors to increased risk. However, there are also other known factors.

Example

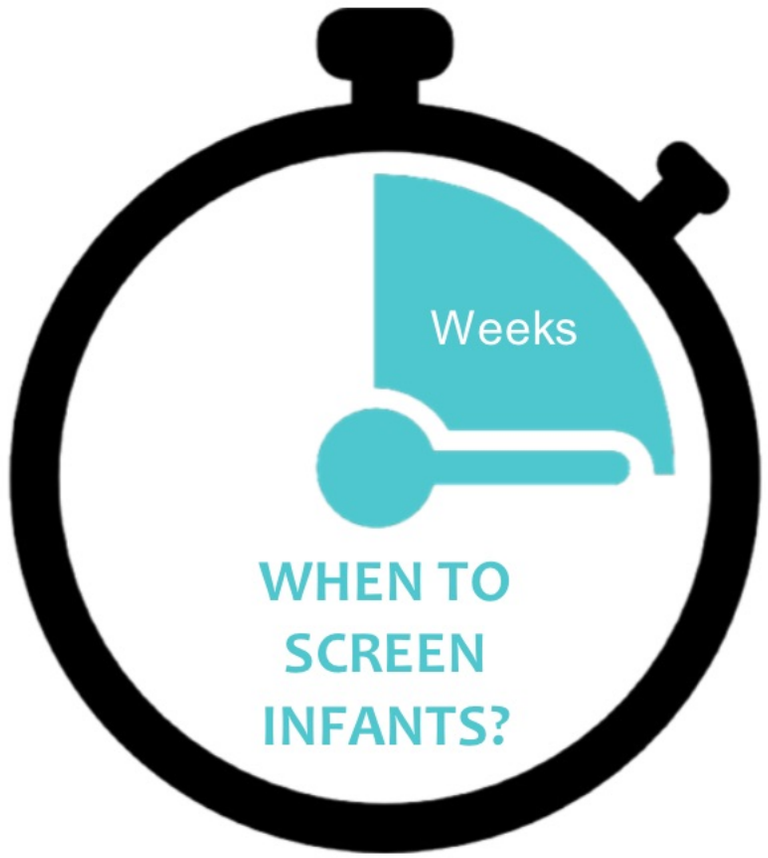
India: < 34 weeks GA and < 1700g BW

In India for example, they have adjusted screening guidelines according to their own demographic data. As a result, infants are screened if the gestational age is less than 34 weeks and the birth weight is less than 1700 grams. Therefore, quite large babies and older babies can be seen.

When Should Infants be Screened for ROP?

Regarding **when to start ROP screening** in infants, population-based studies provide the following evidence for effective and efficient screening programs in all levels of economies:

- Consistent data shows **ROP is governed by postmenstrual age** (PMA), not post-natal age
- Rate of progression through ROP stages is 7 - 10 days
- It is very rare to treat an infant prior to postmenstrual age (PMA) 31 weeks anywhere in the world
- The mean age of treatment of an infant with ROP is **37 weeks** postmenstrual age*



Developed *vs* Developing Countries

Adjusting Onset of Screening by Country

When Should Screening be Terminated?

Click each bar to learn more about when to start and terminate ROP screening

***Early Treatment For Retinopathy Of Prematurity Cooperative Group.** Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003; 121(12): 1684-94.

When to Start Screening Infants for ROP in Developed and Developing Countries

When to begin ROP screening is influenced by the mean PMA's of treatment, as screening needs to begin in advance of severe disease.

- **Developed Countries:**
  Most guidelines recommend onset of ROP screening at **31 or 32 weeks of postmenstrual age** (PMA).

- **Developing Countries:**
  Most guidelines recommend onset of ROP screening **soon after birth**, given the higher gestational age (GA) at risk for ROP, and mean postmenstrual age (PMA) of treatment which is consistently ~37 weeks.

Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee. Retinopathy of prematurity: An update on screening and management. *Paediatr Child Health*. 2016; 21(2): 101-8.

Adjusting the Onset of Screening According to a Countries Own Demographics

It is important to adjust the onset of ROP screening according to each countries own demographics. Some key factors to consider include:

- Data supports that the **natural history of ROP is governed by postmenstrual age** (PMA)
- **Progression** through the stages of disease will be **compressed in larger infants**, especially in aggressive posterior ROP (AP-ROP)
- **Larger infants requiring treatment** in countries such as Vietnam, India and Brazil, **range from a mean PMA of 34 - 37 weeks**. Therefore, these infants sometimes need to be screened very soon (within the first week) after birth.

ADJUST ONSET ACCORDING TO A COUNTRIES OWN DEMOGRAPHICS

Countries Own Demographics

It is very important to adjust the onset of ROP screening according to each countries own demographics

When to Start Screening?

WHEN TO SCREEN

When Should ROP Screening be Terminated?

The information below has been gathered and combined from many guidelines throughout the world.

ROP should be terminated in an infant:

- **Without ROP- vascularised into zone III**
  Infants that have been screened but have never had ROP. There are vessels that require vascularisation into zone III.
- **With ROP- zone III and regressed ROP**
  Infants that have had ROP and require vascularisation into zone III, with good regression of ROP (likely less than stage 2).
- **Treated with laser- regressed ROP and no plus disease**
  Infants that have been treated with laser require good regression of the ROP, with no evidence of plus disease.
- **Treated with anti-VEGF injection - zone III with no ROP (likely PMA of 70+ weeks)**
  Infants that have been treated with anti-VEGF injections require vascularisation into zone III, with no or regressed ROP. This is likely at a postmenstrual age of 70+ weeks.

Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee.
Retinopathy of prematurity: An update on screening and management. *Paediatr Child Health*. 2016; 21(2): 101-8.

AAP, AAPOS, AAO, et al.
Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013; 131(1): 189-95.

Data on the regression and recurrence of ROP post-injection is still being gathered from around the world. Hopefully this data can be used to augment, change and inform the guidelines on when to terminate screening.

Guidelines Developed by Individual Countries

This map shows some of the countries that have developed their own guidelines using national demographic data.

Data in table format

Click each pointer to learn more about different guidelines

Countries that have developed their own guidelines

Mexico and India have the highest gestational age at 34 weeks.

The highest birth weights are 1800g and 1750g; however, the **sickness criteria** does kick in in many of the developing countries, so that infants potentially at risk for disease are screened.

Country	GA & BW	Notes
Argentina[77]	≤32weeks &/or 1500g	Include also 1500 to 2000 g with unstable clinical course, predisposing factors or prolonged oxygen therapy
Brazil[16]	≤32weeks &/or ≤1500g	Include also larger & more mature babies with illnesses & other risk factors, e.g. sepsis, respiratory problems, multiple births
Canada[76]	<31 weeks & <1251g	Include also babies 1251g to 2000g if at high risk due to complex clinical course
Chile[78]	<33 weeks & <1500g	Include also babies between 1500 & 2000g with unstable clinical course, predisposing risk factor or prolonged oxygen therapy
Colombia[80]	≤32weeks &/or ≤1800g	Include also >1800g with unstable clinical course, predisposing factors or prolonged oxygen therapy
Mexico[79]	≤34weeks &/or ≤1750g	
Sweden[75]	<31 weeks	Include also larger babies severely ill
India[17]	<34 weeks &/or <1750g	Include also babies 34 to 36 weeks or 1750-2000g if there are risk factors
UK[73]	<31 weeks or <1251g	Must be screened. No additional sickness criteria
Denmark	<32 weeks or <1750g	No sickness criteria
USA[74]	≤30 weeks or <1500g	Include also 'selected' 1500-2000g or >30 weeks if unstable clinical course with cardiorespiratory support & at high risk
South Africa	<30 weeks & < 1500 g	Also selected 1500-2000 g if risk factors or oxygen monitoring suboptimal – includes guidance on oxygen monitoring

Global ROP Screening Guideline?

A **one-fit-all global guideline for ROP screening** is not that far-fetched. It may be possible in the future if the underlying key concepts are adhered to, such as:

- Knowing the gestational age (GA) and birth weight (BW) of the premature infants most at risk in different countries
- Understanding the natural history of ROP for different countries around the world

How is ROP Screening Performed?

ROP screening options:

- By and large, the gold standard worldwide is **clinical examination using indirect ophthalmoscopy with scleral depression**.
- However, there is a growing adoption of a **telemedicine approach** to ROP screening.

TELEMEDICINE SCREENING

More countries and cities are adopting and adapting to a **telemedicine approach** to ROP screening.

- Many publications, and over 15 years of research, support and document feasibility and accuracy in a telemedicine approach to ROP.
- Several large operational telemedicine ROP systems are in place in many parts of the world. (*KIDROP in India has been very successful since 2008, the USA has a few sites, and Germany and New Zealand are just a few of the countries that have published data on their operational systems*)

Telemedicine Advantages

Longitudinal Image Capture and Comparison

Validity of a Telemedicine System - eROP

Click each bar to learn more about a telemedicine approach to ROP screening

Advantages of a Telemedicine Approach to ROP Screening

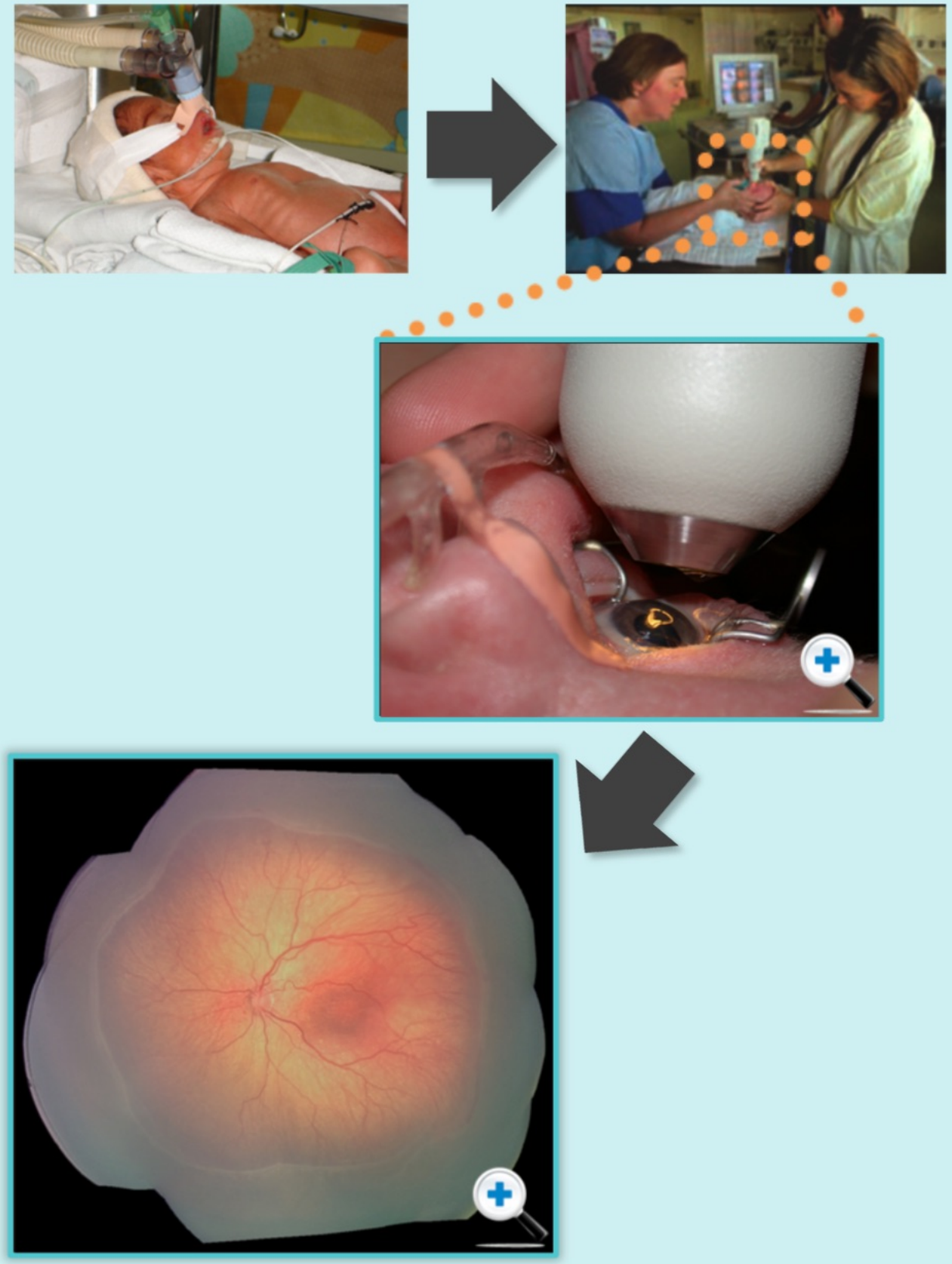
Meeting the growing need for efficient, effective and timely ROP evaluations is international in scope.

A telemedicine approach may be a solution providing improved quality, accessibility and cost-effectiveness, with more objective and standardised diagnosis.

However, adoption is quite slow possibly due to the high financial setup costs.

Advantages of a telemedicine approach to ROP screening include:

- It addresses the **manpower shortage** and **geographical challenges** in many countries. *(Canada, for example, is a massive country and has a huge manpower problem with delivering care. A telemedicine system in Canada would really change and improve how they can screen for ROP)*
- It **standardises diagnosis** with wide-field, digital photographic documentation.
- It **optimises the timing of treatment**. (*shown to be the case in many studies*)



Telemedicine Approach to ROP Screening

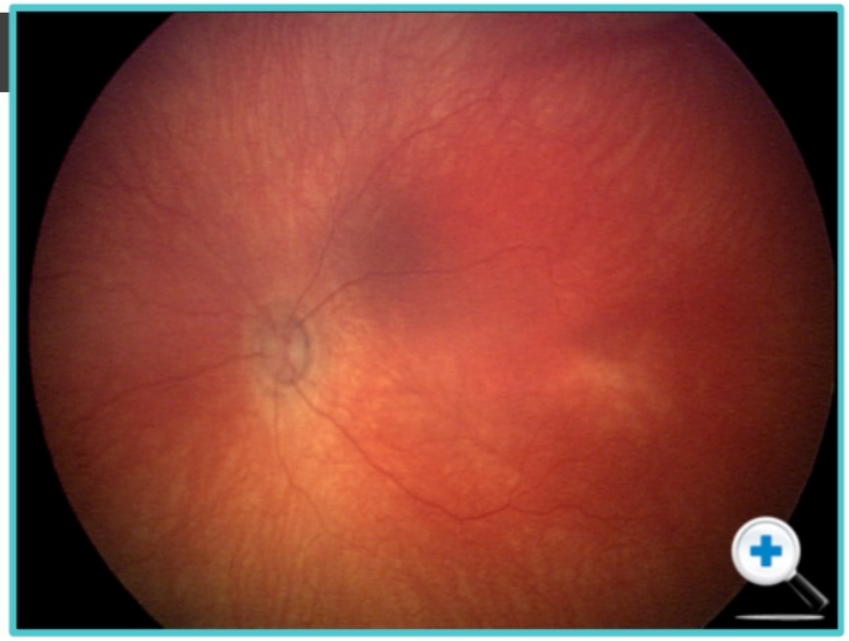
Telemedicine Approach to ROP Screening

Longitudinal Image Capture and Comparison

A **longitudinal image capture** case series from one patient, visit to visit, can really highlight the benefit of a telemedicine approach.

If a point could be reached, where all babies were monitored using a telemedicine approach, it is probable that the delivery of ROP care would change, improve and be maximised.

1



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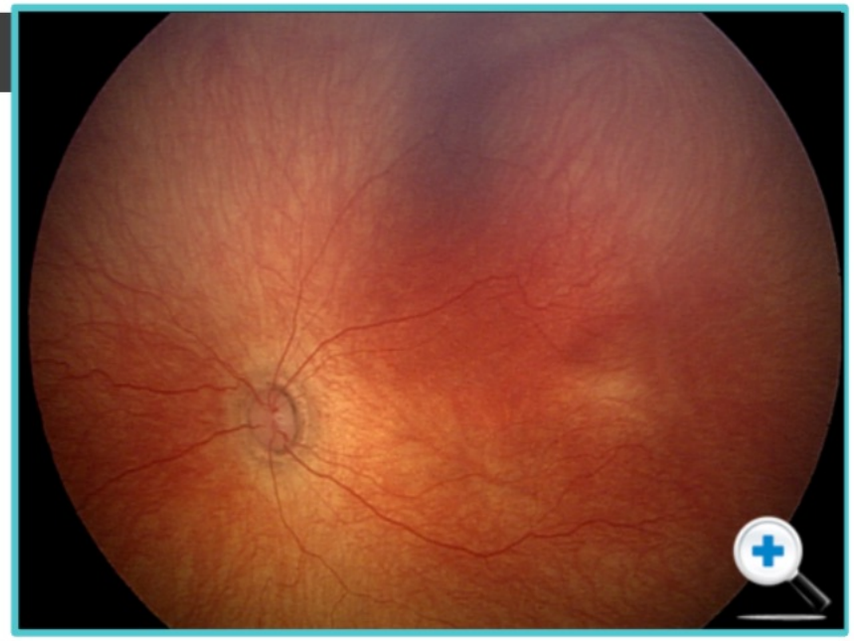

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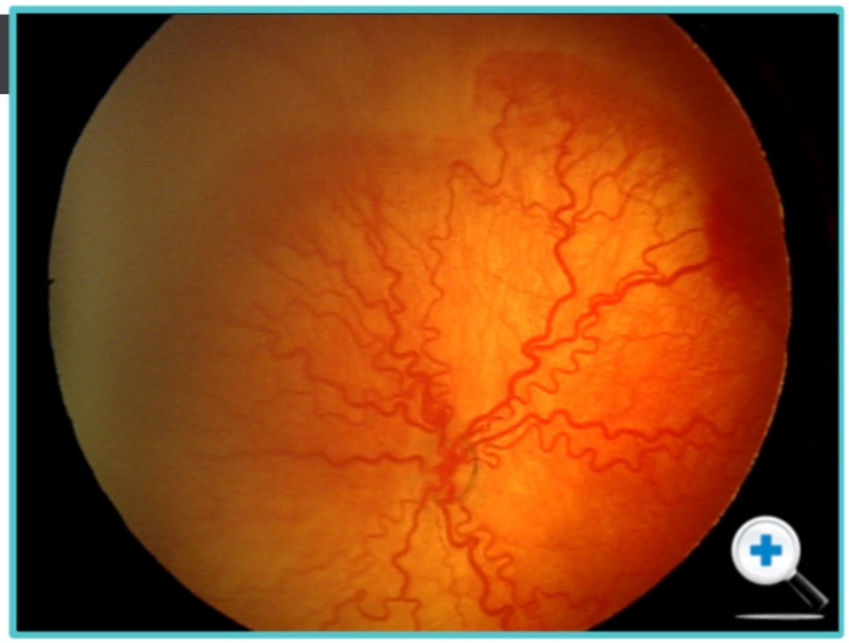

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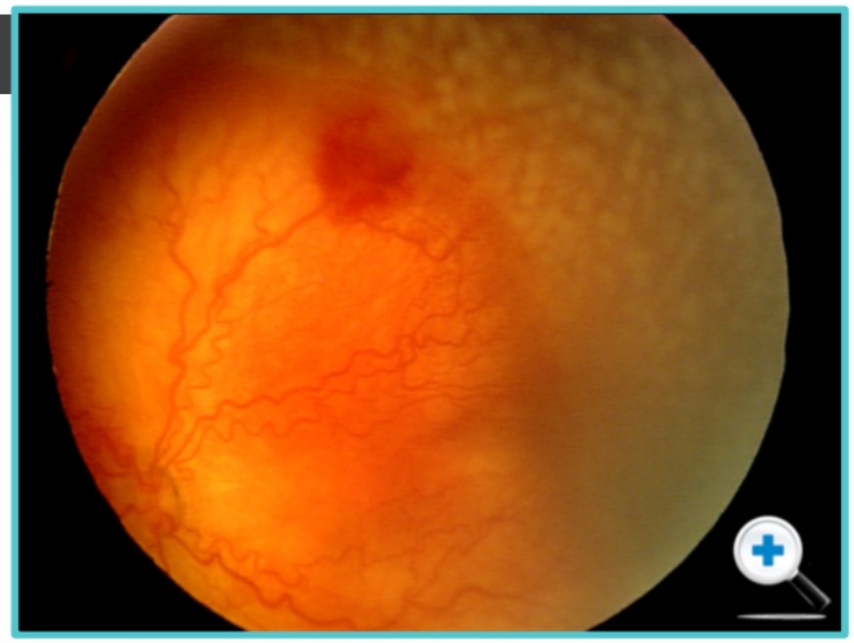
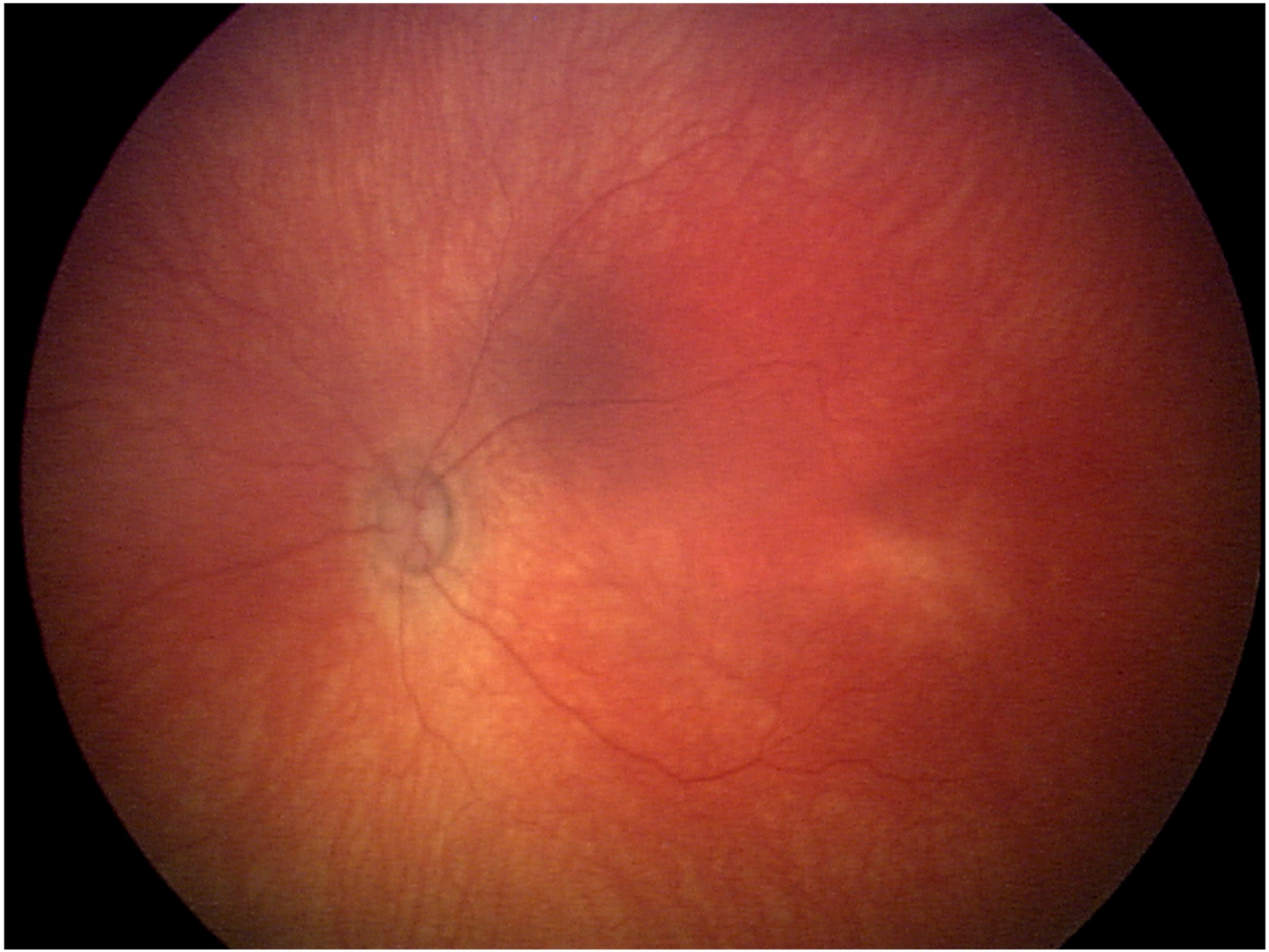


Longitudinal Image Capture and Comparison



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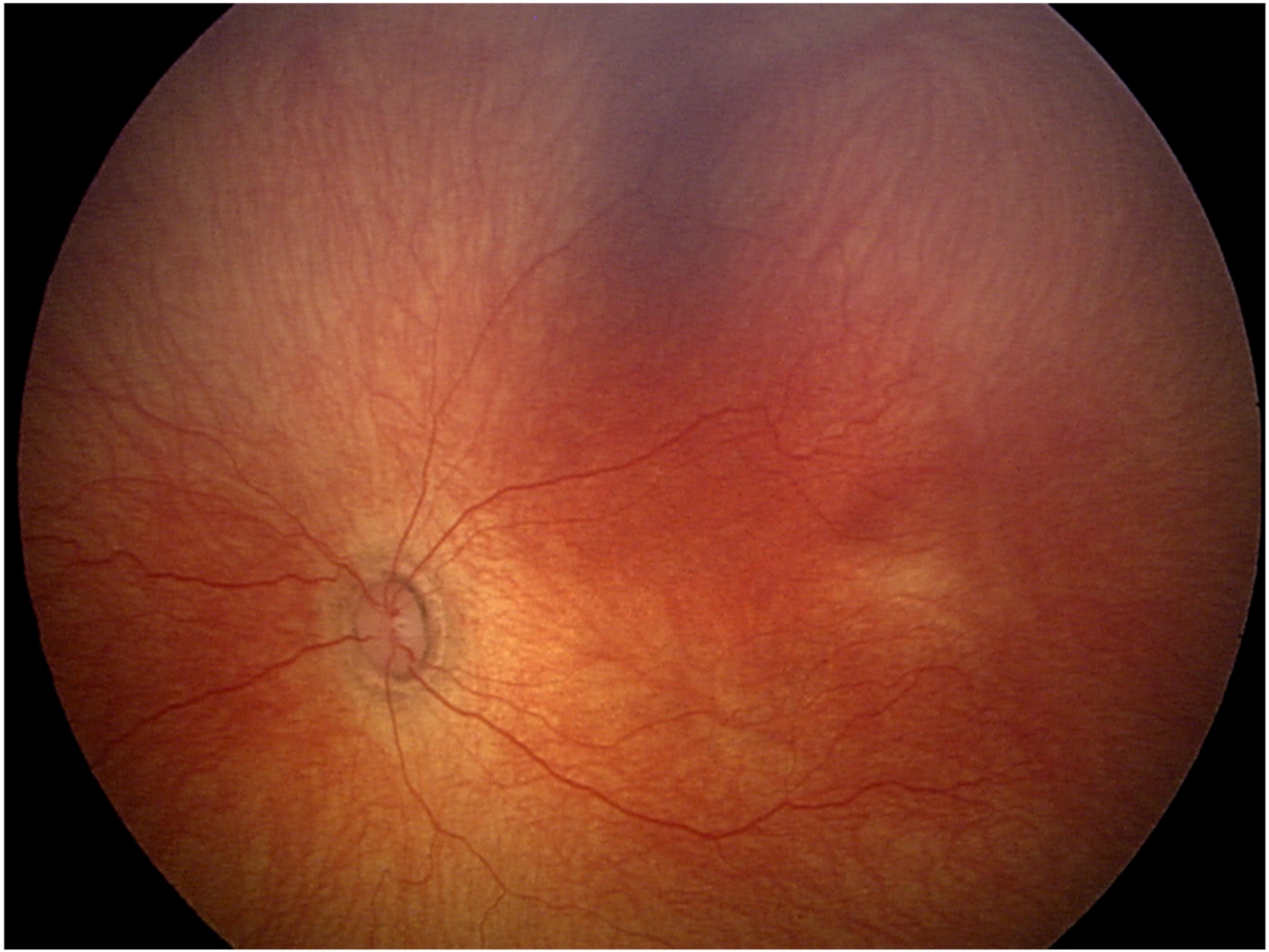

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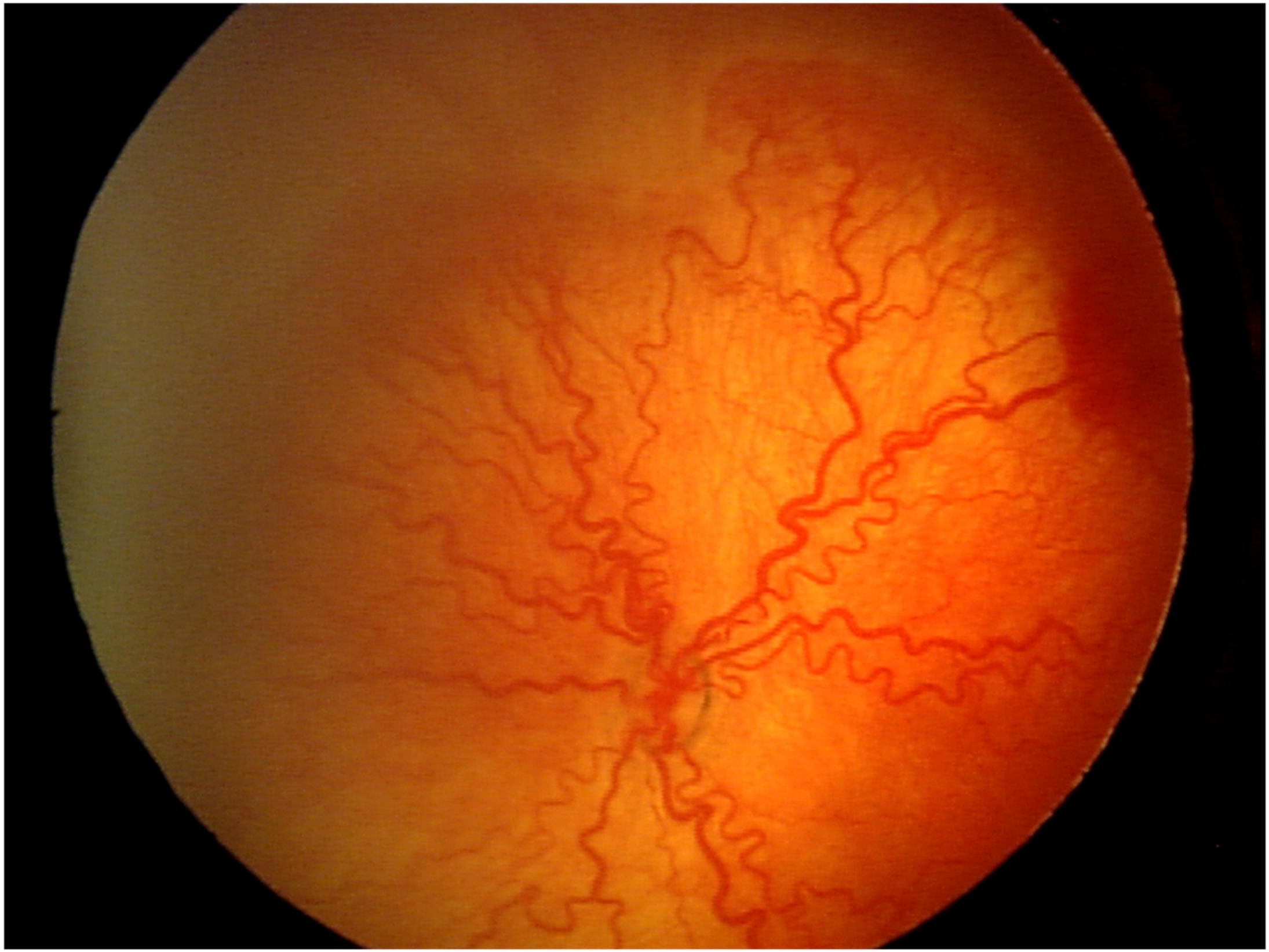

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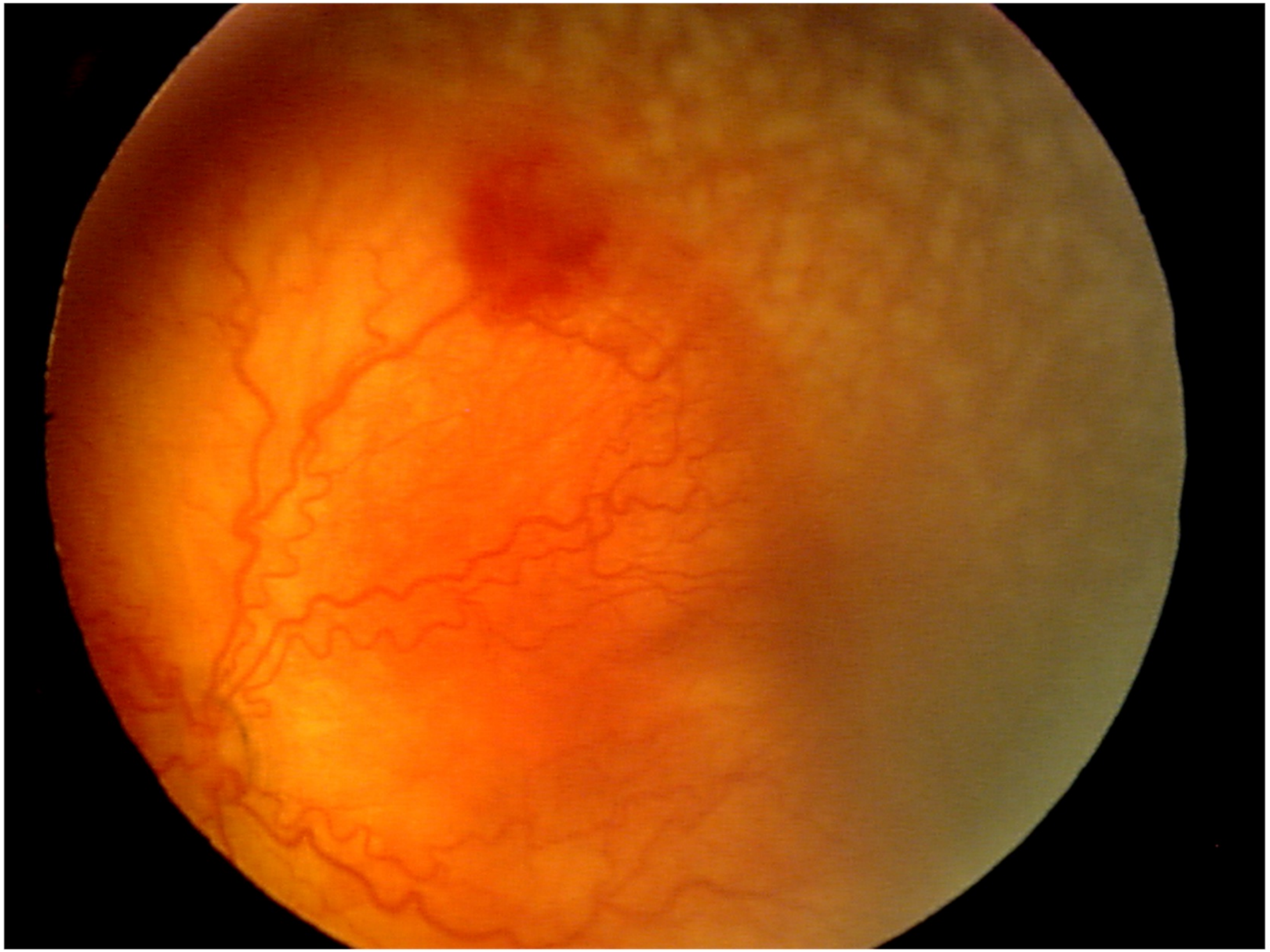


Validity of a Telemedicine System – eROP Study

There are many large studies but the eROP study is the largest and most recent validity of a telemedicine system.

In this study, premature infants from 13 North American centres were assessed by both diagnostic examinations and remotely by non-physician graders using digital imaging.

Quinn GE, Ying GS, Daniel E, et al. e-ROP Cooperative Group. Validity of a telemedicine system for the evaluation of acute-phase retinopathy of prematurity. *JAMA Ophthalmol*. 2014; 132(10): 1178-84.

eROP study:

- A large scale, National Eye Institute (NEI)-funded, multi-centre trial involving imaging of 1200 premature infants
- Showed high sensitivity for diagnosing clinically significant ROP
- Infants were assessed by clinical exam and remotely by non-physician graders using digital imaging
- The sensitivity of remote grading in identifying ROP that required treatment was 90% when both eyes were examined and the negative predictive value (NPV) was 97.3%

Future of ROP Screening

The future of ROP screening most certainly involves the assistance of information technology and computer systems to **inform ophthalmologists which infants are most at risk** and to **help reduce the burden** required, **without adjusting the sensitivity**.

- Less than 10% of infants screened for ROP require treatment*
- The screening process can be improved if predictive factors for the development of severe disease can be reliably identified
- The dichotomous distinction between disease present and disease absent is one of the first critical steps (i.e. is an image normal or abnormal?)

***Quinn GE, Ying GS, Daniel E, et al. e-ROP Cooperative Group.** Validity of a telemedicine system for the evaluation of acute-phase retinopathy of prematurity. *JAMA Ophthalmol*. 2014; 132(10): 1178-84.

Our Digital World & Image Analysis Tools

Click the box to learn more about image analysis tools

Our Digital World

There are many exciting advancements in computer-based image analysis tools of retinal vessels. More specifically, many research teams globally are developing **software mathematical algorithms** that may be used in **computer image analysis for ROP**.

ROP Image Analysis Tools

Various types of mathematical algorithms are used in computer image analysis for ROP. They differ in the mechanism of automated detection of the retina vessels. A few of the image analysis tools available include:

- **CAIAR**
  - computer assisted image analysis of the retina (UK-Wilson, Fielder, Ng)
  - semi-automated vessel detection, width, tortuosity
- **RISA**
  - retina Image multiScale Analysis (Perez)
  - semi-automated vessel detection, width, tortuosity
- **ROPtool** (Duke, NC)
  - semi-automated vessel width
- **IMEDOS** (commercially available, Germany)
  - semi-automated vessel width
- **Gabor filters** (Italy, Calgary)
  - automated vessels analysis

Examples of Image Analysis Tools

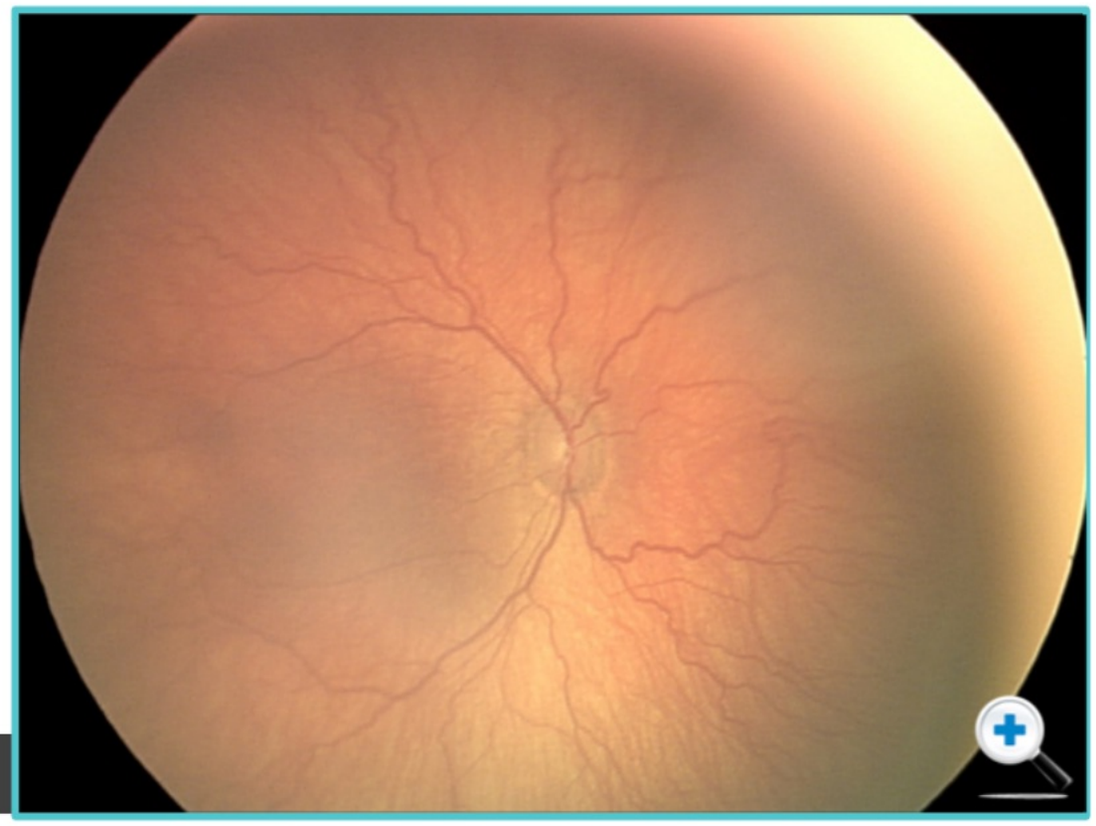
Example 1 | Example 2 | Example 3 | Example 4 | Example 5

Click each button to see examples of image analysis tools

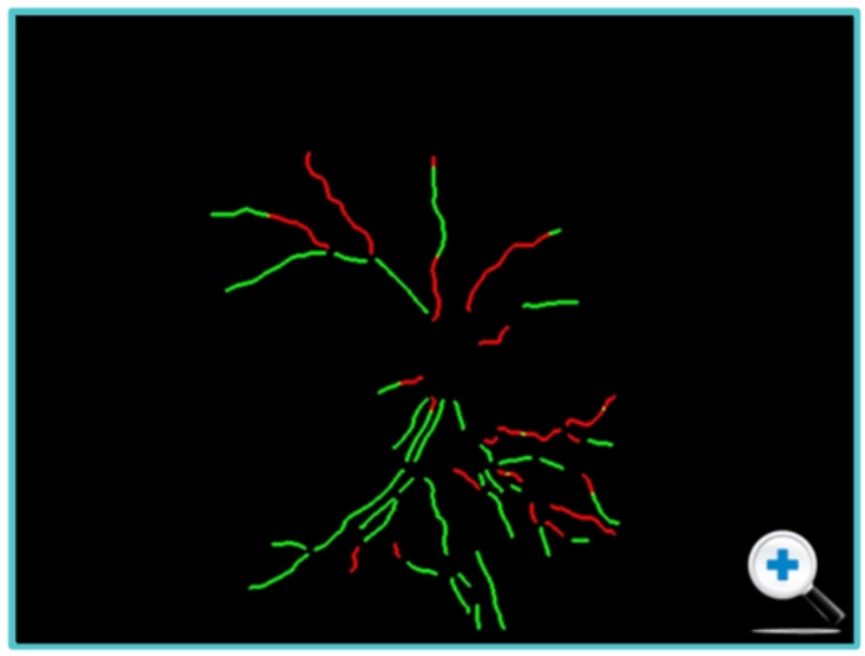
Example 1: Detection and quantification of vascular tortuosity

Module editor, Dr Anna Ells, et al. (2015) have carried out research in Calgary where they are developing algorithms to detect, in an almost completely automated fashion, vascular tortuosity and dilatation.

Oloumi F, Rangayyan RM, Ells AL. Computer-aided diagnosis of plus disease in retinal fundus images of preterm infants via measurement of vessel tortuosity. *Conf Proc IEEE Eng Med Biol Soc*. 2015; 2015: 4338-42.



Plus disease

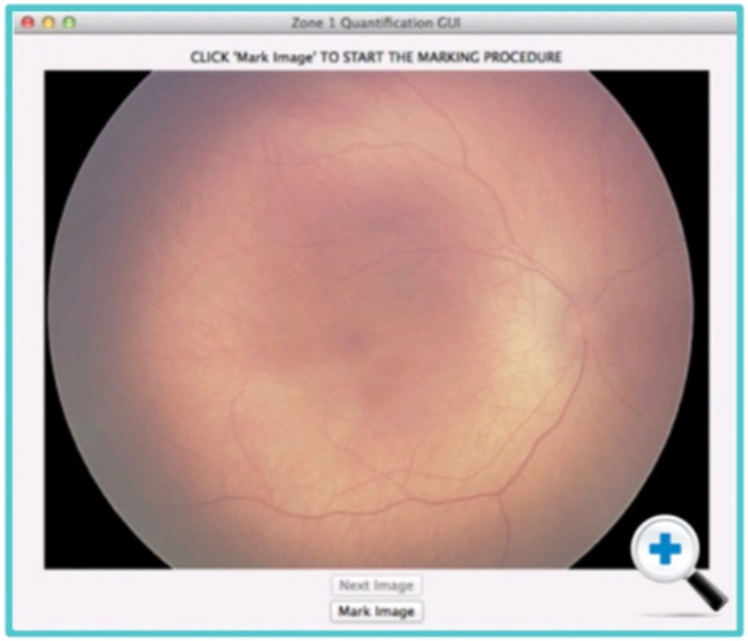


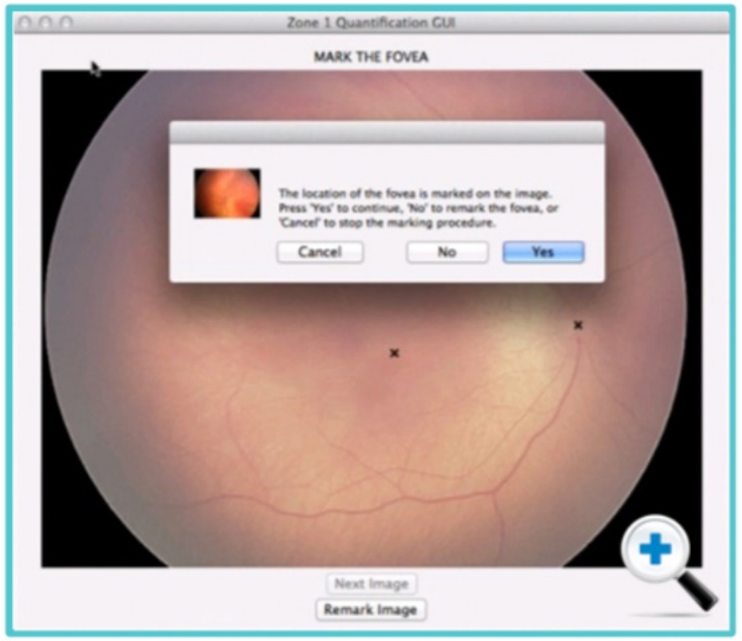
Example 2: Quantification of the radius of zone I

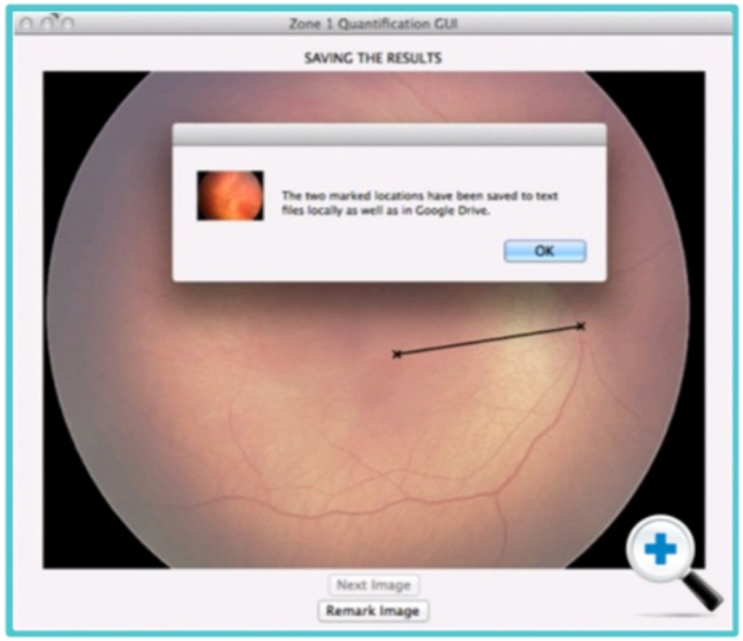
Module editor, Dr Anna Ells, et al. (2003) have carried out research on the quantification of zoning.

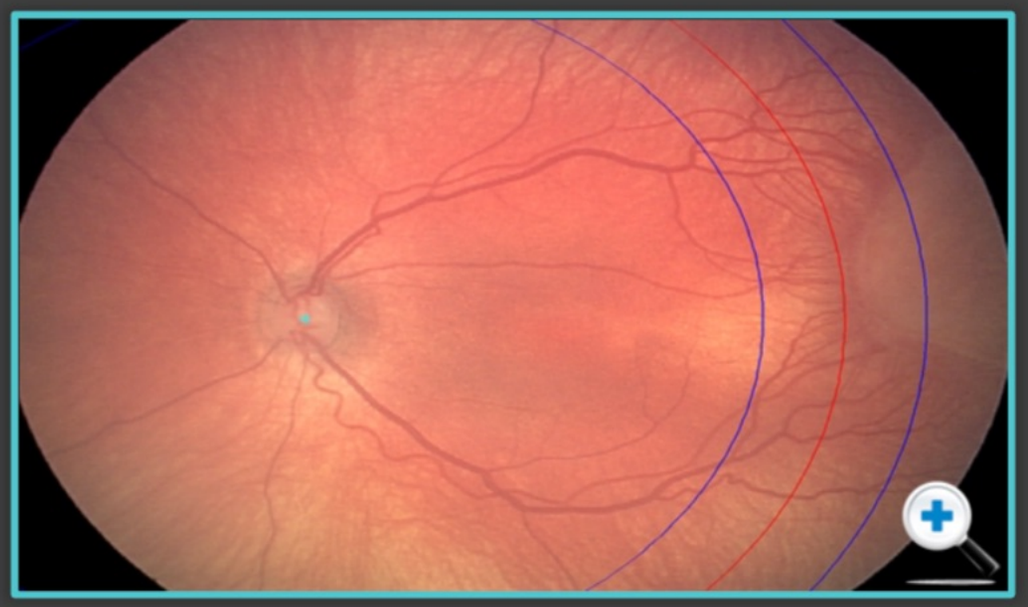
Ells AL, Holmes JM, Astle WF, et al.
Telemedicine approach to screening for severe retinopathy of prematurity: a pilot study. *Ophthalmology*. 2003; 110(11): 2113-7.

Expert marking of the locations and the resulting distance shown as a line.







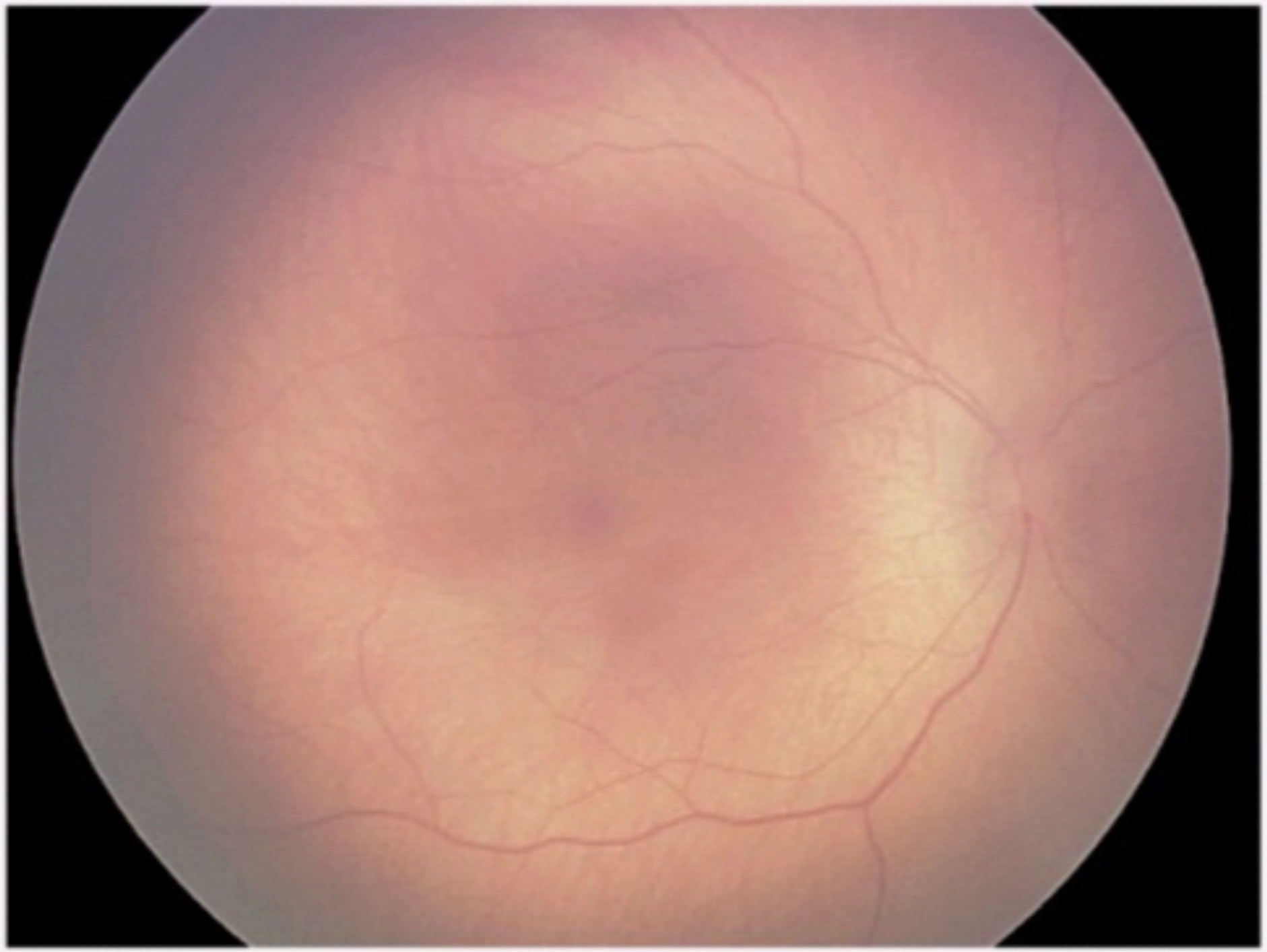


An example image showing how a grader simply marks the centre of the optic nerve, and then the computer algorithm generates a range of zones for the particular image.

This particular image is graded with Stage 3 ROP in Zone II, with plus disease. The red line is the average 800 image marking.

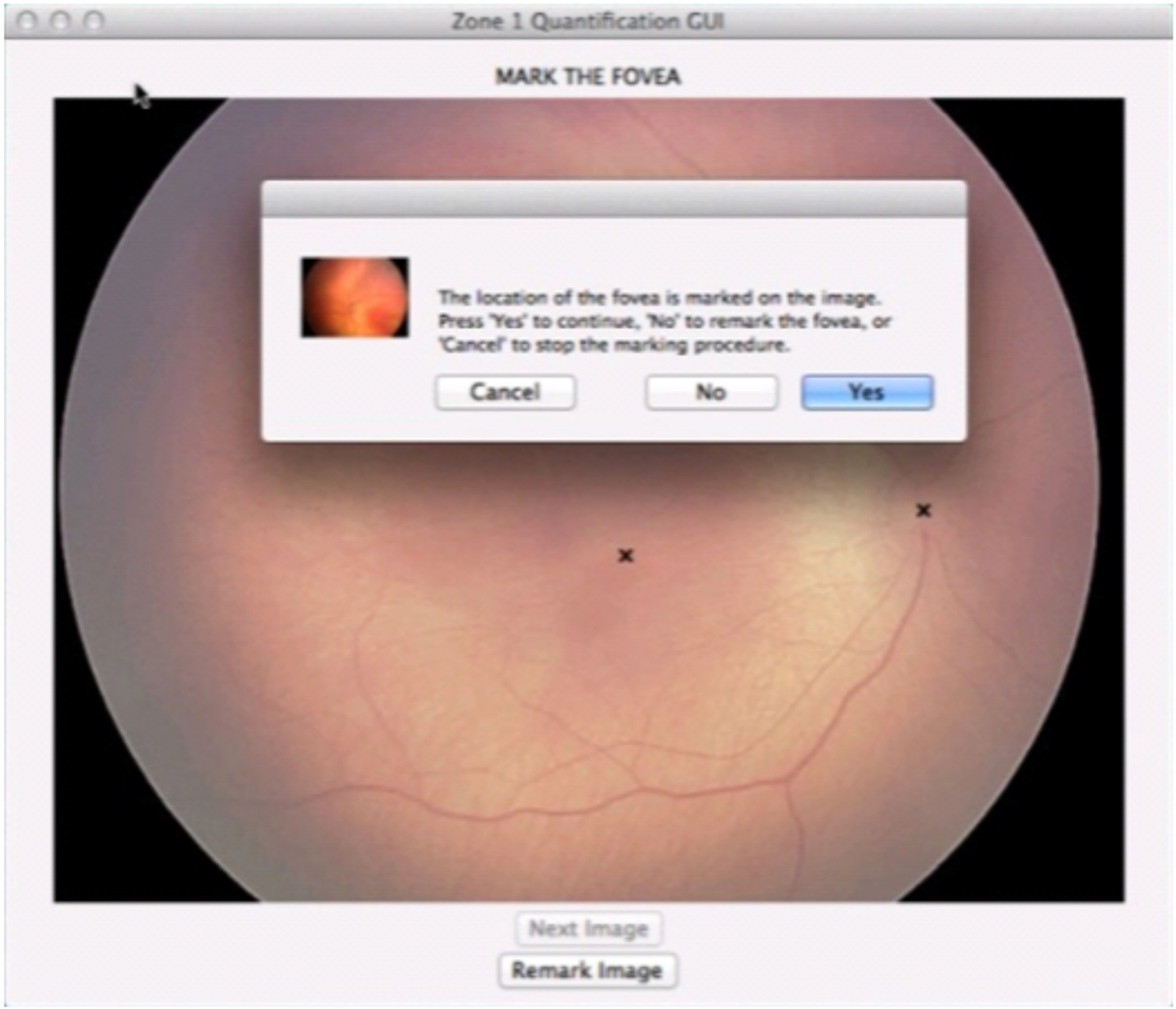
Zone 1 Quantification GUI

CLICK 'Mark Image' TO START THE MARKING PROCEDURE



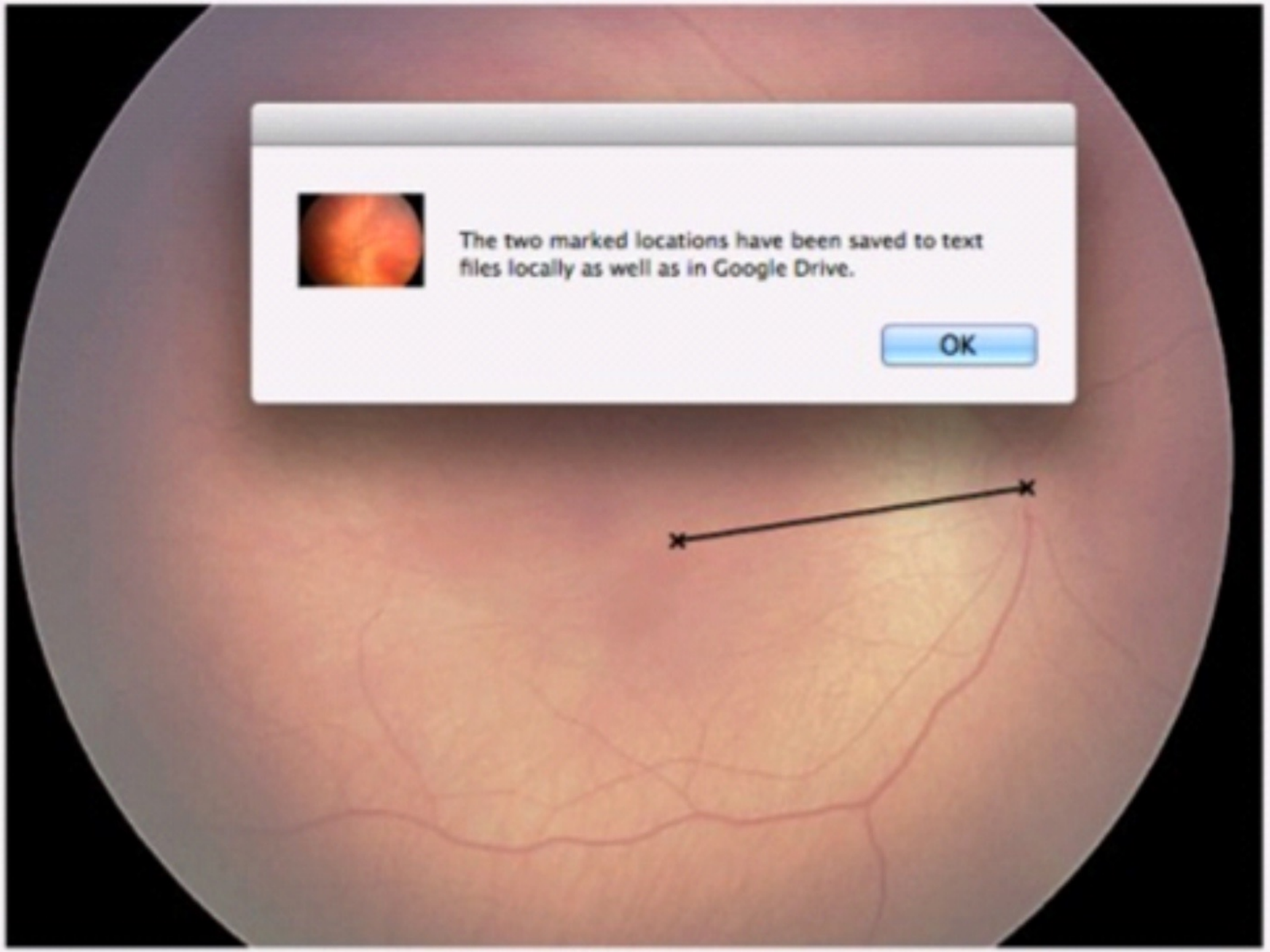
Next Image

Mark Image


Zone 1 Quantification GUI
MARK THE FOVEA
The location of the fovea is marked on the image.
Press 'Yes' to continue, 'No' to remark the fovea, or
'Cancel' to stop the marking procedure.
Cancel
No
Yes
Next Image
Remark Image

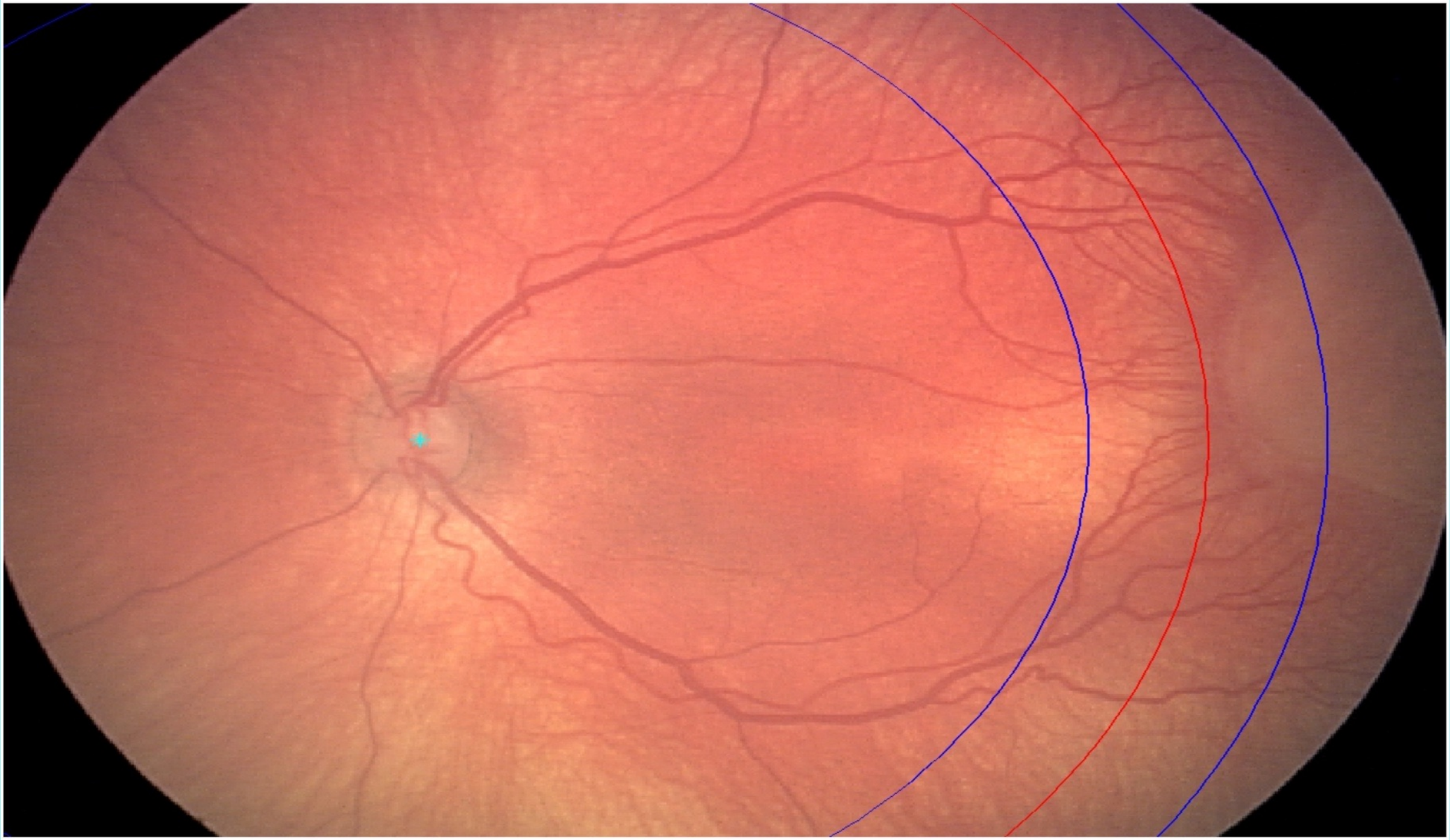
Zone 1 Quantification GUI

SAVING THE RESULTS



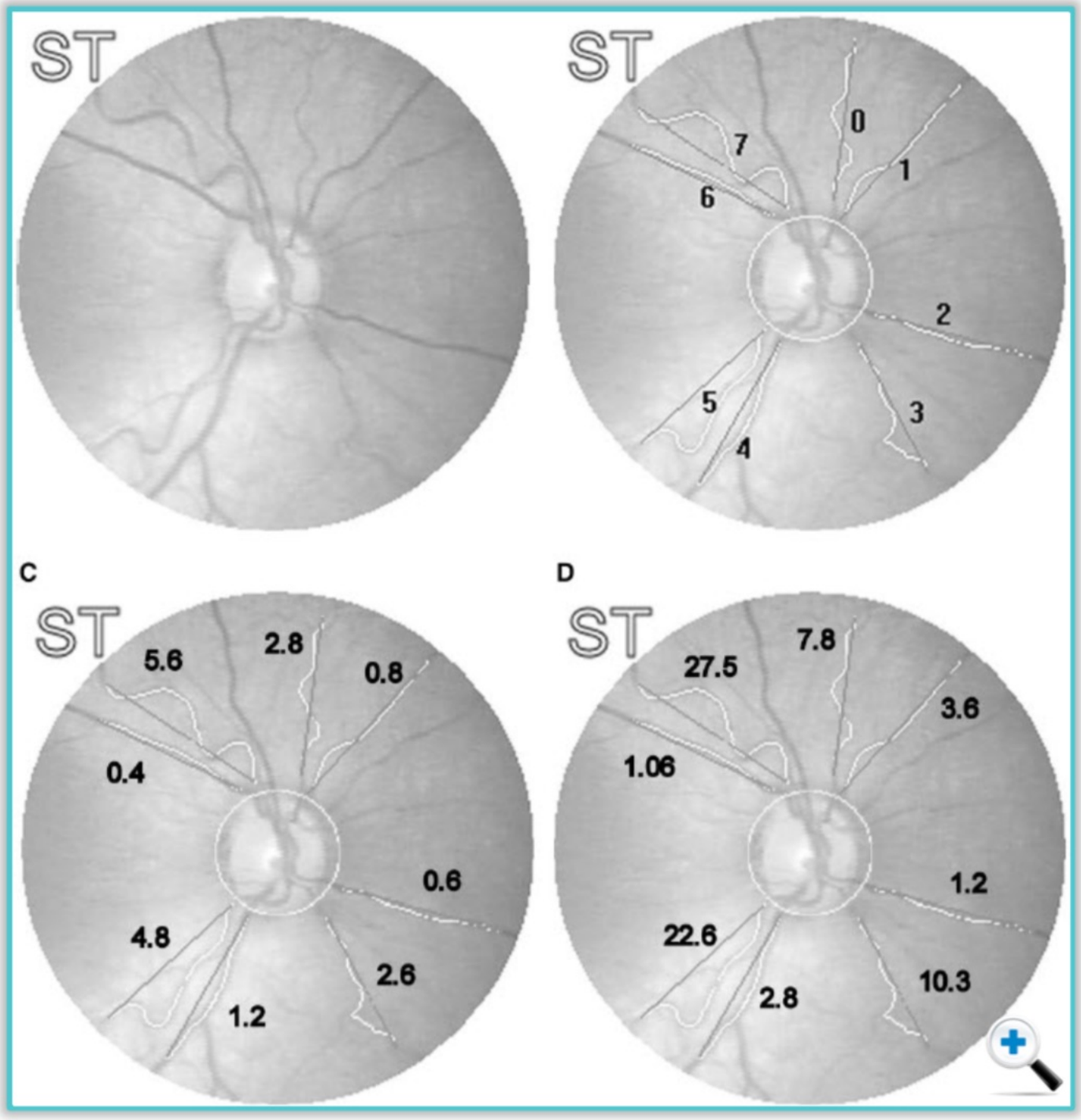
Next Image

Remark Image

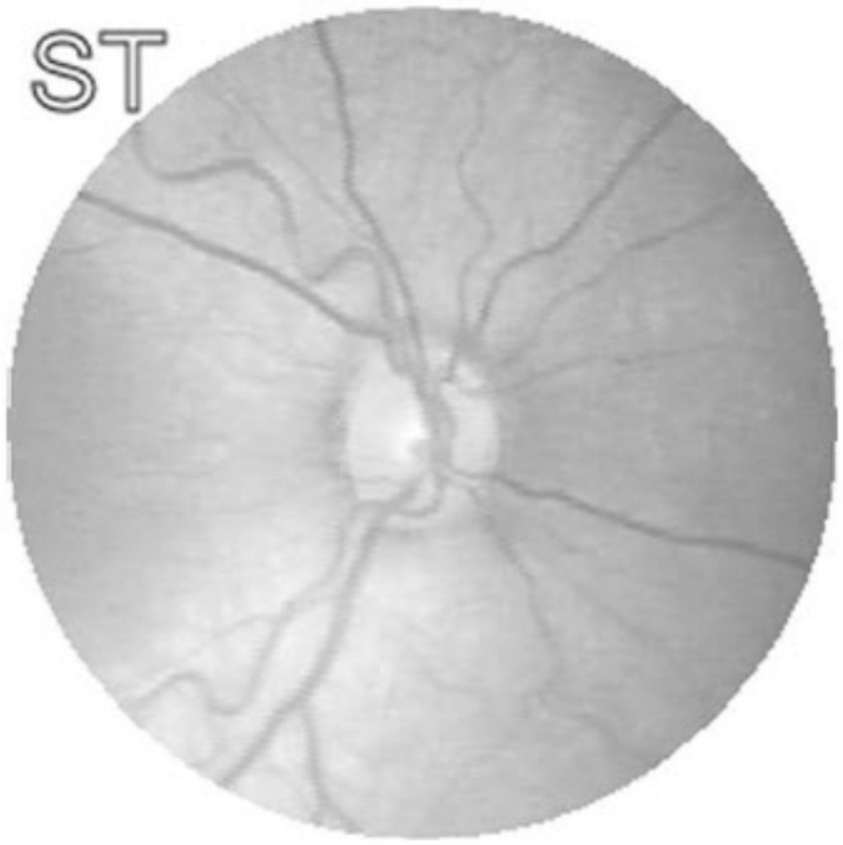


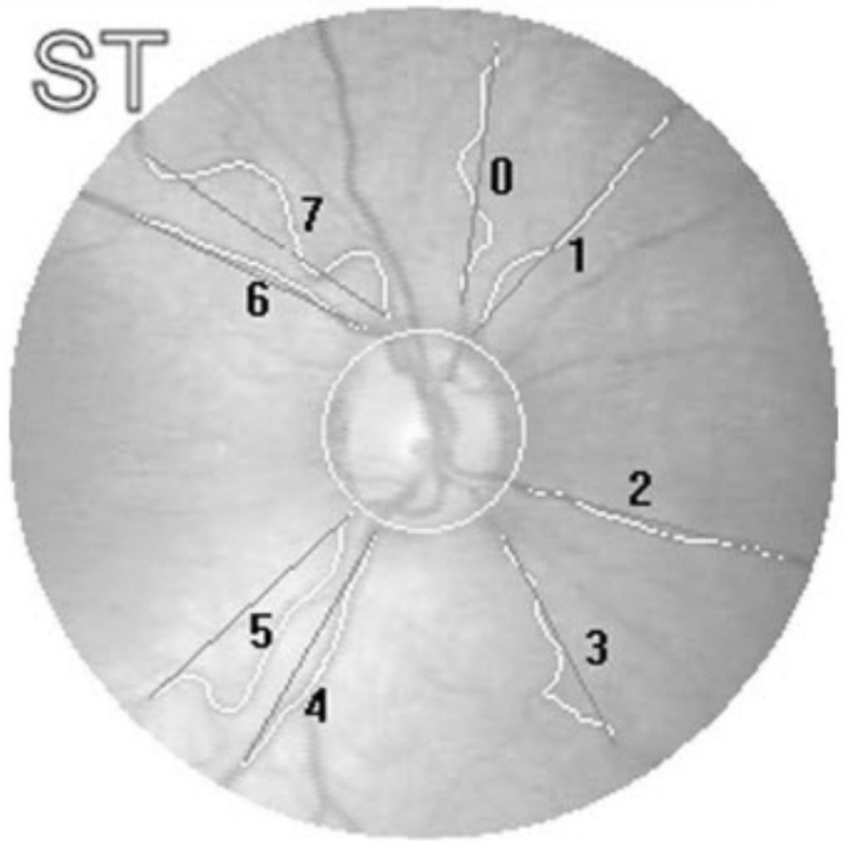
Example 3: Manual marking of vessel along with quantification of vascular thickness and tortuosity

Wilson et al. (2008) from the UK have pioneered much of the work investigating vascular dilation and tortuosity.

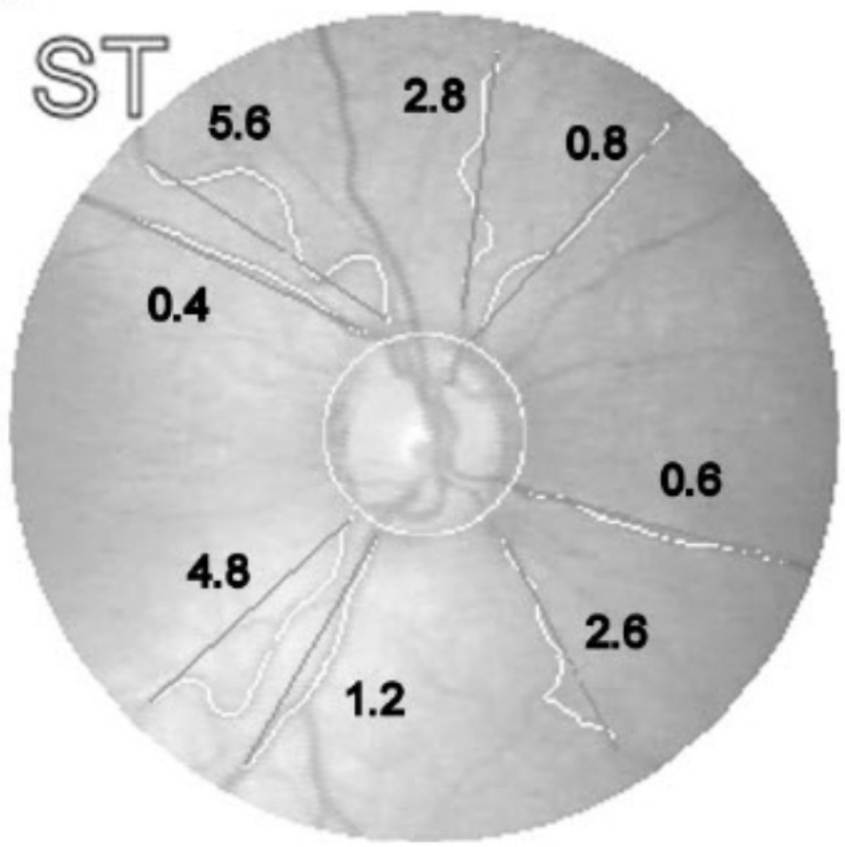


Wilson CM, Cocker KD, Moseley MJ, et al.
Computerized analysis of retinal vessel width and tortuosity in premature infants. *Invest Ophthalmol Vis Sci*. 2008; 49(8): 3577-85.

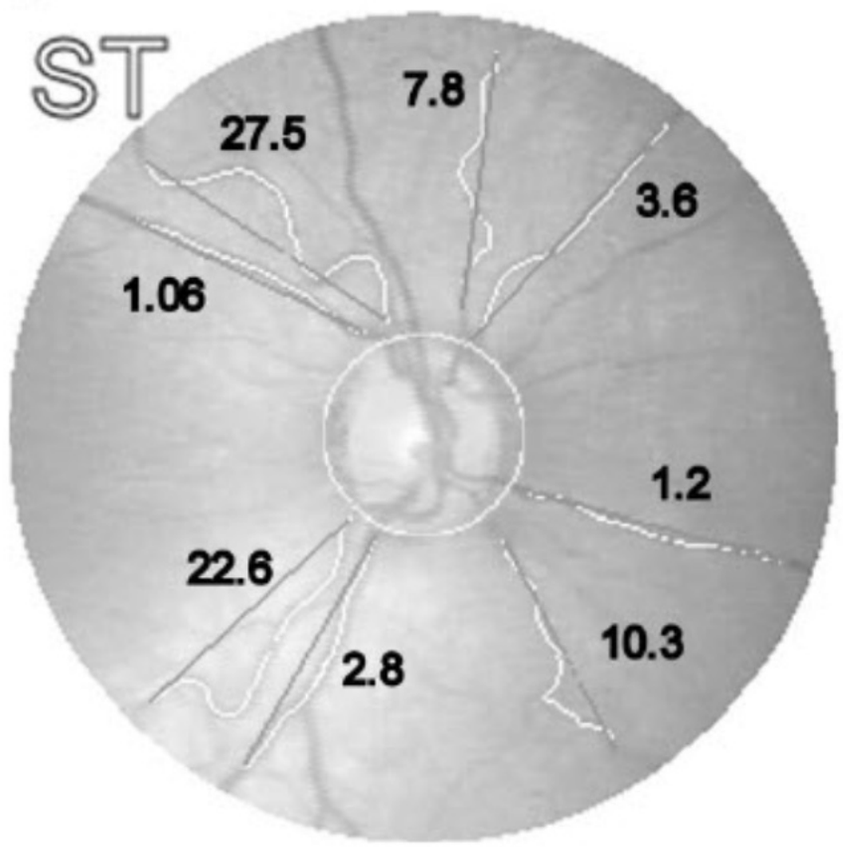

ST


ST
0
1
2
3
4
5
6
7

C


ST
5.6
2.8
0.8
0.4
0.6
4.8
2.6
1.2

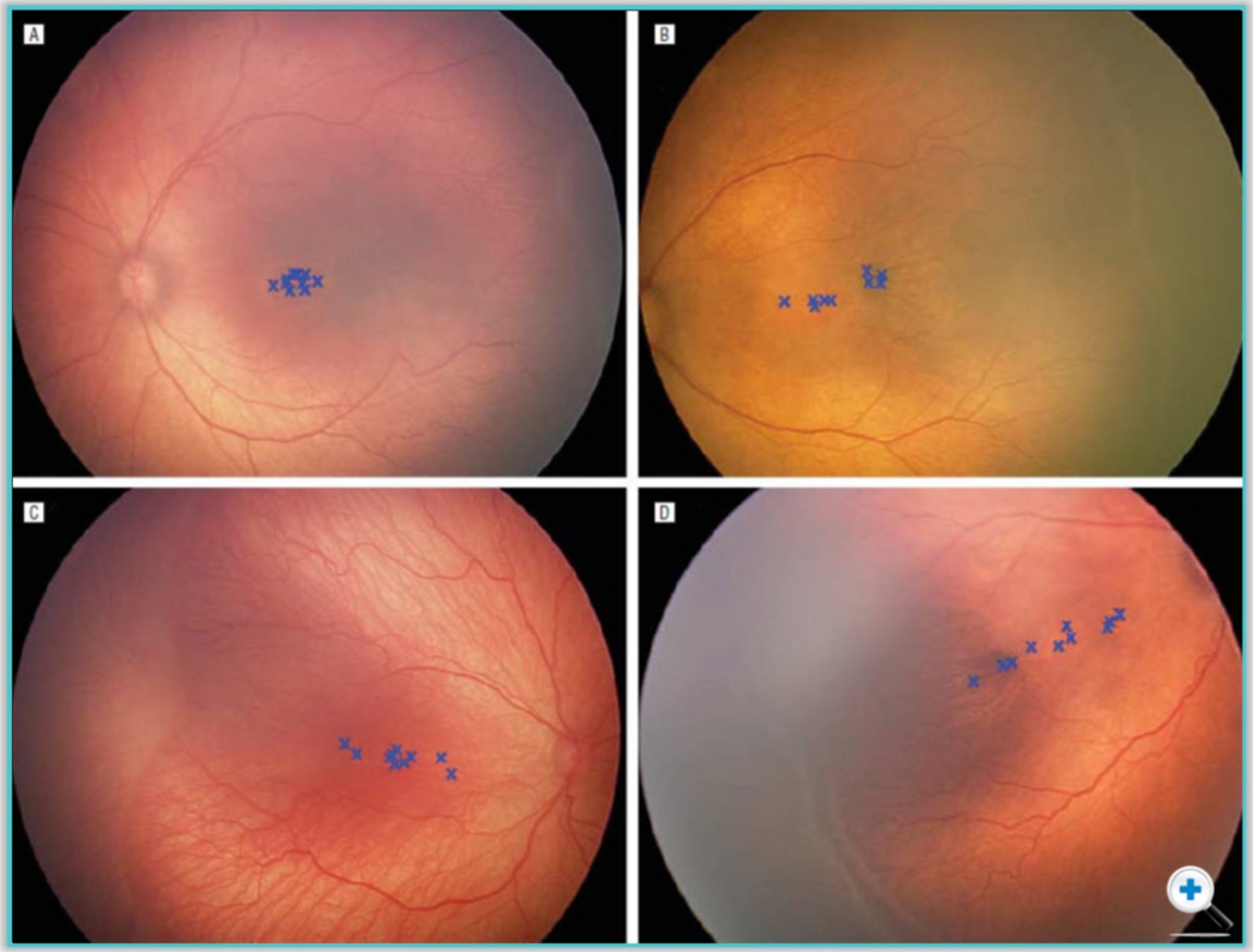
D

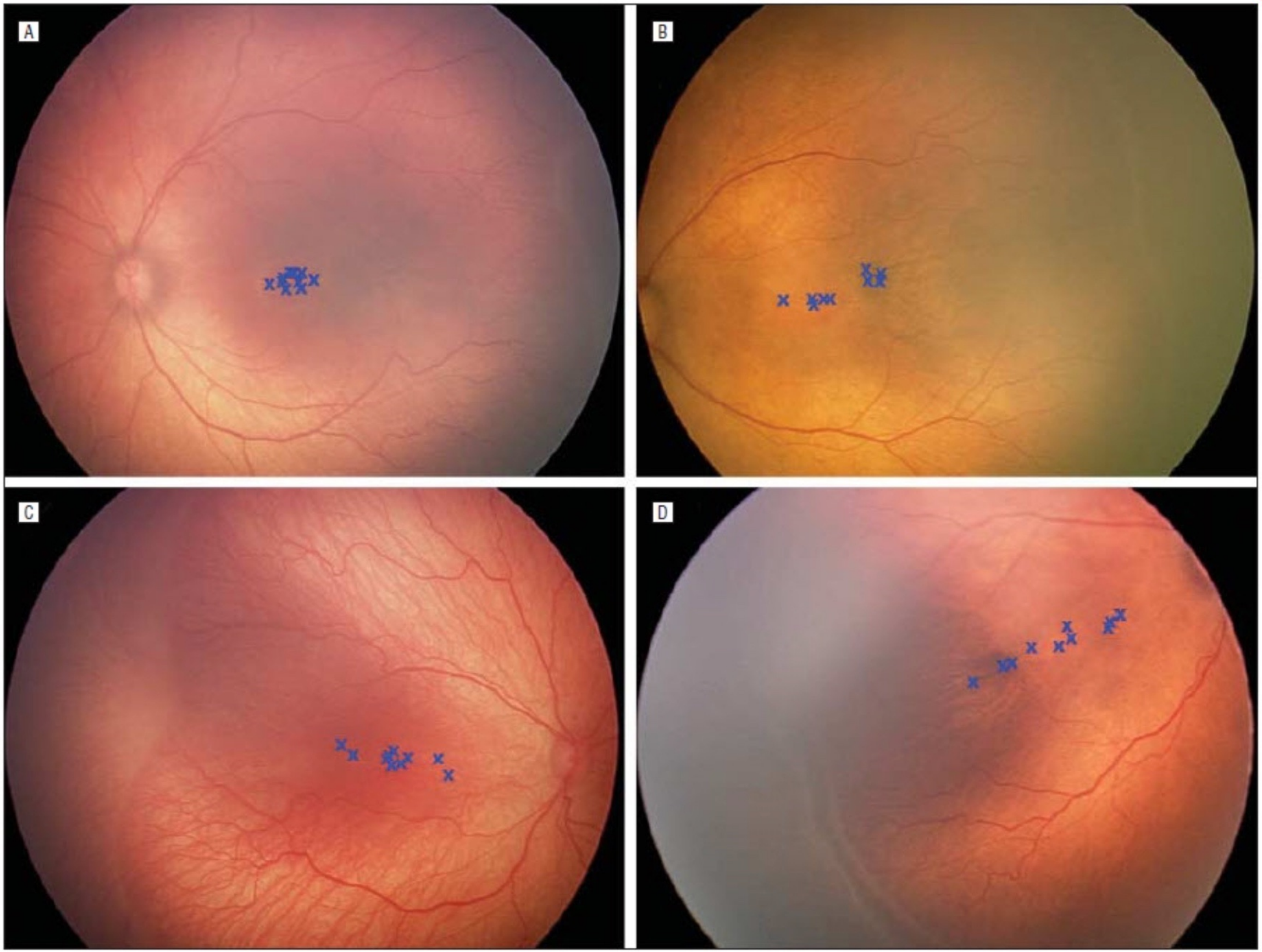

ST
27.5
7.8
3.6
1.06
1.2
22.6
10.3
2.8

Example 4: Interexpert agreement in marking the location of fovea in preterm infants

Chiang et al. (2010) examined the measurement of interexpert agreement in marking the location of the fovea in preterm infants at risk for ROP.

Chiang MF, Thyparampil PJ, Rabinowitz D. Interexpert agreement in the identification of macular location in infants at risk for retinopathy of prematurity. *Arch Ophthalmol*. 2010; 128(9): 1153-9.

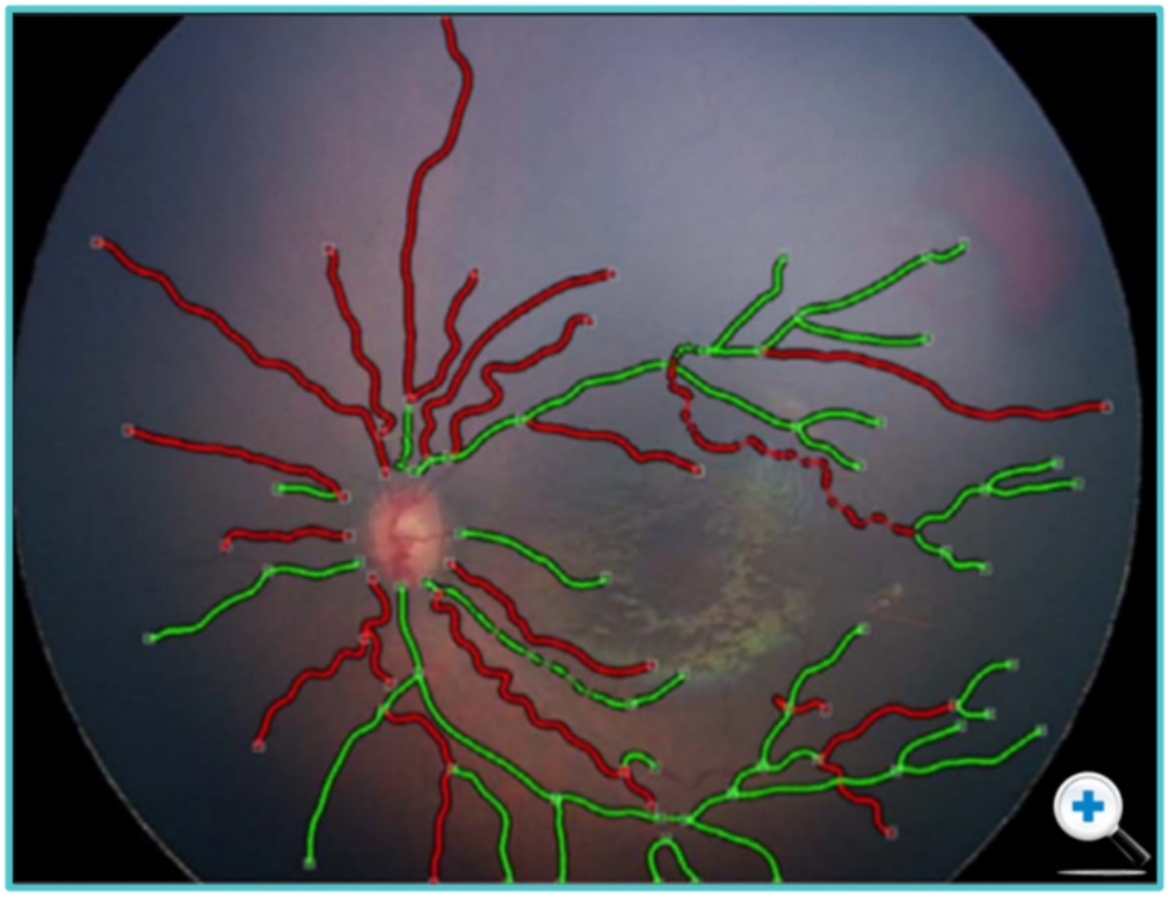


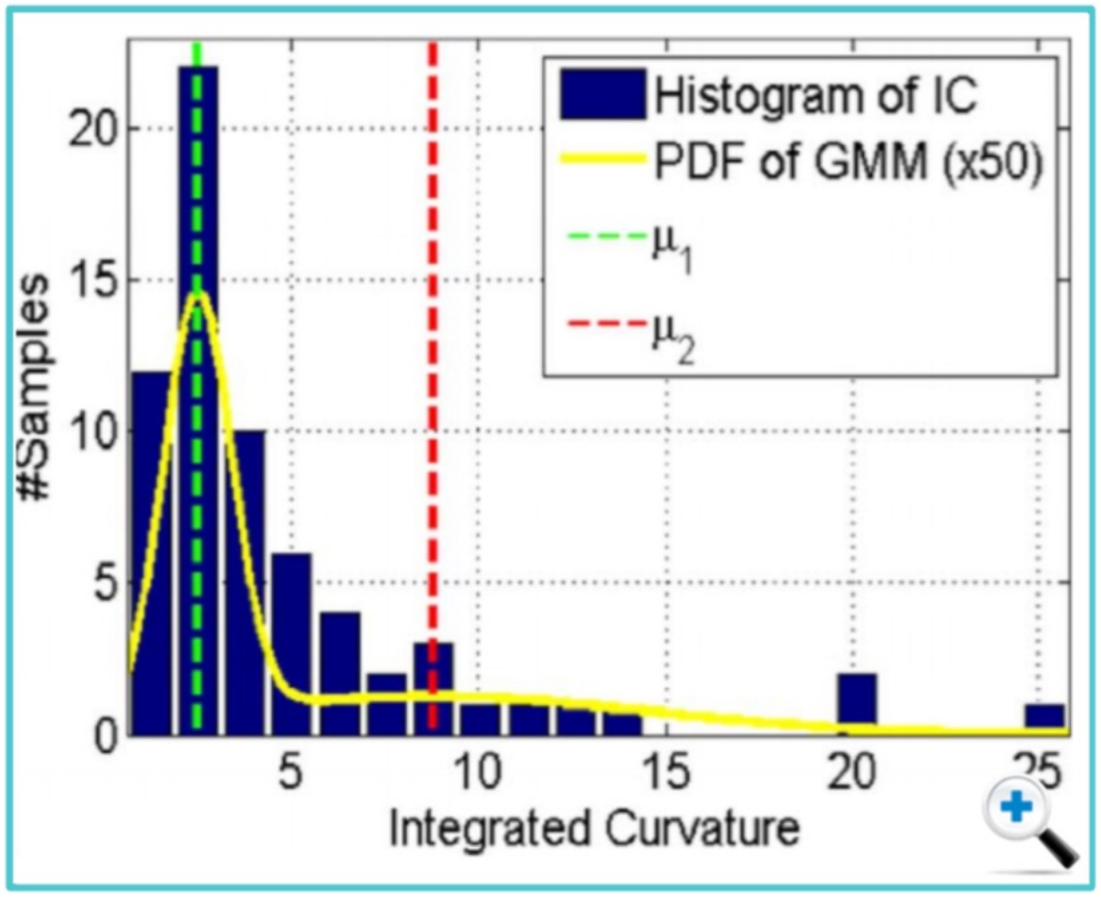

A
B
C
D

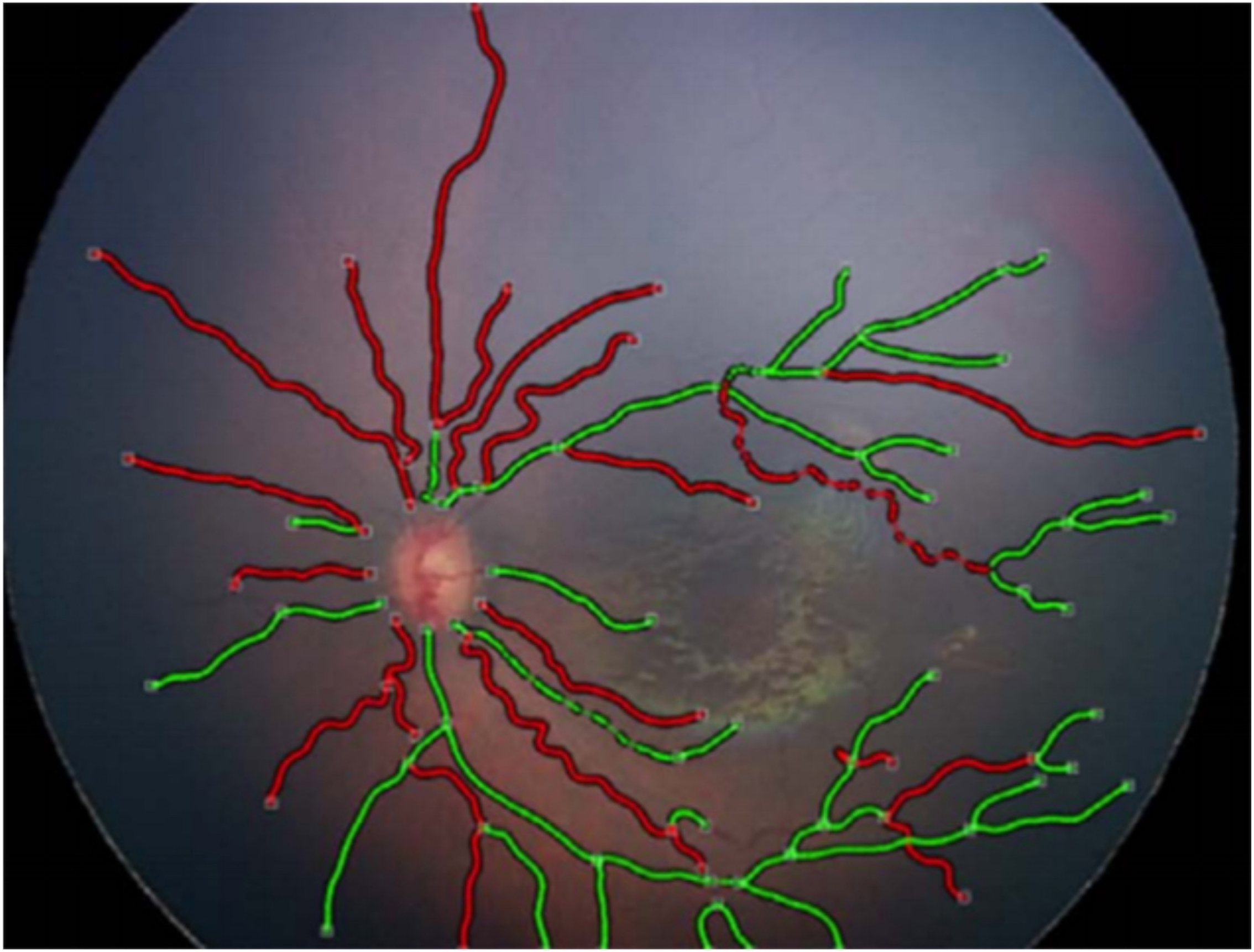
Example 5: Measurement of quantification of vascular tortuosity

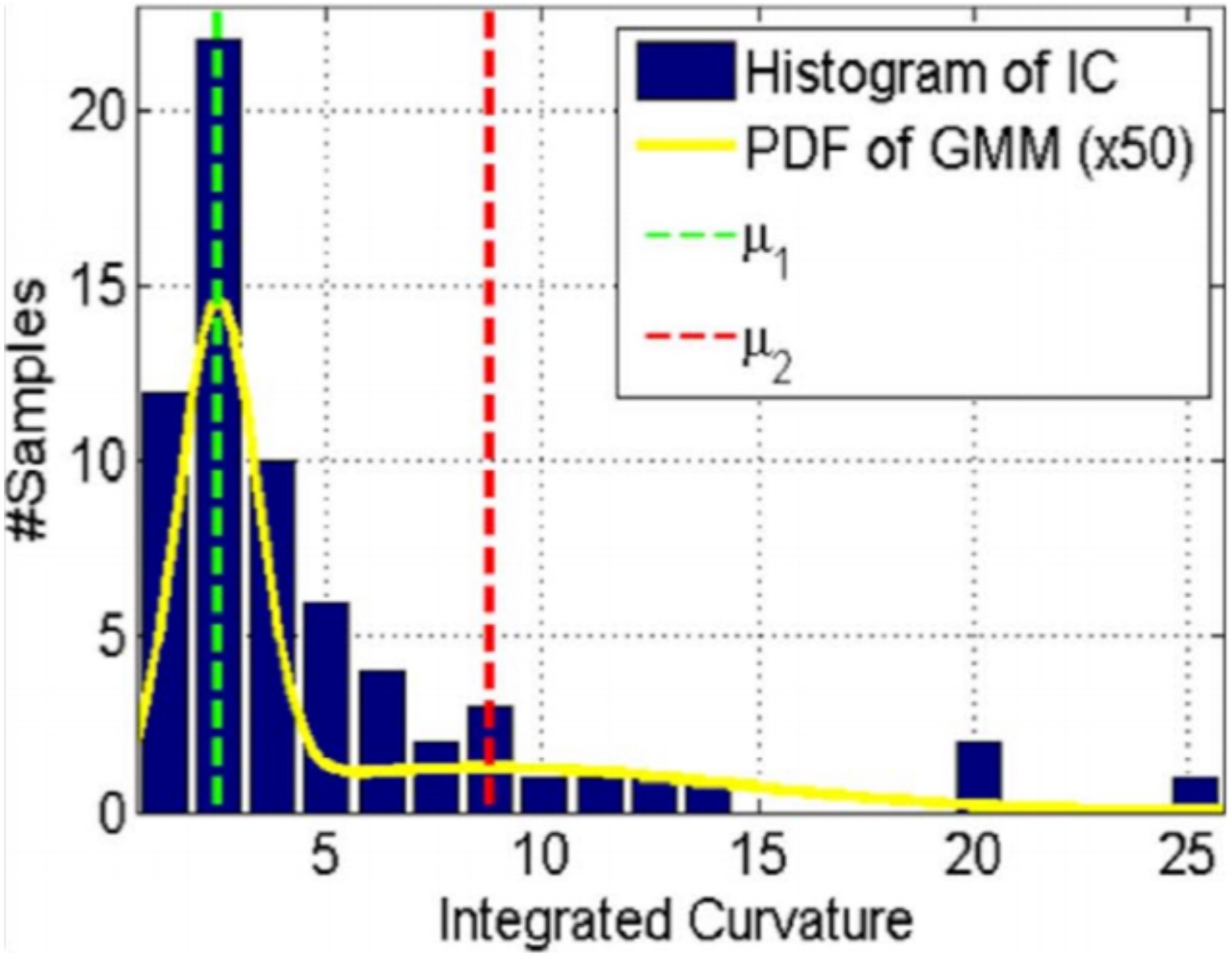
This is a study from a group of researchers in Italy, again showing vascular tortuosity measurements in an automated fashion.

Ataer-Cansizoglu E, Bolon-Canedo V, Campbell JP, et al. Computer-Based Image Analysis for Plus Disease Diagnosis in Retinopathy of Prematurity: Performance of the "i-ROP" System and Image Features Associated With Expert Diagnosis. *Transl Vis Sci Technol*. 2015; 4(6): 5.








Histogram of IC
PDF of GMM (x50)
μ_1
μ_2
#Samples
0
5
10
15
20
5
10
15
20
25
Integrated Curvature

Summary

ROP screening programmes that are **globally accessible** and **standardised** are required in order to identify, in a timely fashion, the infants most at risk for severe ROP.

In the future, screening needs to incorporate:

- Country-based epidemiology of infants at risk for severe ROP needing treatment
- Affordable wide-field digital photographic documentation of disease
- Automated digital image analysis of zone and vascular morphology to identify ROP