CHILDHOOD GLAUCOMA RESEARCH NETWORK

# Annual Meeting at the American Academy of Ophthalmology 2020

2019

The CGRN is an international organization of ophthalmologists who share a mutual interest in childhood glaucoma. CGRN membership currently includes 200+ ophthalmologists, clinicians, and scientists from 48+ countries in North and South America, Europe, Asia, Australia, Africa and the Middle East.

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# Indispensable Duty

”Science and the art of medicine can develop their highest bloom only if people collaborate…Everybody is responsible to include everything for the care of his patient regardless where it originates. So the join co-operation and effort from all of us is essential and indispensable duty.”

~Theodore Axenfeld

13th International Congress of Ophthalmology, Amsterdam 1929

# Impact of COVID-19

COVID 19 has not only changed us individually,

but also CGRN as a whole:

- Education
- Priorities
- New Collaboration
- International outreach
- Membership


# We have made great strides.

# Balkan Center Education

## The Future is Now

**Elena Bitrian, MD**
The Samuel & Ethel Balkan International Pediatric Glaucoma Center
Bascom Palmer Eye Institute
University of Miami

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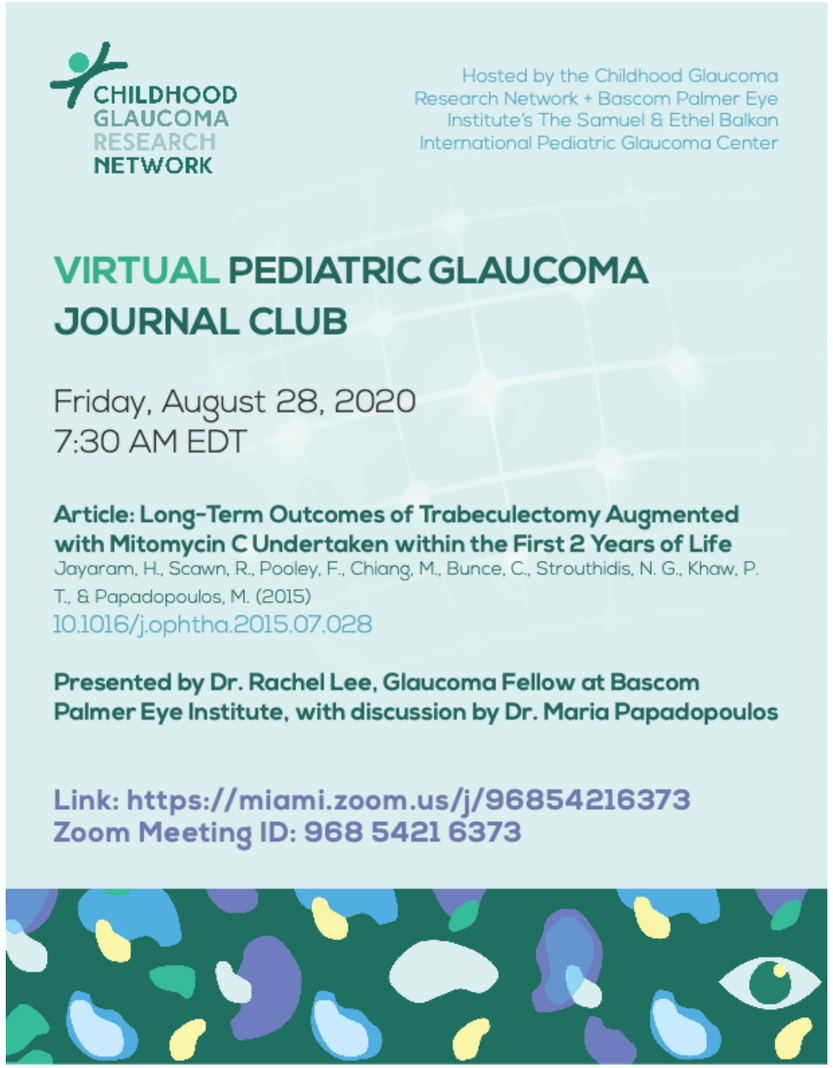
# CGRN Journal Club




- Hosted by the CGRN and Bascom Palmer Eye Institute and The Samuel and Ethel Balkan International Pediatric Glaucoma Center
- Held quarterly

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# Kolokotrones Lecture Series

- CGRN online lecture series
- Supported by the Kolokotrones Family
- Will be held quarterly


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# CGRN Surgery Course

## Course 603:

- **Prerecorded course**
- **Dry Wet Lab home kits**
- **Kits only available for those in the continental US**

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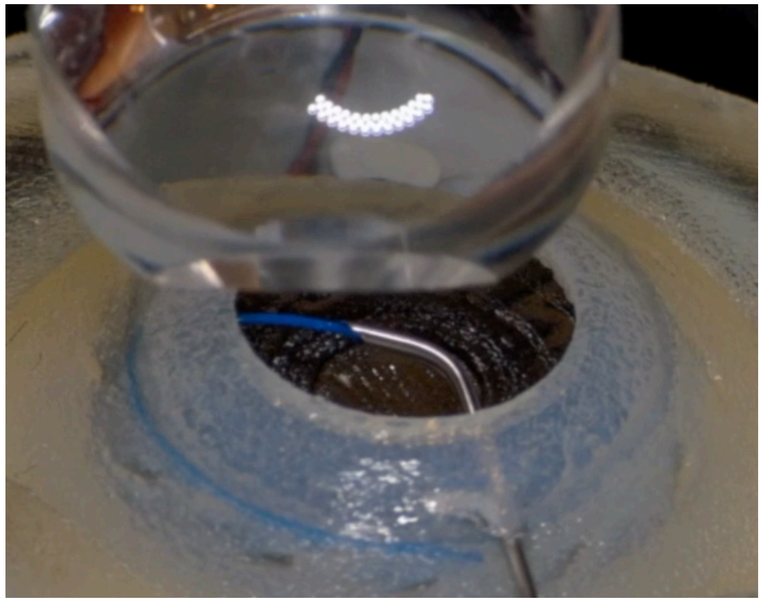

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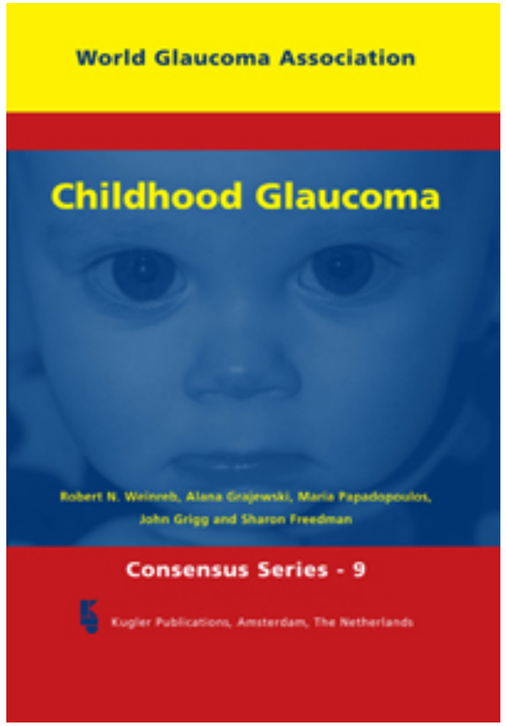
# CONSENSIS 9:  SPANISH TRANSLATION

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The Spanish translation of Consensus Series 9 will be published in **December 2020.**

The publication will be made available online (pdf; via WGA#One dashboard) free of charge to WGA members. The release will be via publication of IGR 21-2.

**WGA Consensus Series 9: Glaucoma Infantil**

Edited by: R.N. Weinreb, A.L. Grajewski, M. Papadopoulos, J. Grigg and S. Freedman

Translated by: E. Bitrian

ISBN: 978-90-6299-288-1

Hard copies are available (at cost) via Kugler Publications

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# WGA CONSENSUS 9: CHILDHOOD GLAUCOMA

The full text of WGA Consensus Series 9 is available free-of-charge through your WGA#One account:

https://wga.one/wga/consensus-downloads/

Consensus 1-8 are also available through the same link


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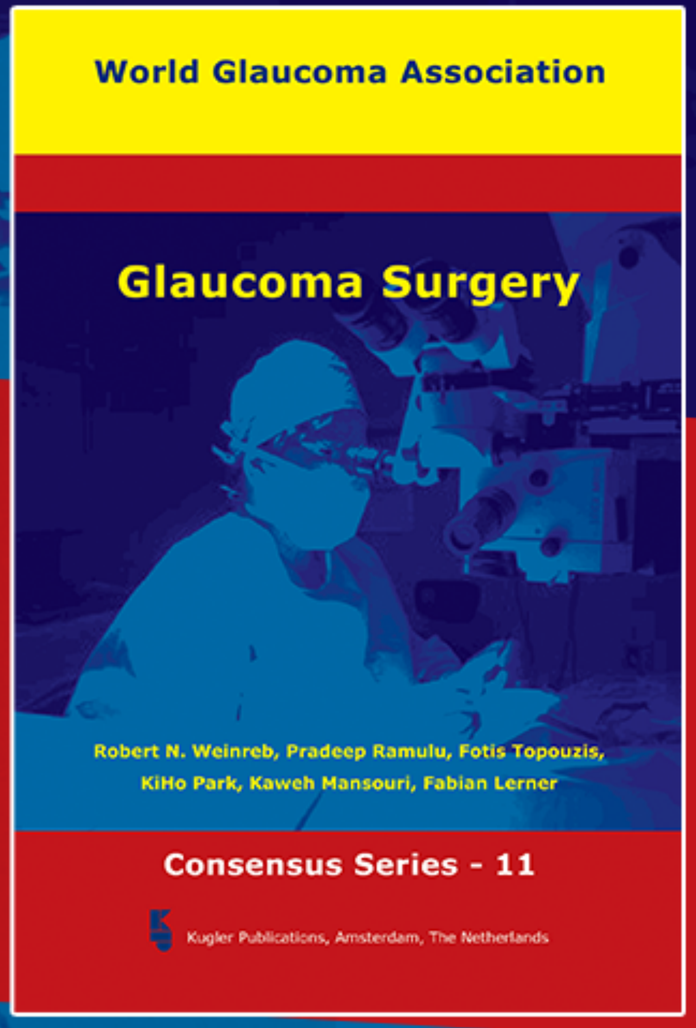


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# MIGS in Kids

**James Brandt**
Vice-Chair for International Programs & New Technology
Director of the Glaucoma Service
Professor of Ophthalmology & Vision Science

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# MIGS in Kids

## *The Role of the CGRN*

CHILDHOOD GLAUCOMA RESEARCH NETWORK


James D. Brandt, M.D.

Professor of Ophthalmology & Vision Science

Vice-Chair for International Programs & New Technologies

University of California, Davis

Director, Glaucoma Service

Tschannen Eye Institute at UC Davis Health

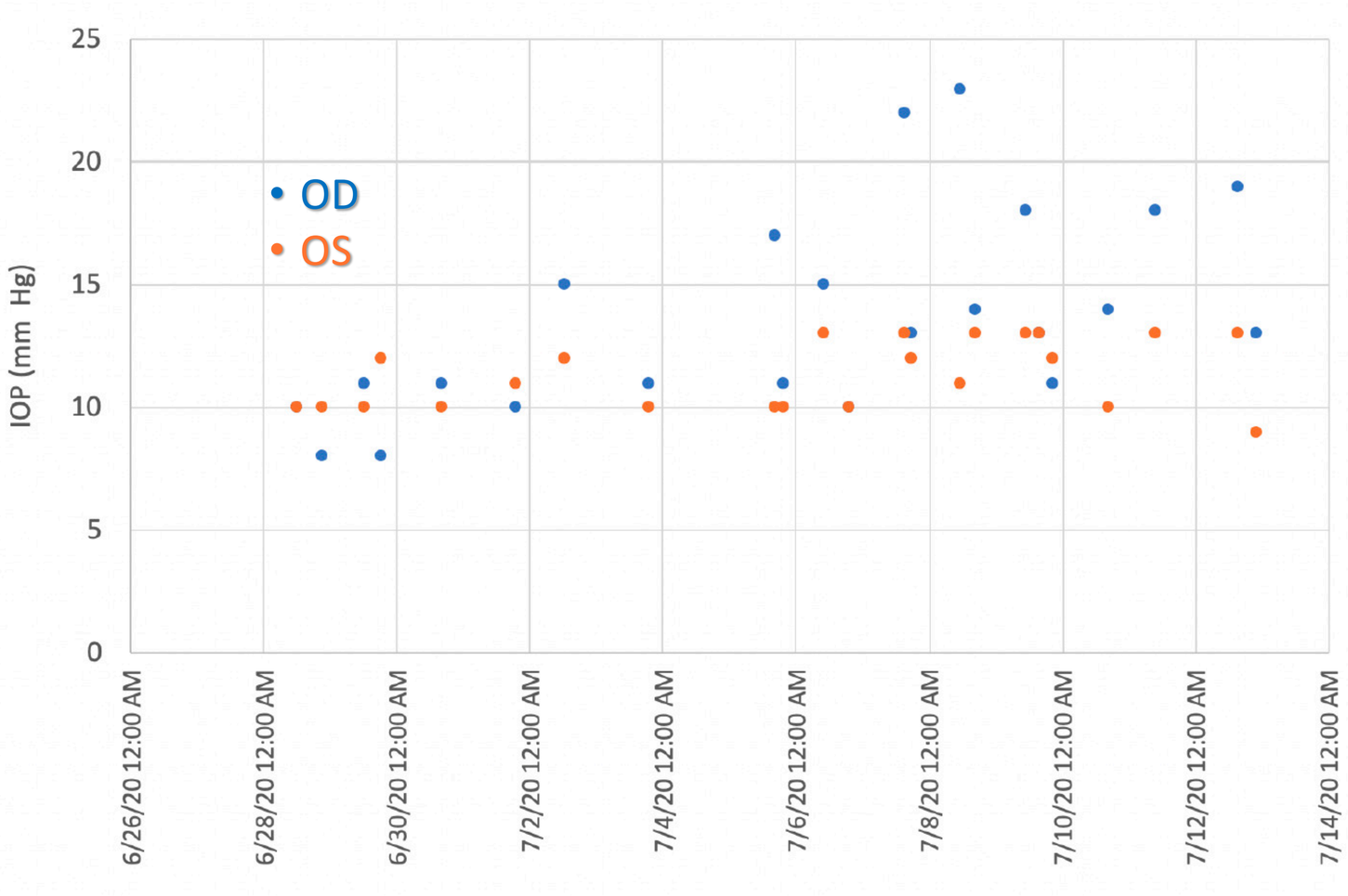
Sacramento, California USA

# Case Example

- 4 year old boy with late-diagnosed PCG
- Underwent bilateral GATT at 1 year
  - Great IOP response with cupping reversal
- In 2020 IOPs begin to drift up OD with increasing myopia, cupping

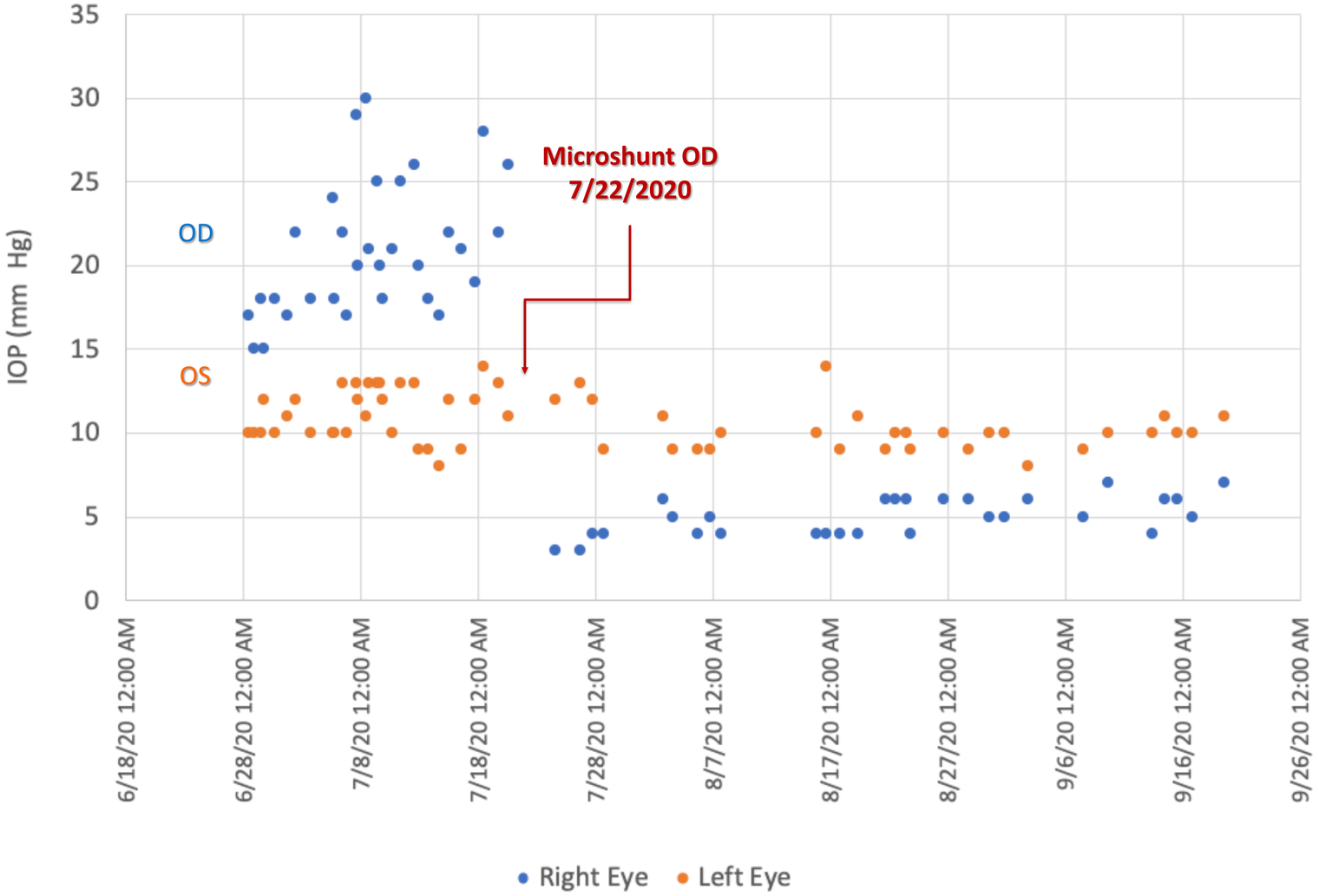
# Home IOP Data

- Dad is an engineer
- Purchased an iCare™ tonometer to monitor his son's IOPs at home



# Pediatric PreserFlo Surgery Video

# Case 10 – IOP Scatterplot



# CGRN & Clinical Trials

- CGRN can play a role in
  - Providing the patients and clinicians for a trial
  - Provide trial infrastructure, e.g., medical monitors, data safety committee, etc.

**Framing the important questions to be answered**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# CGRN & Childhood Glaucoma

## Why Genetics is Important?

**Terri Young MD**
Chair, University of Wisconsin Department of Ophthalmology and Visual Sciences
Peter A. Duehr Distinguished Professor of Ophthalmology
Professor of Pediatrics
Professor of Medical Genetics

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# CHILDHOOD GLAUCOMA RESEARCH NETWORK- WHY GENETICS IS IMPORTANT

Presented by Terri L. Young, MD, MBA, FARVO
Professor of Ophthalmology, Medical Genetics, and Pediatrics
Chair, Department of Ophthalmology and Visual Sciences

DEPARTMENT OF
Ophthalmology
and Visual Sciences
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

**Childhood Glaucoma Research Network**

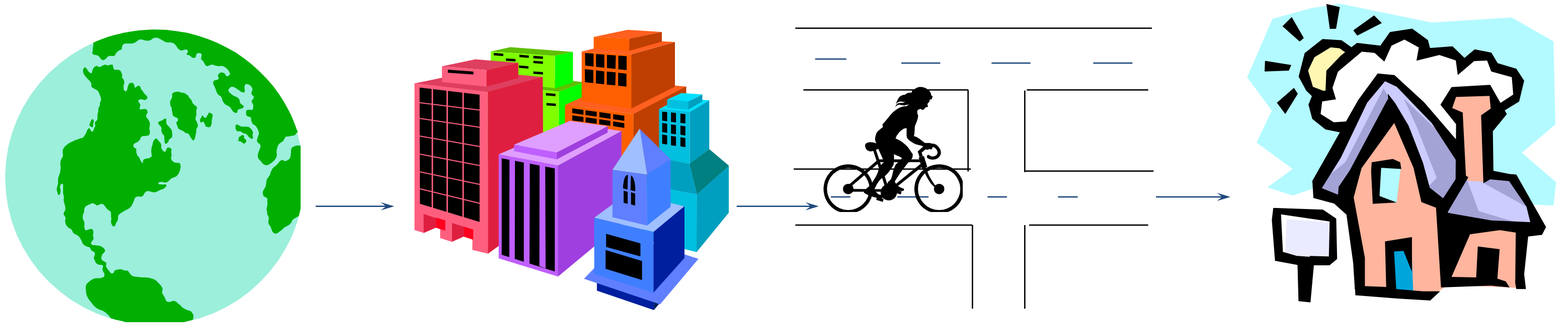
**November 15, 2020**

Disclosure: Aerpio Pharmaceuticals

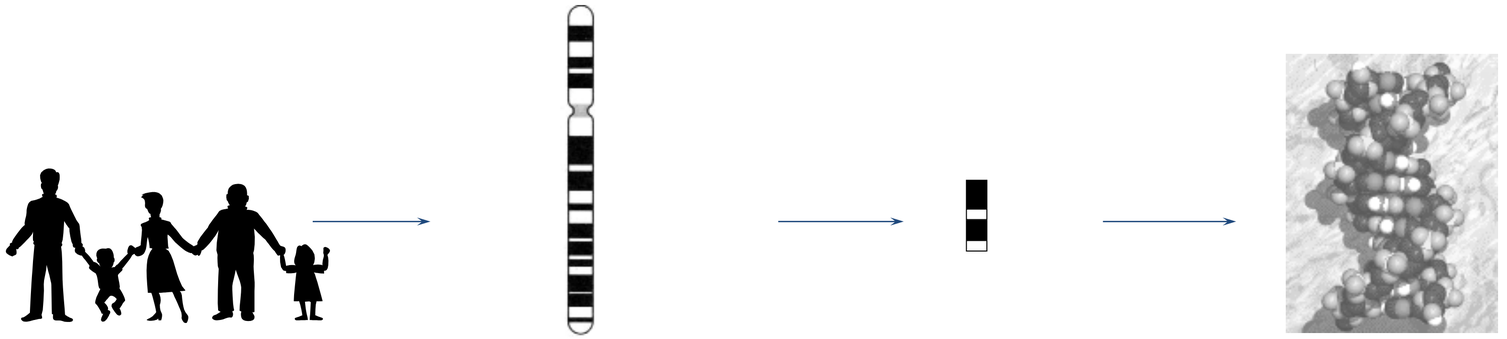
# Alice Walker

- “Look closely at the present you are constructing: it should look like the future you are dreaming.”

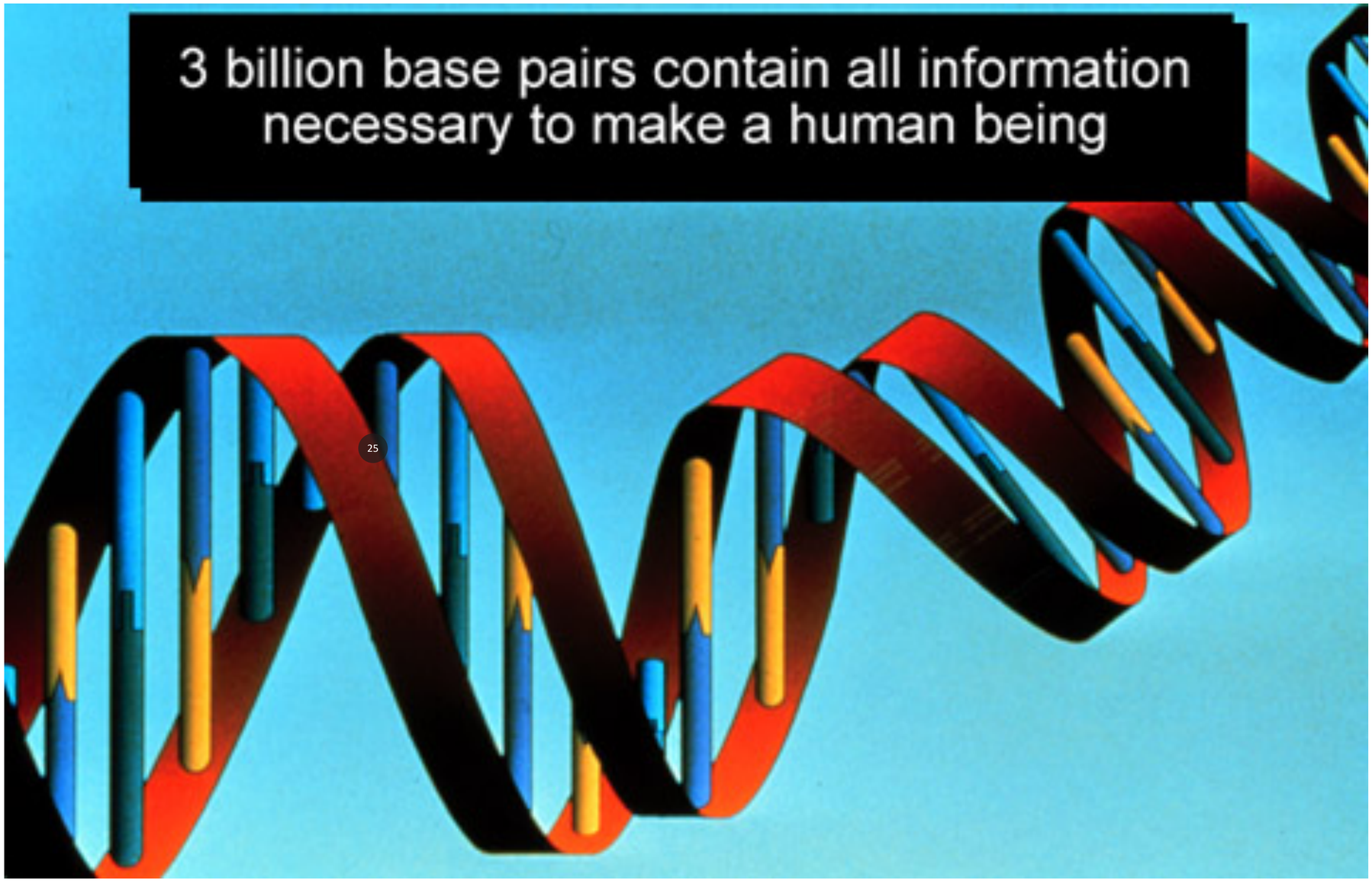
# Search for Disease Genes



Earth → City → Street → Address



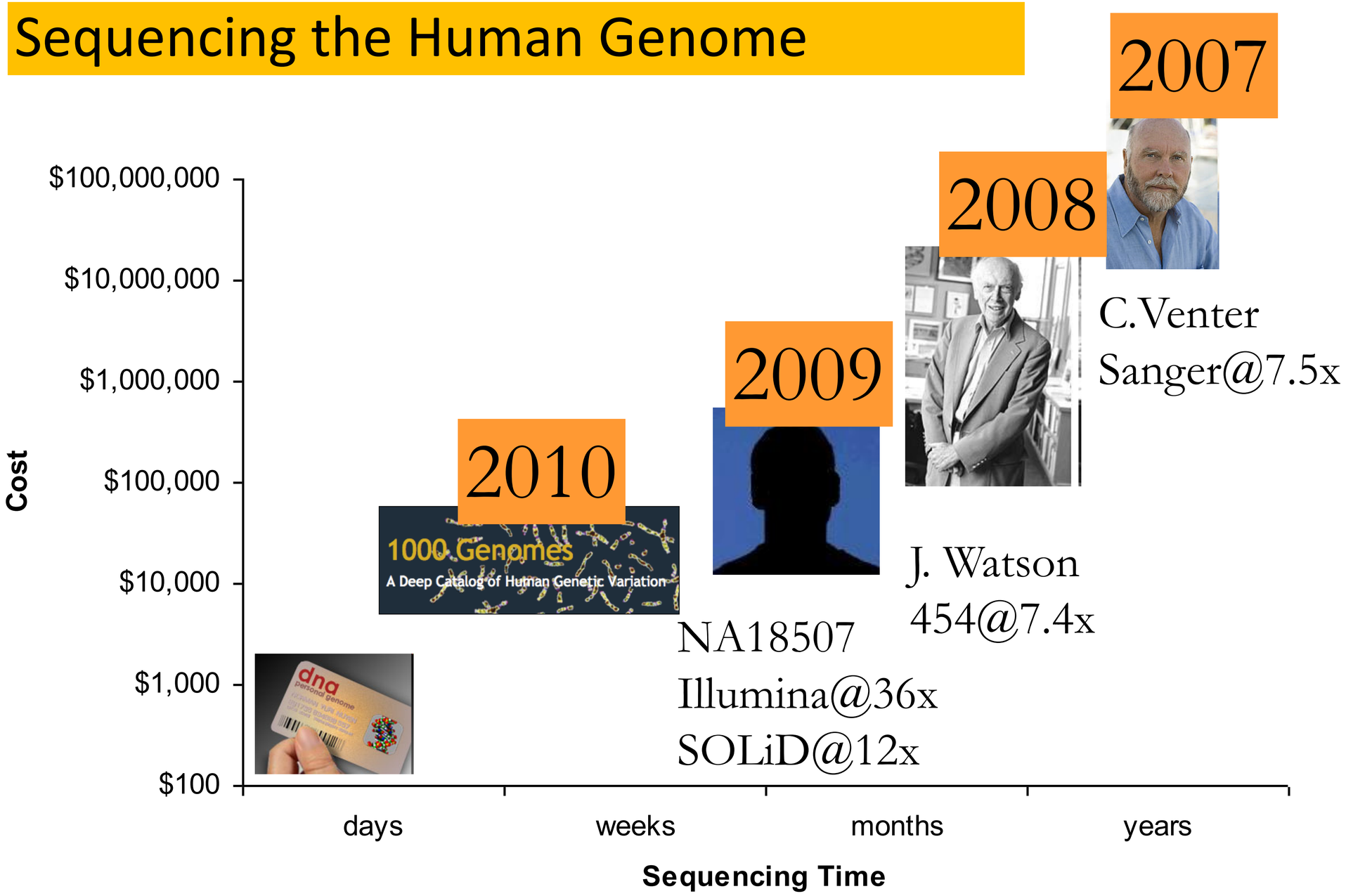
Human Genome → Chromosome → Band → Gene (DNA)






**~30,000 genes in human DNA**

# Sequencing the Human Genome



# What Happens Once We Identify Candidate Genes?

- Determine gene function
- Evaluate gene variations
  - “normal” (polymorphisms)
  - disease causing (mutations)
- Improve clinical management
  - More accurate and earlier diagnosis
  - More accurate prognosis
  - Develop better treatments
    - Right drug to right patient (pharmacogenetics)

# Positive Test IMPACT– ANTICIPATORY AND PROACTIVE

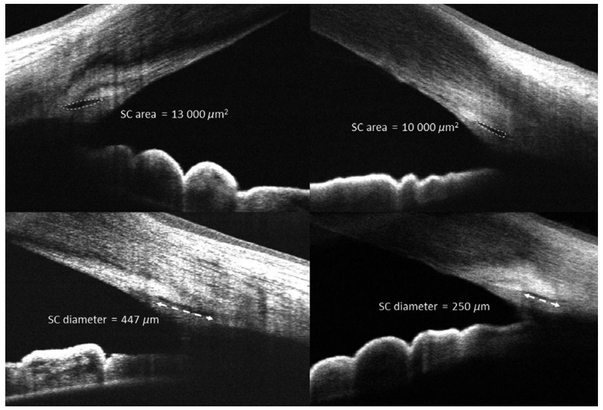
- Surveillance
- Possible life-style change- instituted early - diet, educational program
- Surgery
- Chemotherapy for treatment or prevention
- Genetic counseling

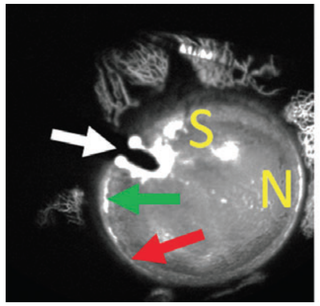
# Imaging of Schlemm's Canal and Aqueous Flow in Pediatric Glaucoma Surgery

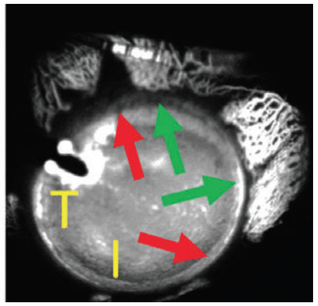
**Microscope integrated AS OCT**

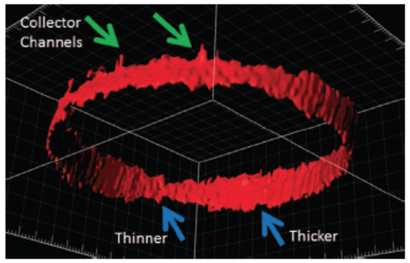
**Aqueous angiography**

**Individualized surgery, with better outcomes**




Comparative Intraoperative Anterior Segment OCT Findings in Pediatric Patients with and without Glaucoma.**Bradfield Y**, Barbosa T, Blodi B, Tompson SW, McLellan GJ, Struck M, Young TL. Ophthalmol Glaucoma. 2019 Jul-Aug;2(4):232-239.

# Genomics of Childhood Glaucoma

**Next-generation sequencing of families with glaucoma**

- **Functional assays**
- **I*n-silico* bio-informatics**
- **CRISPR Cas 9 transgenic mouse modeling**
- **Therapeutic development**
- **Prognostic and treatment strategy information to families**

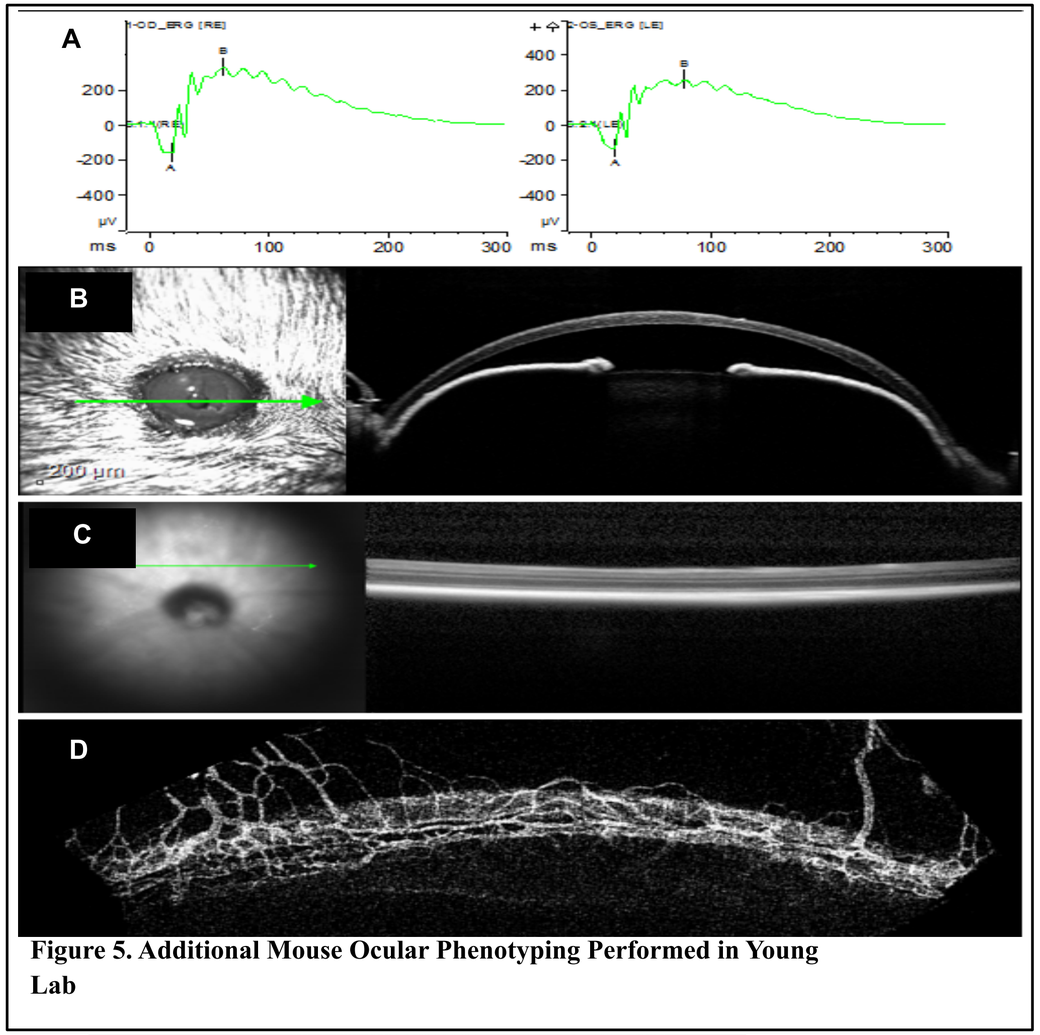
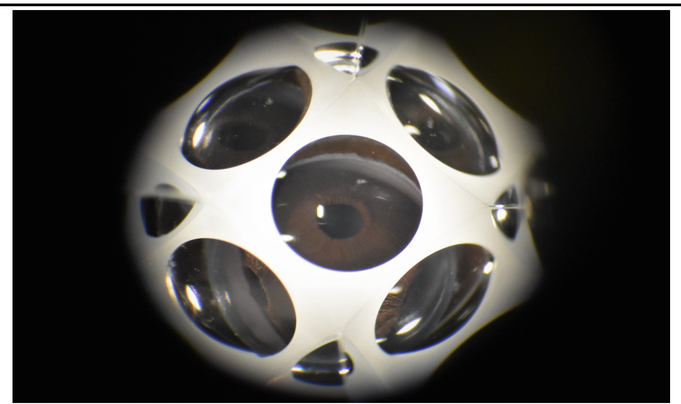
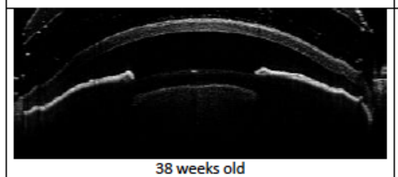
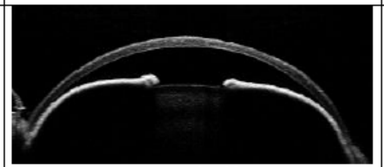
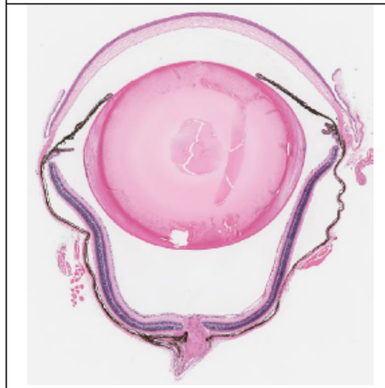
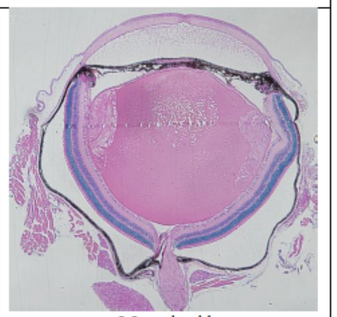



**Figure 5. Additional Mouse Ocular Phenotyping Performed in Young Lab**




**Preliminary Data: Possible Angle Closure in *Gja1* Heterozygous Mice**

| WILD-TYPE | HETEROZYGOUS | HOMOZYGOUS |
|---|---|---|
|  38 weeks old |  38 weeks old |  3.6 weeks old |
|  15 weeks old |  5 weeks old |  3.3 weeks old |

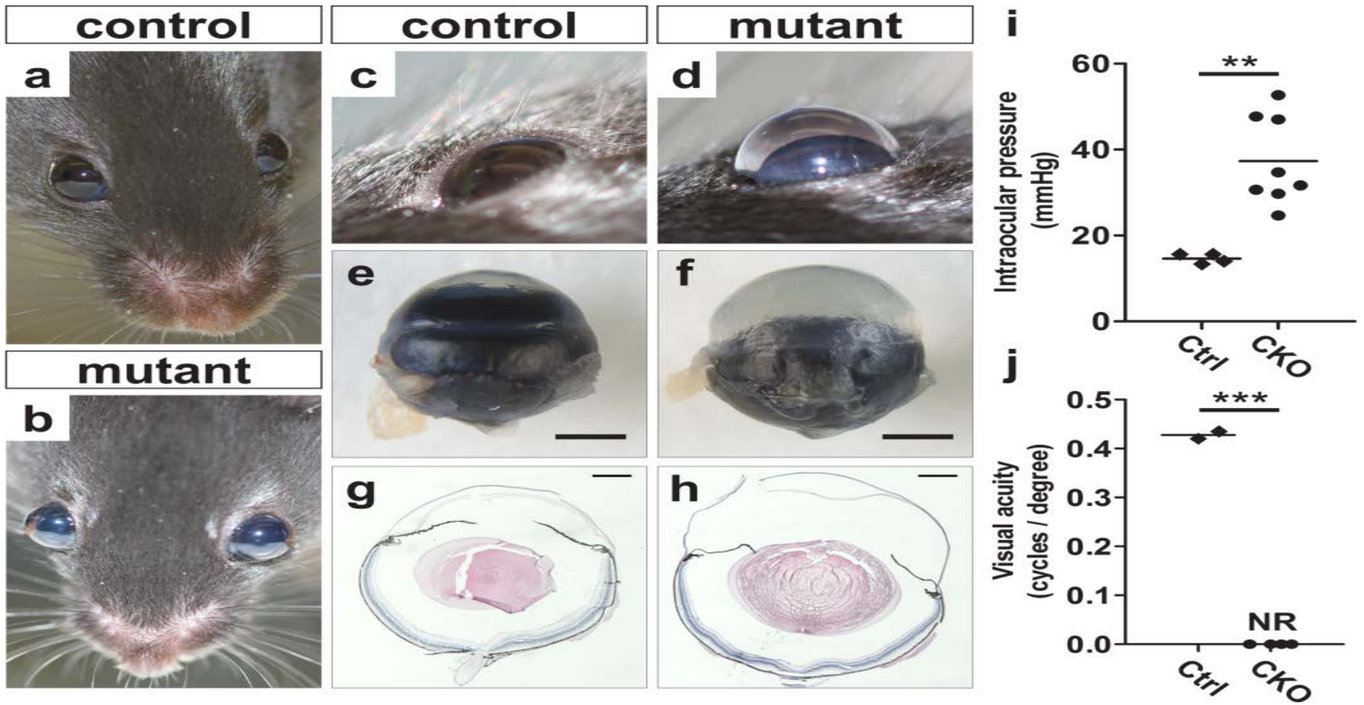
UBM of an infant eye with PCG, narrow angle and large lens
Courtesy of Drs. Chang and Grajewski

Zhao Y, ET AL. (2013) Cyp1b1 Mediates Periostin Regulation of Trabecular Meshwork Development by Suppression of Oxidative Stress. Mol. Cell. Biol. 33(21):4225-40.

- Shebani et al. previously showed that mice deficient in Cyp1b1 (Cyp1b1-/-) exhibit increased oxidative stress (OxS) and degeneration of the trabecular meshwork (TM) due to decreased periostin production and disintegration of collagen fibrils, which maintain TM structure and function.

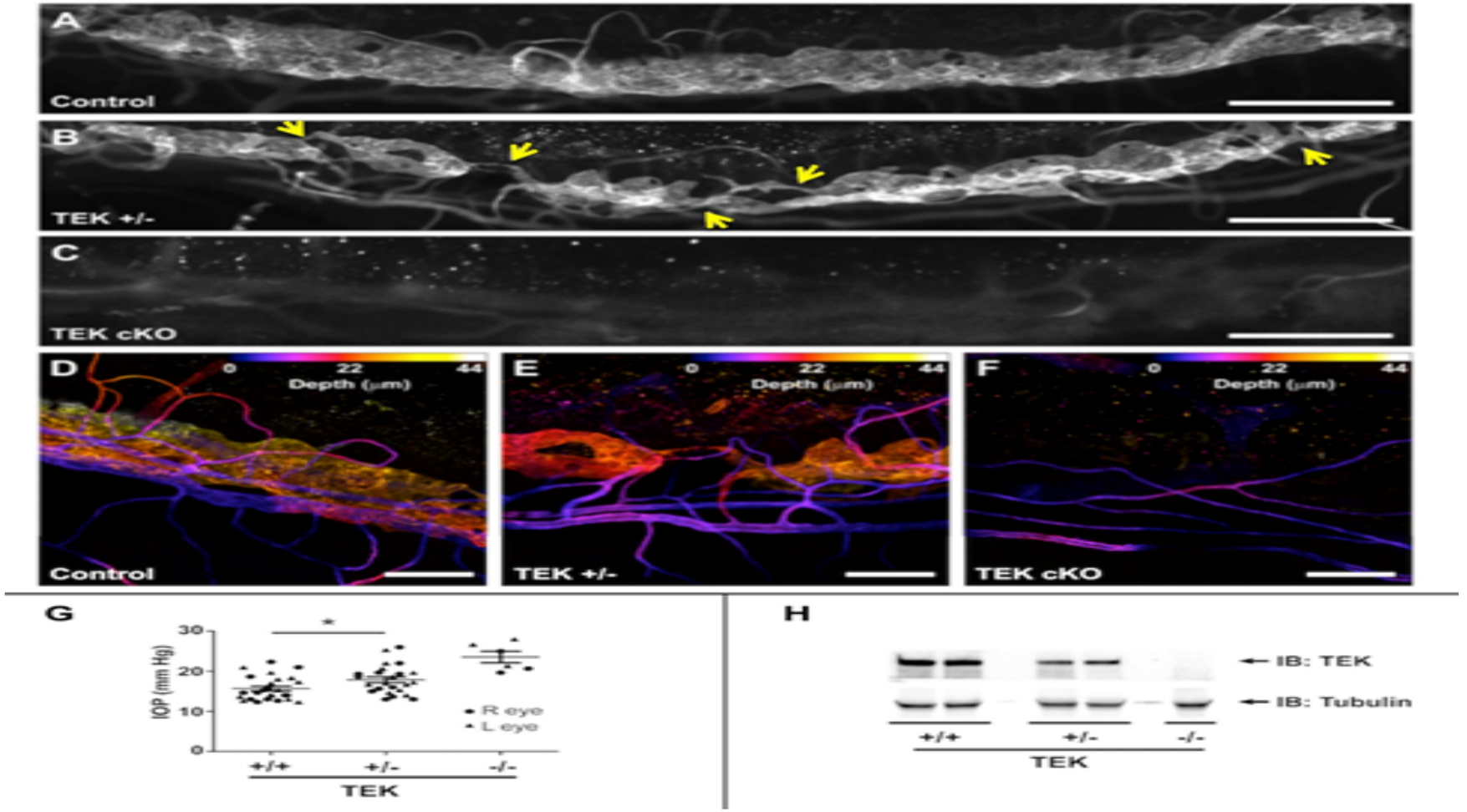
- Attenuation of OxS restores normal development of SC and TM tissues associated with Cyp1b1 deficiency. Potential protective impact using the antioxidant N-acetylcysteine.

# Tie2 (TEK) Knock Out Mouse

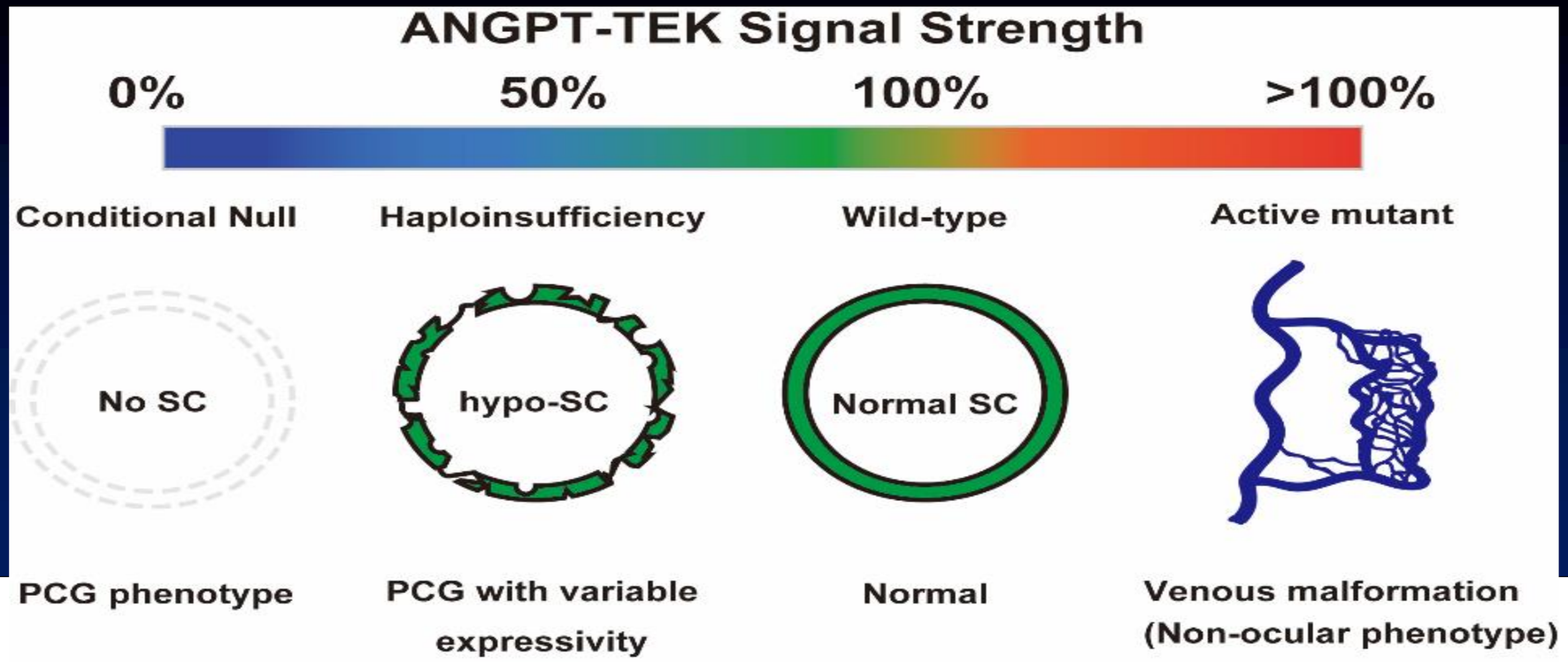



Thomson BR, Heinen S, Jeansson M, et al. A lymphatic defect causes ocular hypertension and glaucoma in mice. J Clin Invest 2014;124:4320-4.

# Schlemm's Canal Imaging



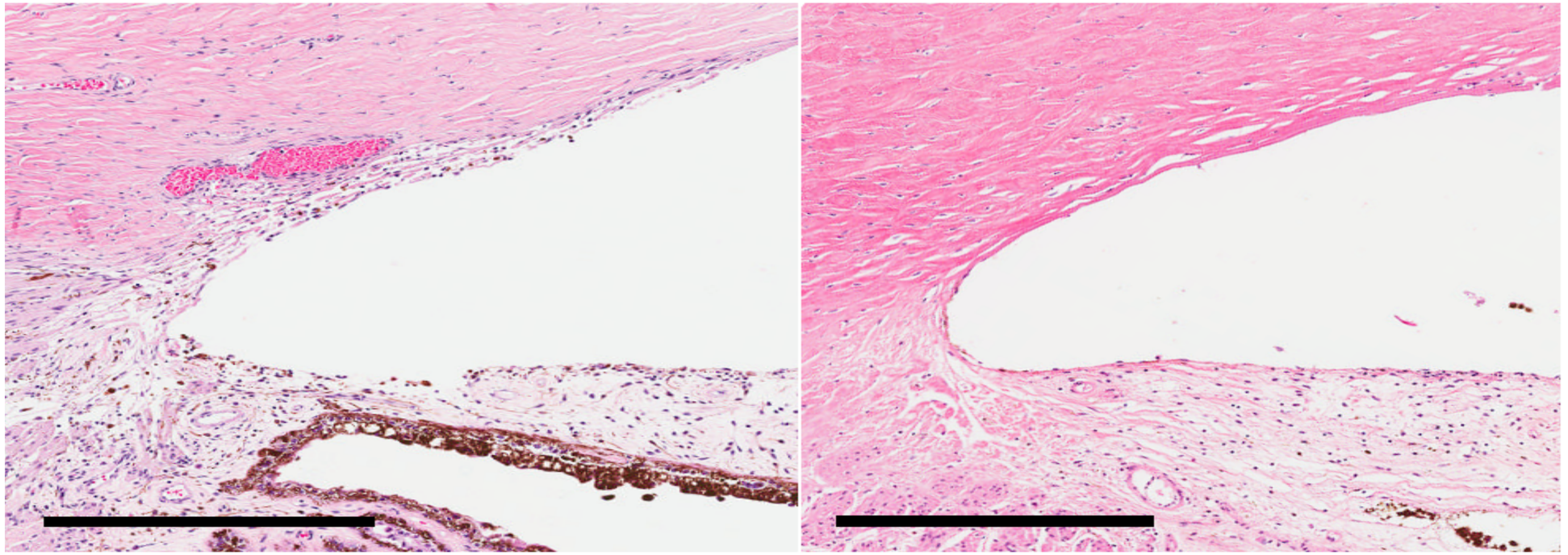

Souma T, et al. . Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity. J Clin Investi. 2016 Jul 1;126(7):2575-87.




**Model for ANGPT-TEK signal strength and human disease.** Shows the importance of ANGPT-TEK signal strength as a critical determinant of ocular and non-ocular vascular phenotypes. In the complete absence of ANGPT-TEK signaling after embryonic day 17.5,
Schlemm's canal (SC) is not formed and conditional null mice exhibit a severe PCG-like phenotype. 50% reduction of the signal leads to severely hypomorphic SC formation with elevated IOP in mice, and PCG in humans with variable expressivity. In human patients, gain-of-function mutations in *TEK* result in venous malformations in non-ocular tissues.

**Thomson BR, *et al*. Angiopoietin-1 is required for Schlemm's canal development in mice and humans. J Clin Invest. 2017 Nov 6**

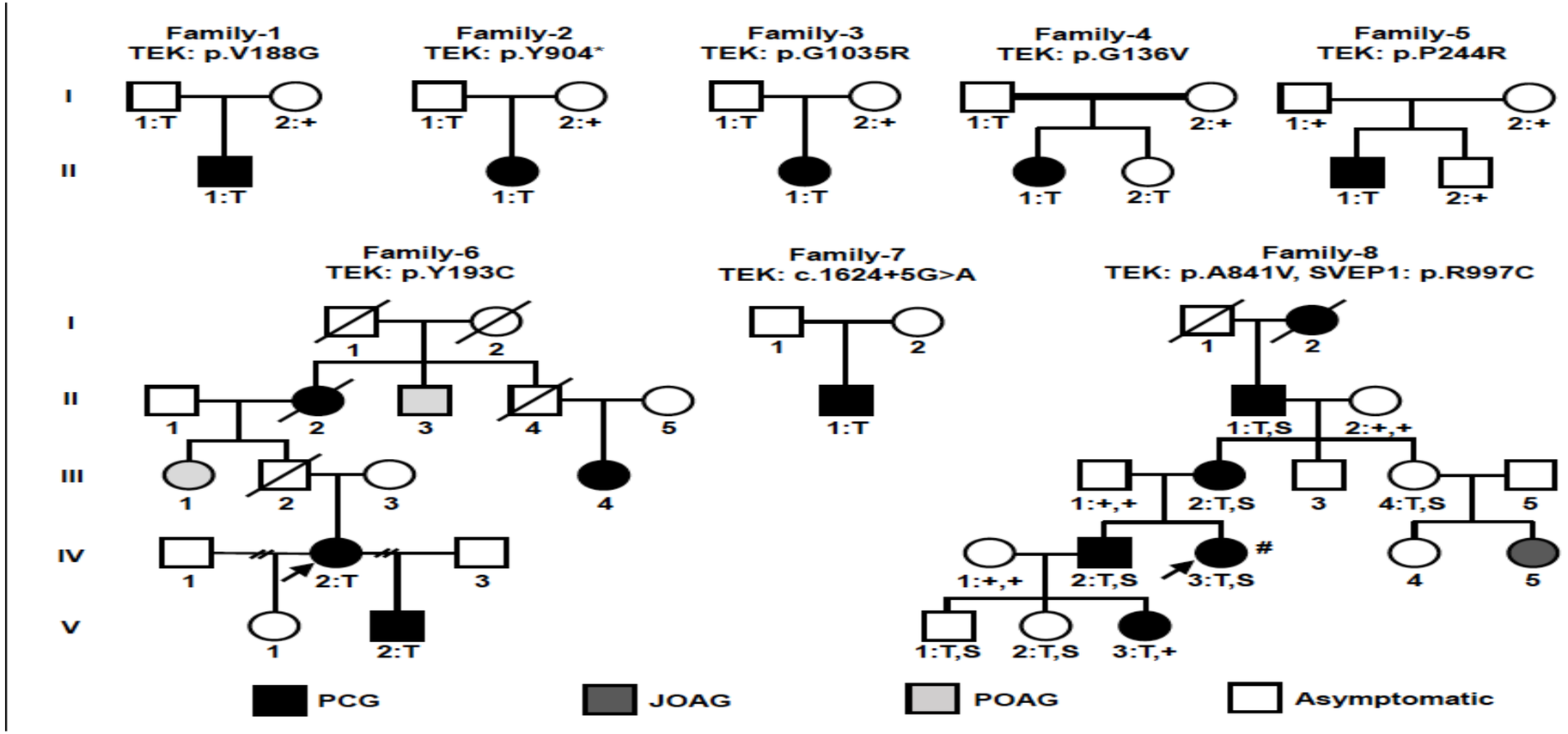
# SVEP1 Modifier to TEK Mutation



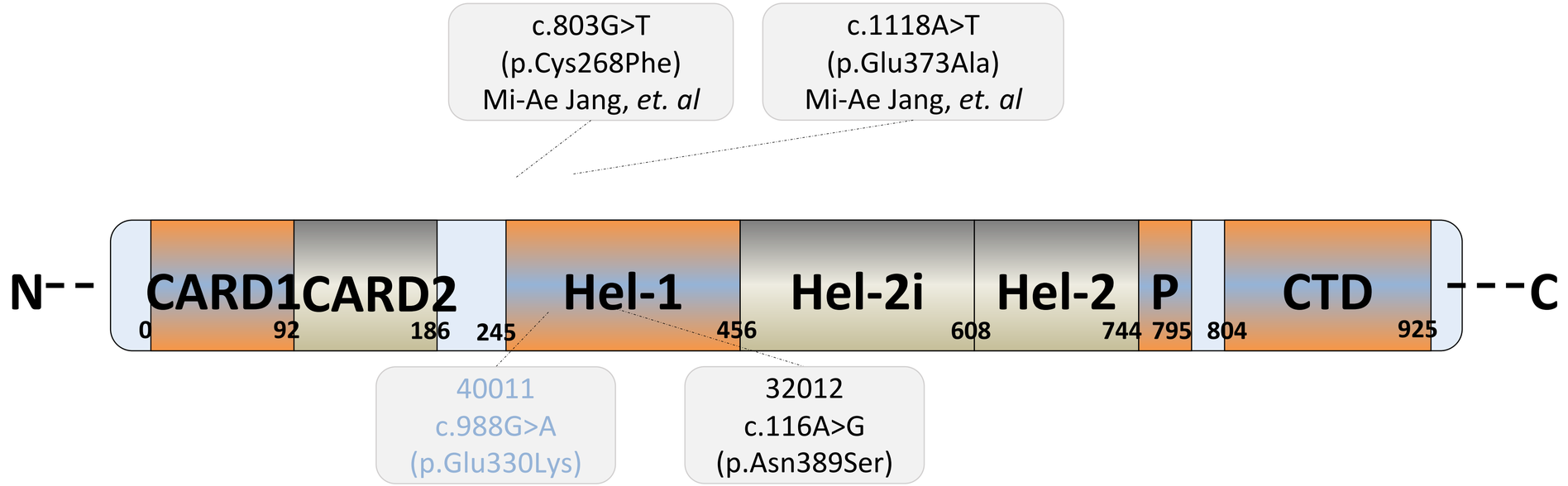
**Pathology of iridocorneal angles from a PCG-affected member of Family-5 (right) and an unrelated age-matched control without ocular disease (left).** Histological sections were hematoxylin and eosin stained. Note: Schlemm's canal is blood-filled in the control eye, as this globe was enucleated following a BB gun injury. Scale bar 400um.

# Tompson ST, *et al*. SVEP1 as a genetic

# SVEP1 modifier to TEK mutations



# Mutations Primarily Cluster within the Hel-1 Domain




**CARD**, caspase activation recruitment domain; **CTD**, C-terminal domain; **Hel**, helicase domain (Hel-1 and Hel-2 are the two conserved core helicase domains, and Hel-2i is an insertion domain conserved in DDX58-like helicase family); and **P**, pincer of bridge region connecting Hel-2 to the CTD involved in binding dsRNA.

**DDX58 is DExD/H-Box Helicase 58, aka RIG-1 (retinoic-acid inducible gene 1); highest ocular expression in choroid / retinal pigment epithelium and trabecular meshwork.**

**Young TL, *et al*. Novel DDX58 gene mutation associated with childhood glaucoma. *Invest. Ophthalmol. Vis. Sci.*. 2019; 60(9):2835.**

# Points of Interest

- **PARADIGM SHIFT**
  - New mechanistic explanation of PCG etiology- CYP1B1, TEK/ ANGPT pathway, DDX58, GJA1
  - Autosomal dominant inheritance with incomplete penetrance
  - Variable expressivity- PCG in the context of a manifestation spectrum- infant to adult with variable degrees of severity (incorporates early POAG clinical category)

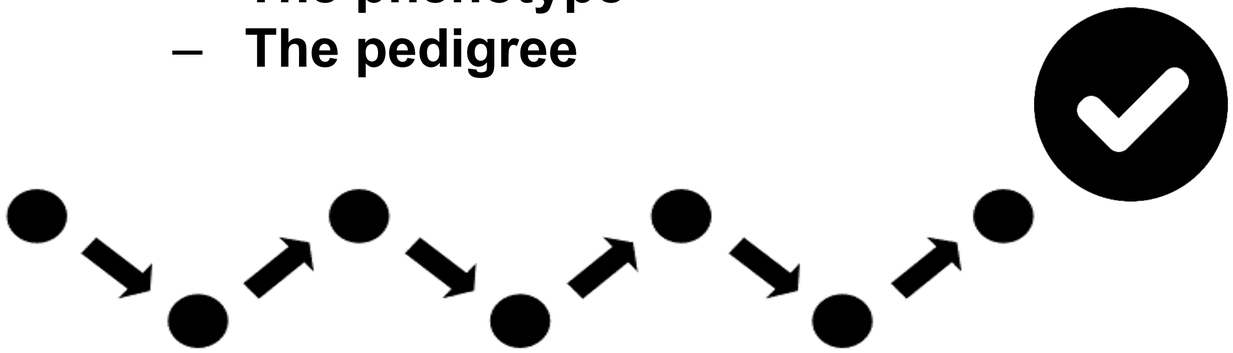
- **THERAPEUTIC PERSPECTIVE**
  - Important to collect families and any systemic findings
  - May influence initial treatment strategy
  - New avenue for developing therapies

- **Impaired angiopoietin/Tie2 signaling compromises Schlemm's canal integrity and induces glaucoma.** J Clin Invest. 2017 Oct 2;127(10):3877-3896.
- **Targeting Schlemm's canal in the medical therapy of glaucoma: current and future considerations.** Adv Ther. 2017 May;34(5):1049-1069.

# Multiple Steps- BUT THE BIG QUESTION IS WHY DO WE TREAT ALL CONGENITAL GLAUCOMA WITH THE SAME HAMMER?

- Interpretation
- Mutation versus polymorphism
- Does the result match?
  - The phenotype
  - The pedigree

- Co-segregation analysis
- Prognosis
- What else to look for
- Treatment



GENETIC TESTING

# Acknowledgements

**Patients and their families!**

- Research to Prevent Blindness, Inc.
- The University of Wisconsin Centennial Scholar Funds
- The NIH / National Eye Institute (R01 EY014685)
- The University of Wisconsin Peter A. Duehr Endowed Professorship

# Acknowledgements


- U of Wisconsin- Madison: **Stuart Tompson, Kristina Whisenhunt, Sean Martin**
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- Dean McGee Eye Institute, University of Oklahoma, Oklahoma City, Oklahoma: **Tammy Yanovitch**
- University of Western Australia, Perth: **Luba Kalaydjieva, Dimitar N. Azmanov, David Mackey**
- Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany :**Francesca Pasutto**
- Department of Ophthalmology, Flinders University, Adelaide, Australia: **Jamie Craig, Kathryn Burdon, Owen Siggs**
- Massachusetts Eye and Ear Infirmary: **Janey Wiggs**
- Bioinformatics Institute, Agency for Science Technology and Research, Singapore: **Vachiranee Limviphuvadh, Sebastian Maurer-Stroh**
- University of Sao Paolo, Brazil: **Simone Finzi**

# The CGRN-Harley Registry

**Alex Levin, MD**
Adeline Lutz - Steven S.T. Ching, M.D. Distinguished Professorship in Ophthalmology
Chief, Pediatric Ophthalmology and Ocular Genetics
Flaum Eye Institute
Chief, Pediatric Genetics
Golisano Children's Hospital

**Presented by Alana L. Grajewski, MD**
The Samuel & Ethel Balkan International Pediatric Glaucoma Center
Bascom Palmer Eye Institute
University of Miami

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# CGRN-HARLEY: UPDATES

Transition of leadership: Alex Levin – Director at the University of Rochester

The CGRN-Harley registry is **ongoing.**

**800+ patients , 40 centers, 20+ countries,** across **all 5 continents.**

## Currently undergoing a renovation of the some of the fields to make data entry easier.

**Thanks to funding from Rochester and Harley fund**

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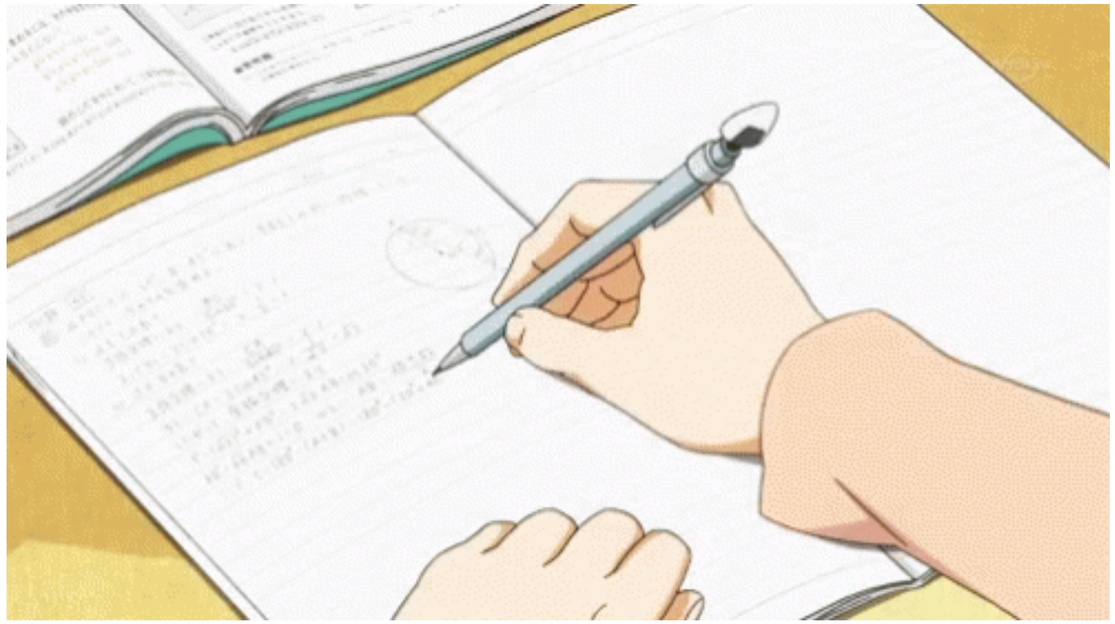
# CGRN-HARLEY: WHAT'S NEXT

We are looking **to collaborate**.



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# CGRN-HARLEY: CONTACT UPDATES

**Alex Levin** - **alex_levin@urmc.rochester.edu**
Codirector

**Lisa Latchney - lisa_latchney@urmc.Rochester.edu**
Coordinator

Or contact CGRN

**Anthony Broad** – **abroad@med.Miami.edu**

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# Severity Staging System of Childhood Glaucoma

## A Proposal for Multicenter CGRN Collaboration

**Huda Sheheitli**
Assistant Professor of Glaucoma
University of Minnesota

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# SSSCG: BACKGROUND

Establishing a staging system would allow clinician to use a standard severity scale for patient stratification in research studies and clinical trials worldwide.

This would help analyze the outcomes and efficacy of alterative treatments among the different disease severity states and ultimately guide treatment decision-making.

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# SPECIFIC AIMS

- Examine the long-term effect of early candidate traits on visual acuity and IOP control outcomes in childhood glaucoma patients by modeling retrospectively collected data.

- Construct a Severity Staging System in Childhood Glaucoma (SSSCG) using a weighted point-value system based on the relative contribution of each trait, or risk factor, to the final visual acuity and IOP outcomes.

- Assess the validity of SSSCG using the retrospectively collected data from an independent cohort of patients.

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# METHODS

Childhood Glaucoma Research Network (CGRN), a consortium of childhood glaucoma tertiary care centers

- UC Davis, Dr. James Brandt as PI
- Akron Children Hospital, Dr. Rachida Bouhenni as PI
- Minnesota Lion's Children's Eye Clinic, Dr. Raymond Areaux as PI
- The Children's Mercy Hospital, Dr. Erin Stahl as PI
- Oregon Health & Science University (OHSU), Dr. Beth Edmunds as PI
- Centro Hospitalar Lisboa Norte (CHLN), Portugal, Dr. Luis Pinto as PI
- American University of Beirut, Lebanon, Dr. Christiane Al-Haddad as PI

Patients with childhood glaucoma (diagnosed prior to age of 18 years)

- Followed for at least five years

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# PRELIMINARY DATA

**TABLE 3.** Variables From Third Visit (Mean 6.69 mo Following Presentation) Associated With Final LogMAR Visual Acuity

| Variable | Increase in Final LogMAR | 95% CI | *P* |
|---|---|---|---|
| Presence of anterior segment dysgenesis | 0.64 | 0.12, 1.15 | 0.016 |
| Presence of nystagmus | 0.76 | −0.01, 1.53 | 0.052 |
| Failed angle surgery | 0.58 | −0.03, 1.18 | 0.062 |

LogMAR indicates logarithmic minimum angle of resolution; CI, confidence interval.

**TABLE 4.** Variables From 3-year Visit Associated With Final LogMAR Visual Acuity

| Variable | Increase in Final LogMAR | 95% CI | *P* |
|---|---|---|---|
| Failed amblyopia therapy | 1.30 | 0.65, 1.96 | <0.0001 |
| Failed angle surgery | 1.34 | 0.88, 1.80 | <0.0001 |
| Presence of nystagmus | 1.21 | 0.55, 1.87 | 0.0003 |
| Presence of media opacity | 0.85 | 0.14, 1.57 | 0.018 |
| Presence of anterior segment dysgenesis | 0.64 | 0.12, 1.15 | 0.016 |

LogMAR indicates logarithmic minimum angle of resolution; CI, confidence interval.

**TABLE 5.** Variables From 3-year Visit Associated With Final IOP-control Categories

| Variable | Proportional Odds Ratio | 95% CI | *P* |
|---|---|---|---|
| Presence of media opacity | 12.88 | 1.01, 163.92 | 0.049 |
| Failed angle surgery | 6.77 | 1.05, 43.53 | 0.044 |

IOP indicates intraocular pressure; CI, confidence interval.

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# NEXT STEPS

- **Step 1:** Bascom Palmer Test of Concept
  - **Complete**
- **Step 2:** Test the hypothesis on a larger patient population
  - Data collection and analysis underway
- **Step 3:** Deduce a scale from the variables
- **Step 4:** Validate the scale




CHILDHOOD GLAUCOMA RESEARCH NETWORK

# PPB:
# Pediatric Preventable Blindness

## The Suriname Project

**Adriana Grossman, MPH, MHA, MS**
The Samuel & Ethel Balkan International
Pediatric Glaucoma Center
Bascom Palmer Eye Institute
University of Miami

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# PPB: PROVIDING EARLY VISION SCREENINGS

PPB is screening infants and children in Suriname through collaboration with vaccination clinics

Screening will expand to other Caribbean nations

**We’re starting small, but going global by creating a model that can be used anywhere**

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# PPB: PEDIATRIC OCULAR DISEASE SCREENING MODEL

>>> Reaching the children early in disease process

>>> Screening children where they are

>>> Create a referral system for each country

>>> Centers of excellence can accommodate newly discovered patients

>>> Every child has access to screening, evaluation, and care

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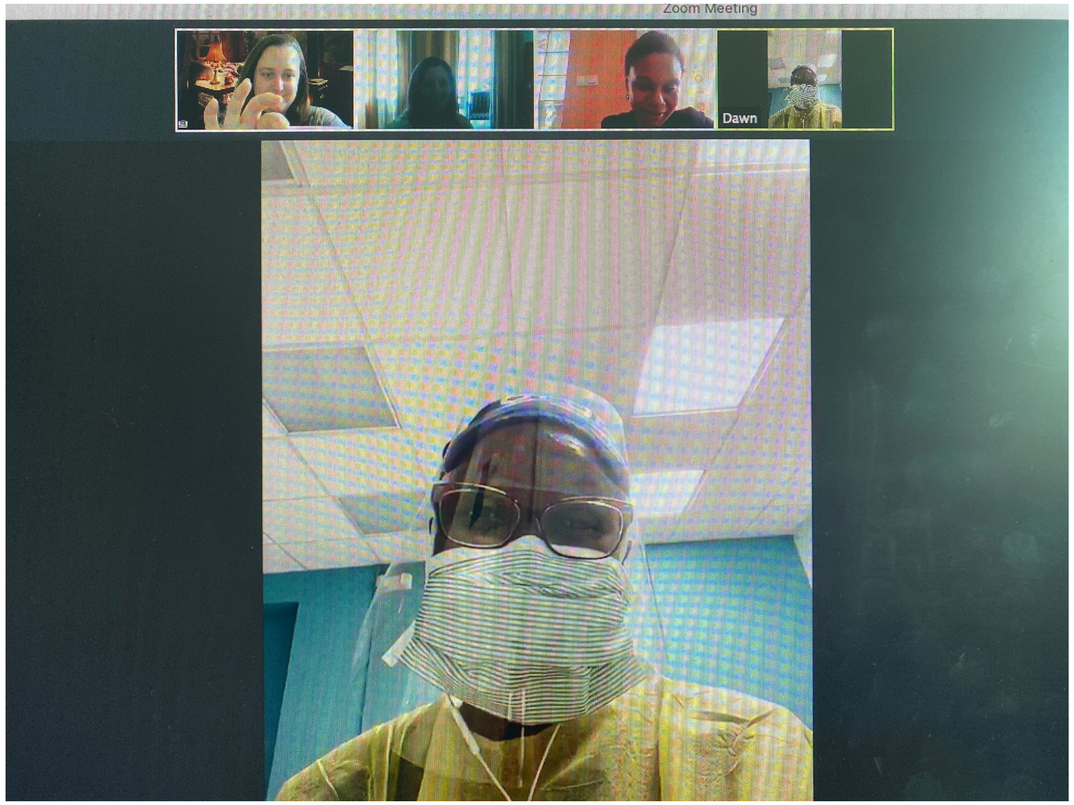
PPB: PREVENTABLE BLINDNESS
IN THE CARIBBEAN

# The issue of data

## We are now collecting data

Between Suriname and now Barbados our data collection has started and has persisted despite COVID19 obstacles.

**Triweekly meetings and new members**

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# New Members

Dr. David Callender – Pediatric Ophthalmologist in Barbados

Dr. Euclid Morris – Professor of Family Medicine at the UWI

# PPB: PREVENTABLE BLINDNESS IN THE CARIBBEAN


## The Pre-Policy Stage

### Building our Barbados partnership

### Ongoing data collection and training in Suriname

CHILDHOOD GLAUCOMA RESEARCH NETWORK

# PPB: PROGRAM DIRECTORS

**Director:** Alana Grajewski, MD – Bascom Palmer Eye Institute

**University of Suriname:**

Denise Doelwijt, MD - Program Director, Suriname Eye Centre

**University of the West Indies (UWI):**

**Barbados:** Dawn Grosvenor, MBBS, MRCOphth, FRCS (Glasg), FRCOphth—Lecturer in Ophthalmology, Faculty of Medical Sciences, UWI at Cave Hill

**Jamaica:** Lizette Mowatt, MBBS, FRCS (Ed), FRCO, CEST, Mmedsci—Head of Ophthalmic Division, Consultant Ophthalmologist, Associate Lecturer, UWI at Mona

**Trinidad and Tobago:** Desiree Murray, MBBS, FRCOphth, MSc(Lond)—Senior Lecturer in Ophthalmology, The UWI at St. Augustine

**Acknowledgement:** Matthew Javitt, MD

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# Childhood Glaucoma Research Network
# Upcoming Meetings & Events

## International

**Anthony Broad -** Program Coordinator
The Samuel & Ethel Balkan International Pediatric Glaucoma Center
Bascom Palmer Eye Institute
University of Miami

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# CGRN: WEBSITE AND YOUTUBE CHANNEL

Website: **childhoodglaucoma.com**

- Information available on published articles, presentations from past meetings and news on upcoming meetings from around the globe

YouTube Channel: **Childhood Glaucoma Research Network**

- Please contact, Anthony Broad, Clinical Program Manager, balkancenter@miami.edu for technical support, to post materials of interest to CGRN members, or for feedback and suggestions

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# UPCOMING CGRN: JOURNAL CLUB > 11/20/20

**Speaker:** Raymond Areaux, MD – University of Minnesota

**Article:** Follow-Up Adherence and Barriers to Care for Pediatric Glaucomas at a Tertiary Care Center

**REGISTER ON OUR WEBSITE OR THROUGH OUR INVITATION**

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# UPCOMING CGRN: UKPGS > ONLINE > 2021

REGISTER SUBMIT AN ABSTRACT

UKPGS

## UK Paediatric Glaucoma Society

Home Register Abstract submission 2021 Meeting Past Meetings About us

## UK Paediatric Glaucoma Society Annual Meeting

**Saturday 23rd January 2021, 10:30 - 16:30 GMT**

## Virtual Meeting only

Leading international specialist paediatric glaucoma researchers and clinicians sharing research and clinical experience

**Confirmed '*Pearls of Wisdom*' Speakers**

**James Brandt, USA - Sharon Freedman, USA - Julian Garcia-Feijoo, Spain**

69 Days 06 Hours 46 Mins

Registration open! REGISTER

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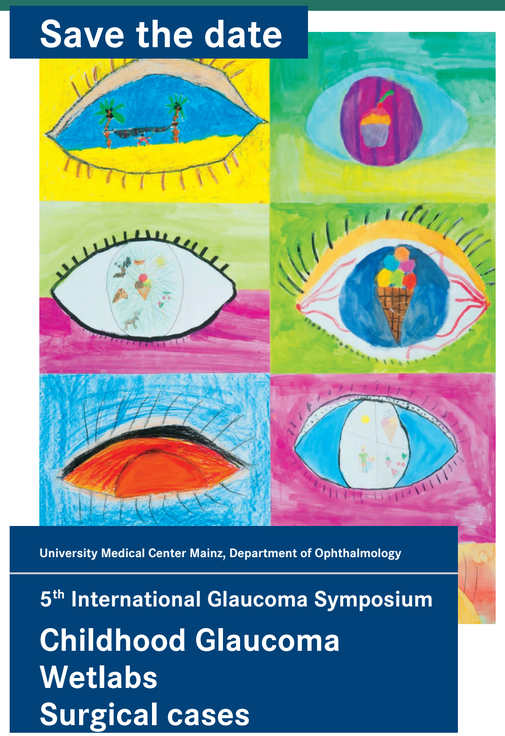
# PEDS GLAUCOMA: MAINZ, GERMANY > 2021




After careful consideration and with great regret Professor Esther Hoffmann and the congress organisation have taken the difficult decision to **postpone** the 5th International Glaucoma Symposium due to the COVID-19 pandemic.

**The meeting will be rescheduled to 3rd – 4th September 2021.**

All registered participants will be contacted to discuss the transfer of registrations to the new date.

In the meantime, we wish you and your loved ones good health.
We will be delighted to welcome you in Mainz 2021!

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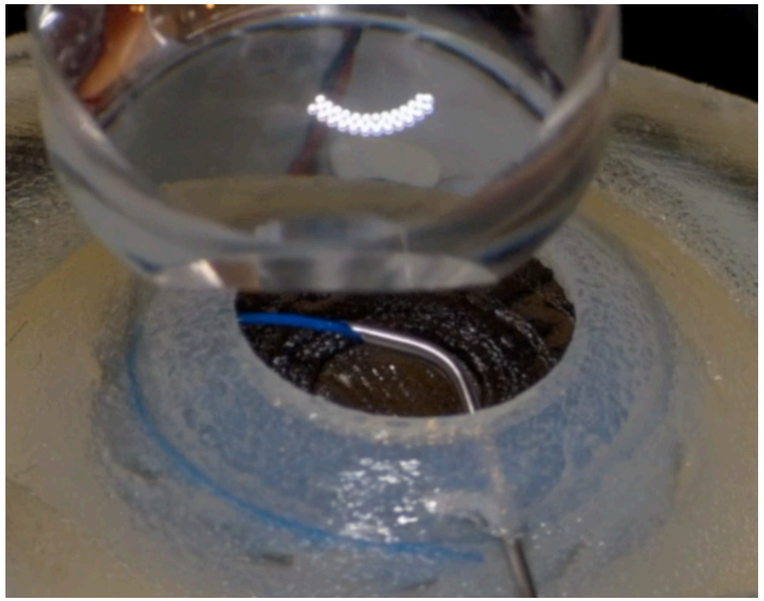
# CGRN Surgery Course

## Claim on –demand video until October 2021

### Course 603:

**Prerecorded course available for Dry Wet Lab from Home (kits available for Continental US only)**



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# Course Instructors

**Allen D. Beck, MD**
Emory Eye Center
*Atlanta, GA*

**Ta Chen Peter Chang, MD**
Bascom Palmer Eye Institute
*Miami, FL*

**James D. Brandt, MD**
UC Davis Health System
*Sacramento, CA*

**Elena Bitrian, MD**
Bascom Palmer Eye Institute
*Miami, FL*

**Sharon F. Freedman, MD**
Duke Eye Center
*Durham, NC*

**Karen Joos, MD**
Vanderbilt University
*Nashville, TN*

# THANK YOU

200+ members in 48+ countries

**Thank you for helping us change the way the world treats children with glaucoma.**

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