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WELCOME

DEAR MEMBERS AND GUESTS,

WELCOME TO LONDON! The Retina Society has not often held meetings outside the continental United States. However, with the change in bylaws allowing for full membership in the Society regardless of country of residence, meeting in England with easy access to Europe is so fitting.

The meeting will be held at the charming Landmark Hotel with across the street access to the Underground and thereby all of London. The Landmark, built circa 1899, is a renowned luxury hotel with 5-star facilities and services. The hotel is almost entirely booked by Retina Society Members and Guests, so in a sense it will be our totally private getaway.

WE ARE GRATEFUL to our Host Committee (CHAIR JIM BAINBRIDGE with BILL AYLWARD, ALAN BIRD, TIM JACKSON, and MICHEL MICHAELIDES), UK retinal specialists extraordinaire, for help in planning our meeting. In recognition of this international event a select number of eminent UK retinologists were invited to submit abstracts. I know we will all enjoy the input from several of our esteemed local colleagues.

WE KICK OFF on Wednesday afternoon at 12:30 pm with the popular Interesting Cases and Videos conference, to be followed by exceptional scientific sessions, posters and special lectures. This will be the 2nd year of our Innovations in Retina Lecture with the goal of introducing an aspect of medicine which will strongly affect our specialty but was not likely a part of our primary training. The topic this year is CRISPR, genetics and the unimaginable future that lies ahead. We are privileged to have as our distinguished speaker PROFESSOR JAMES BAINBRIDGE from UCL and Moorfields.

WE WILL CONTINUE TO experiment with our meeting APP to allow questions to be posed using a smart device. Of course, at the microphone comments are primary, but also comments from the audience (anonymous if you like) can be submitted through the APP, screened by the moderator and interjected when appropriate. Make sure you download the APP in advance of the meeting on your IOS or Android device. In post meeting reviews our members have consistently asked for more discussion. The program committee, aiming to fulfill this need, has assigned many more talks for discussion.

WE ARE QUITE FORTUNATE to have CAROL SHIELDS from Wills as our Gass Lecturer, and JAMES FUJIMOTO from MIT as our Retina Research Foundation Schepens Lecturer. Carol will talk about Uveal Melanoma and the Immune System, and Jim about future prospects for OCT. We also look forward to addresses from our Margherio fellowship awardee SALLY ONG from Wilmer and the Fellowship Research Awardee HARRIS SULTAN from Washington University.

THE SOCIAL PROGRAM IS SENSATIONAL! The welcome reception, a chance to reacquaint with old friends, will be at the Landmark Wednesday evening. On Thursday evening after a short bus ride we will be treated to dinner at The Guildhall, an unbelievable English meeting hall dating from early Renaissance! Our scientific meeting Friday is a half day, and in the afternoon we all head to Hampton Court, palace of Henry VIII. Return will be either by bus (or in part by boat on the Thames from HC for those who so elected) all in time for dinner or theater on your own in London. Saturday is a half-day, with afternoon time to explore some of your favorite London sites. That evening our Banquet will take...
place at the Landmark. You will enjoy listening/dancing to the super energetic music of the British group “The Rockets.” Our closing half-day is Sunday. And what a closing day it is! Stay around for hot off the press Late Breakers, among many other fascinating talks.

There are so many wonderful things to see and do around London. One of my personal favorites is the Old Operating Theater Museum dating from 1822. Surgery with neither anesthesia nor antisepsis, hmmm.... Options abound for exploring, dinner, theater or you name it. I hope many of you will be able to arrive early or extend your stay to see some of what London has to offer.

**THE BEST PART**, as in every annual RS meeting, is sharing time with old and new friends as we learn about future horizons in retinal research.

Bernie Doft, MD
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THE 52ND ANNUAL SCIENTIFIC MEETING | 9
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1994–1995       J. Wallace McMeel
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2002–2003       Harry W. Flynn
2004–2005       C. Pat Wilkinson
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2008–2009       Donald J. D’Amico
2010–2011       Mark S. Blumenkranz
2012–2013       Charles C. Barr
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2016–2017       Mark W. Johnson

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JANUARY, 2019

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Glenn Yiu, MD, PhD
Young Hee Yoon, MD, PhD
Akitoshi Yoshida, MD, PhD
Shigeo Yoshida, MD, PhD
Marc Yoshizumi, MD
Lucy Young, MD, PhD
Seung-Young Yu, MD, PhD
Lucy Young, MD, PhD
Seung-Young Yu, MD, PhD

David Zacks, MD, PhD
Nicholas Zakov, MD
Hadi Zambarakji, FRCSophth DM
Marco Zarbin, MD, PhD
Hernando Zegarra, MD
Ingrid Zimmer-Galler, MD
Keith Zinn, MD
Leonidas Zografos, MD
NEW MEMBERS 2019

ROBERT AVERY, MD
Santa Barbara, CA

CHRISTOPHER BRADY, MD, PhD
Burlington, VT

IAN CONSTABLE, FRANZCO
Nedlands, Australia

PETER GEHLBACH, MD, PhD
Baltimore, MD

ROGER GOLDBERG, MD, MBA
Walnut Creek, CA

MRINALI GUPTA, MD
New York, NY

MINEO KONDO, MD, PhD
Mie, Japan

ELEONORA LAD, MD, PhD
Durham, NC

SAUG JOON LEE, MD, PhD
Busan, S. Korea

PHOEBE LIN, MD, PhD
Portland, OR
NEW MEMBERS 2019

BRANDON LUJAN, MD
Portland, OR

D. WILKIN PARKE III, MD
Minneapolis, MN

EHSAN RAHIMY, MD
Palo Alto, CA

DIMITRA SKONDRA, MD, PhD
Chicago, IL

DIMITRA SKONDRA, MD, PhD
Chicago, IL

GLENN YIU, MD, PhD
Sacramento, CA

JOHN MILLER, MD
Boston, MA

YANNIS PAULUS, MD
Ann Arbor, MI

RAJEEV MUNI, MD, MSC, FRCS(C)
Toronto, Ont, Canada

Rupert Strauss, MD
Linz, Austria

Brandon Lujan, MD
Portland, OR

John Miller, MD
Boston, MA

Rajeev Muni, MD, MSC, FRCS(C)
Toronto, Ont, Canada

D. Wilkin Parke III, MD
Minneapolis, MN

Ehsan Rahimy, MD
Palo Alto, CA

Rupert Strauss, MD
Linz, Austria

Glenn Yiu, MD, PhD
Sacramento, CA

Dimitra Skonda, MD, PhD
Chicago, IL

Yannis Paulus, MD
Ann Arbor, MI
**Objectives**

*At the conclusion of this activity, learners should be able to:*

- Identify and discuss areas where genetic treatment can be of value clinically for patient care.
- Review how to use advances in imaging technology to more properly diagnose patients with retinal disease with less potential risk and better diagnostic acumen.
- Identify various vascular diseases that result in capillary non-perfusion and apply appropriate treatments.

**CME Accreditation and Credit Designation**

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Beaumont Health and The Retina Society. Beaumont Health is accredited by the ACCME to provide continuing medical education for physicians.

Beaumont Health designates this live activity for a maximum of 25.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

*Number of credits subject to change; final credits will be determined based on final agenda and will be listed on the final CME handout provided in advance of the seminar.*

**Staff and Content Validation Reviewer Disclosure**

The CME Committee members and CME staff involved with this activity as content validation reviewers have reported no relevant financial relationships with commercial interests.

**Resolution of Conflicts of Interest**

In accordance with the ACCME Standards for Commercial Support of CME, Beaumont Health implemented mechanisms, prior to the planning and implementation of this CME activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

**How to Claim Credit**

Please see separate CME handout for instructions on how to claim CME credits and conflicts of interest information.
PROGRAM-IN-BRIEF

WEDNESDAY | SEPTEMBER 11
7:00 am Speaker Ready Room Set Up — Champagne Room
8:00 am Exhibit Set Up — Marble Ballroom
11:00 am Speaker Ready Room Opens
9:00 am – noon The Retina Society Executive Committee Meeting — Landmark I
11:00 am – 5:00 pm Meeting Registration — Ballroom Hall
12:30 – 3:45 pm Interesting Retinal Cases/Video Presentation — Grand Ballroom
4:20 – 6:35 pm Scientific Session
7:00 – 10:00 pm Welcoming Reception — Winter Garden

THURSDAY | SEPTEMBER 12
7:00 am Meeting Registration — Ballroom Hall
Exhibits/Continental Breakfast/Breaks — Marble Ballroom
7:30 am – 10:00 am Spouses/Guests Hospitality — Garden Terrace
9:30 am – 3:00 pm Spouses Tours to Buckingham Palace or British Museum
(see pages 24 & 25 for bus information)
7:30 am – 11:17 am Scientific Session — Grand Ballroom
11:17 am – 11:57 am Annual Business Meeting — Retina Society Members only
12:54 – 1:39 pm Dessert and Poster Viewing — Empire Room
6:30 – 11:00 pm Reception/Dinner — Guildhall (see page 27 for bus information)

FRIDAY | SEPTEMBER 13
7:00 am Registration — Ballroom Hall
Continental Breakfast/Exhibits/Breaks — Marble Ballroom
7:00 am – 10:00 am Spouses Hospitality Suite — Garden Terrace
7:30 am – 12:30 pm Scientific Session — Grand Ballroom
1:00 pm – 6:00 pm Off-site Trip — Hampton Court Palace (Henry VIII)
(see page 28 for bus information)
Evening FREE

SATURDAY | SEPTEMBER 14
7:00 am Registration — Ballroom Hall
Continental Breakfast/Exhibits/Breaks — Marble Ballroom
7:00 am – 10:00 am Spouses Hospitality Suite — Garden Terrace
7:30 am – 12:54 pm Scientific Session — Grand Ballroom
Afternoon FREE
7:00 pm – 11:00 pm Banquet — Grand Ballroom

SUNDAY | SEPTEMBER 15
7:00 am Registration — Ballroom Hall
Continental Breakfast/Exhibits/Break — Marble Ballroom
7:30 am – 12:41 pm Scientific Session — Grand Ballroom
ADJOURN
SOCIAL PROGRAM

WEDNESDAY, SEPTEMBER 11
7:00 – 10:00 PM
WELCOMING RECEPTION
WINTER GARDEN — LANDMARK HOTEL

Kick off this year’s meeting by greeting friends, colleagues and guests at the Winter Garden, a tranquil oasis known and loved for its soaring eight-story, glass roof atrium, towering palm trees and extravagant service. Dine on sumptuously prepared modern European cuisine in a luxurious, alfresco atmosphere brimming with historic opulence.

THURSDAY, SEPTEMBER 12 – SATURDAY, SEPTEMBER 14
7:00 – 10:00 AM
HOSPITALITY SUITE
GARDEN TERRACE
SPOUSES & GUESTS

The Garden Terrace, overlooking the Winter Garden, is a fresh, relaxed setting for spouses and guests to enjoy coffee, tea and breakfast. It is also the perfect place to meet friends. On Sunday, spouses and guests are welcome to a continental breakfast in the Marble Ballroom.

THURSDAY, SEPTEMBER 12
9:30 AM – 3:00 PM
Meet in lobby at 9:00 am for buses
BUCKINGHAM PALACE
SPOUSES & GUESTS

For just a short period each summer when the Court has left London for summer vacation in Scotland, it is possible for the public to view the State Rooms of Buckingham Palace. Your arrival is at the Ambassador’s Entrance, where diplomats to the Queen and Court of St. James, arrive by carriage to present the credentials of their Country. Following their route across the courtyard, you will enter the main palace to view the staterooms.
where the queen entertains heads of state and diplomatic audiences.

In the Great Hall near the Grand Staircase, you will behold the magnificent furnishings that set the stage for the grandeur that lies ahead. Feel free to meander about at your own pace, as the audio tour is self-guided, allowing you to pause in areas you find the most interesting. In time, you will depart from Buckingham Palace through the Bow Room and on into the gardens. These exquisite gardens provide a walled sanctuary in the middle of London.

You will also find an elegant gift shop for selecting quality gifts that have been personally approved by The Queen and Members of the Royal Family.

After the tour, we will gather for a delicious lunch at Brown’s, a brasserie renown for their impeccable preparations of the finest quality, seasonal ingredients.

**THURSDAY, SEPTEMBER 12**

**9:30 AM – 3:00 PM**

Meet in lobby at 9:00 am for buses

**BRITISH MUSEUM**

**SPOUSES & GUESTS**

Set in the picturesque and historically rich neighborhood of Bloomsbury, the British Museum was the first public national museum in the world, opening in 1759. It has dedicated itself to the sharing of human history, art and culture specializing in antiquities from the Greek, Roman and Egyptian ages as well as British natural history. Its permanent collection of some eight million works is among the largest and most comprehensive in existence.

We will head on a must-see *Top Item Tour* of the museum with our guide showing us around some of the most popular artifacts in the collection, including the famous Rosetta Stone, dating from the Hellenistic Period. The Rosetta stone is well known for being the first ancient artifact with
which archaeologists could interpret hieroglyphs, paving the way for a huge breakthrough in the study of Ancient Egypt. Other objects include the Oxus Treasure, an amazing collection of ancient Persian Gold and Silver ornaments discovered in the 19th century. The detail and metalwork on the miniature statues along with the mystery surrounding the date of their exact finding make them highly valued. The tour will also incorporate artifacts from medieval Japan, the Scottish Highlands and much more. Following the tour, everyone will have a chance to wander around various other exhibitions.

After the tour we will gather at Bill’s in Holborn, a charming establishment founded by the greengrocer Bill Collison. We will enjoy a delicious lunch and relax in a Sir Edwin Lutyens-designed premise, originally built in 1907.
THURSDAY, SEPTEMBER 12
7:00 – 11:00 PM

Buses depart hotel at 6:30 pm

RECEPTION AND DINNER
AN EVENING AT THE GUILDHALL

Located in the heart of the City, the Guildhall has for centuries been a hub of London life. Completed in 1440, the Guildhall has borne witness to many of the defining moments of London and British history, being the location for some of Henry VIII’s most infamous trials, surviving the Great Fire of 1666, hosting the triumphant generals of Waterloo and withstanding the Blitz of World War II.

On arrival at the Guildhall, gather in the Crypts for our pre-dinner reception, then meander over to the City of London Corporation’s magnificent art collection where docents will be available to provide insight into the works on display. A highlight is John Singleton Copley’s Defeat of the Floating Batteries at Gibraltar; it is one of the most remarkable works on display.

On hearing the call from the heralds, you will be directed to the Great Hall, where the Banquet will begin. Enjoy the sumptuous feast while being watched over by the statues of Britain’s national heroes, from Lord Nelson to Winston Churchill. The splendid hall has hosted luminaries throughout the centuries including countless Lord Mayors of London, saw Frédéric Chopin’s last public concert and greeted guests for Queen Elizabeth II’s 90th birthday celebrations.
FRIDAY, SEPTEMBER 13
1:00 – 6:00 PM
Buses depart from hotel at 12:45 pm

EXCURSION: HAMPTON COURT PALACE

Join us as we walk in the footsteps of the Tudors and explore the magnificent surroundings of Hampton Court Palace. The Palace was begun in the early 16th century by Henry VIII’s favourite, Cardinal Wolsey. After falling foul of the king, the cardinal gifted it to his monarch in an attempt to win back favour. King Henry wasted no time in making his mark on the palace, undertaking a huge expansion project for his mammoth court of over 1000.

After entering through Anne Boleyn’s gate, completed in 1540, we will tour the palace interior, including the famous kitchens used to feed Henry VIII’s ever expanding court, as well as the beautiful gardens and intricate maze located in the palace grounds.
The palace has been the setting for many important national events and since being opened to the public by Queen Victoria in the 19th century, it has remained a magnet to visitors from far and wide, drawn to the grandeur, the ghosts and the fabulous art collection.

After touring Hampton Court Palace, those who opted will gather at the pier to begin a leisurely boat trip up the Thames to Richmond, where a coach will be waiting to take you back to the hotel. This cruise is the perfect way to view the Thames. Sit back, relax and recuperate before heading back to the bustle of the city.

SATURDAY, SEPTEMBER 14
7:00 – 11:00 PM
RECEPTION AND BANQUET
GRAND BALLROOM — LANDMARK HOTEL
Black Tie Optional

The lush grandeur, sophistication and elegance of the Landmark London extends graciously into the Ballroom where you can unwind and relax with colleagues and friends. Enjoy legendary service and world-class cuisine while we celebrate the Society’s newest members and bow to our host city, note the special moments of the meeting; then take to the dance floor to rock out with London’s best dance band, The Rockets.
In 2006, The Retina Society inaugurated the J. Donald M. Gass lectureship. Dr. Gass was a peerless observer of the fundus. His unique and repeated ability to identify fundamental patterns of disease from the mass of seemingly chaotic details invites sincere comparison to Michelangelo working in marble. With this lectureship, we honor his memory as a warm and cherished member and friend as well as his inestimable importance to our patients and our field.

AWARD SELECTION COMMITTEE:
MARK JOHNSON, MD, CHAIR • EMILY CHEW, MD • BERNARD DOFT, MD
IVANA KIM, MD • STEPHEN KIM, MD • CARL REGILLO
Carol Lally Shields was born into a large and boisterous family in the Pittsburgh suburbs and grew up playing sports, excelling at school, and enjoying the camaraderie of a wide circle of friends and relations.

Dr. Shields went on to become one of the first women to enter the University of Notre Dame, performing with remarkable distinction in the classroom as well as on the basketball court, where she was one of the inaugural founders of Notre Dame’s women’s varsity basketball team. Among her many “Domer” accolades was the Byron Kanaley Award (1979) given to the top student-athlete at the University of Notre Dame. She was the first woman awarded this prize. Following graduation she went on to serve her alma mater at the highest level on the school’s athletic advisory boards, as an honored speaker, and in 2005 became the first alumna to be presented with an honorary degree from Notre Dame. Dr. Shields went on to medical school at the University of Pittsburgh where she had a brilliant track record and was inspired to become an ophthalmologist, following in her older brother’s footsteps not only in the profession, but also at Wills Eye Hospital, where she came in 1984 — and the rest is history! After her training in ophthalmology at Wills she went on not only to fellowships in ocular pathology, orbital surgery and oncology, but also to marriage with Dr. Jerry Shields, building a lifelong and uniquely productive professional and personal partnership that has resulted in the world’s number one oncology practice and seven children! Each year the Oncology Service manages approximately 500 patients with uveal melanoma, 120 patients with retinoblastoma, and numerous other intraocular, orbital, and adnexal tumors from the United States and abroad. Together the Shieldses have pioneered the treatment of ocular cancer and trained a generation of ocular oncologists not only in Pennsylvania, but all over the globe.

In addition to her busy clinical practice, Dr. Carol Shields serves as Director of the Wills Oncology Service, and has been a tremendous educator, mentor, and prolific scientific contributor, an author of 11 textbooks, 323 chapters in edited textbooks, over 1700 articles in major peer-reviewed journals, has given over 850 lectureships and has received numerous professional awards. Notable amongst her honors have been the Donders Award (2003) given by the Netherlands Ophthalmological Society every 5 years to an ophthalmologist worldwide who has contributed extensively to the field of ophthalmology, the AAO Lifetime Achievement Award (2011), induction into the Academic All-American Hall of Fame for lifetime success in athleticism and career, election as President of the International Society of Ocular Oncology and the Macula Society, and being named to all 3 of the “Power Lists” from Ophthalmologist, naming the top global leaders in the profession.

Dr. Shields is a member of numerous ocular oncology, retina and pathology societies and serves on the editorial/advisory board of 31 journals including JAMA Ophthalmology, Retina, Ophthalmic Plastic and Reconstructive Surgery, and International Journal of Clinical Oncology.

The Shields name has conferred great added distinction on Wills Eye Hospital, and Carol and Jerry have served as top ambassadors for our profession all over the planet. The Shieldses are very arguably the most renowned ophthalmologists in the entire world.

The Retina Society is proud to honor with this year’s J. Donald M. Gass Award, innovator of life-saving and vision-saving therapies for ocular tumors, clinician, scholar, surgeon, mother of seven, athlete and worldwide contributor, Dr. Carol Lally Shields.

– Julia Haller, MD
The Award of Merit in Retina Research was created in 1978 by Retina Research Foundation, Houston, Texas, to recognize outstanding vision scientists whose work contributes to knowledge about the retina and retinal diseases. Each year, the awardee is invited to give the Charles L. Schepens Lecture, a highlight of The Retina Society annual meeting that was established in honor of the founder of the Society.

The award offers a $50,000 cash prize that includes a $5,000 honorarium and a $45,000 research grant. The recipient is chosen by the Awards Committee of The Retina Society. Funding for the Award of Merit is provided by the Retina Research Foundation through a series of endowed gifts that are dedicated to the Award. The Retina Research Foundation of Houston, Texas presents the Award of Merit in Retina Research to a vision scientist whose work represents: 1. A single outstanding achievement in retina research, or; 2. A potentially significant contribution to new knowledge about the retina, its role in the visual process and/or vitreoretinal diseases or disorders.

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AWARD SELECTION COMMITTEE:
MARK JOHNSON, MD, CHAIR • EMILY CHEW, MD • BERNARD DOFT, MD
IVANA KIM, MD • STEPHEN KIM, MD • CARL REGILLO

PAST AWARD RECIPIENTS

1978 CHARLES L. SCHEPENS, MD, Boston, MA
1979 RICHARD W. YOUNG, PhD, Los Angeles, CA
1980 ROBERT MACHEMER, MD, Durham, NC
1981 JOHN E. DOWLING, PhD, Boston, MA
1982 HARRY G. SPERLING, PhD, Houston, TX
1983 ARNALL PATZ, MD, Baltimore, MD
1984 WERNER K. NOELL, MD, Kansas City, MO
1985 OLEG POMERANTZEFF, DIP. ENG., Boston, MA
1986 J. DONALD M. GASS, MD, Miami, FL
1987 HARRIS RIPPS, PhD, Chicago, IL
1988 HARVEY A. LINCOFF, MD, New York, NY
1989 MATTHEW D. DAVIS, MD, Madison WI
1990 MATTHEW M. LAVAL, PhD, San Francisco, CA
1991 RONALD MICHELS, MD and BERT GLASER, MD, Baltimore, MD
1992 INGRID KREISSIG, MD, Tubingen, Germany
1993 W. RICHARD GREEN, MD, Baltimore, MD
1994 DR. KATHLEEN DOREY and DR. FRANCOIS DELORI, Boston, MA
1995 D. JACKSON COLEMAN, MD, New York, NY
1996 GABRIEL COSCAS, MD, Paris, France
1997 STUART L. FINE, MD, Philadelphia, PA
1998 JOE G. HOLLYFIELD, PhD, Cleveland, OH
1999 LAWRENCE A. YANNUZZI, MD, New York, NY
2000 BARBARA E. KLEIN, MD, MPH, and ROBERT KLEIN, MD, MPH, Madison, WI
2002 BRADLEY R. STRAATSMAN, MD, Los Angeles, CA
2003 STEPHEN J. RYAN, MD, Los Angeles, CA
2004 EMILY Y. CHEW, MD, Bethesda, MD and FREDERICK L. FERRIS III, MD, Bethesda, MD
2005 ANTHONY P. ADAMS, MD, Boston, MA
2006 CAROL SHIELDS, MD, Philadelphia, PA
2007 LLOYD PAUL AIello, MD, Boston, MA
2008 WILLIAM S. TASMAN, MD, Philadelphia, PA
2009 MARK S. HUMAYUN, MD, PhD, Los Angeles, CA
2010 ELIOT L. BERSON, MD, Boston, MA
2011 MICHAEL F. MARMOR, MD, Stanford, CA
2012 RICHARD F. SPAIDE, MD, New York, NY
2013 CYNTHIA A. TOOTH, MD, Durham, NC
2014 PETER CAMPOCHIARO, MD, Baltimore, MD
2015 THOMAS GARDNER, MD, Ann Arbor, MI
2016 STEVE CHARLES, MD, Memphis, TN
2017 MICHAEL KLEIN, MD, Portland, OR
2018 PAUL STERNBERG JR, MD, Nashville, TN
James Fujimoto obtained his Bachelor, Masters and Doctorate from the Massachusetts Institute of Technology. He is Elihu Thomson Professor of Electrical Engineering at MIT, visiting professor of ophthalmology at Tufts University School of Medicine, and adjunct professor at the Medical University of Vienna. His group and collaborators were responsible for the invention and development of optical coherence tomography (OCT).

Researchers who have trained in Jim’s lab have established important laboratories of their own worldwide. The invention and development of OCT has affected many branches of medicine, but some its biggest impact has been on the study of vitreo-retinal disease. Dr. Fujimoto published over 500 peer-reviewed journal articles.

There are many amazing things about Jim Fujimoto. We gravitate to his colossal invention of OCT, but he possesses many other personal qualities that are at least as important as his technical prowess. Jim is a very kind, inquisitive, and humble. He is always willing to lend an ear to hear a new idea or to answer a question. He really enjoys the interaction, not just with optical scientists, but medical doctors, residents, anyone really. Whoever talks to him ends up being enriched by the conversation; I know I have, and probably to a much greater extent than any reciprocal enrichment. Jim Fujimoto is a hard-working, happy, brilliant guy that everyone loves, independent of OCT. The one exception may be his wife’s cat.

Jim has received many important awards including the Champalimaud Vision Prize in 2012, the National Academy of Engineering Fritz J. and Dolores H. Russ Award in 2017 and the European Inventor Award in 2017. He also received the Zeiss Research Award in 2011, the Optical Society of America Ives Medal in 2015 and the Beckman-Argyros Award in Vision Research in 2017. These awards came from organizations of peers in the optics and engineering arenas. The award he now is receiving from the Retina Society is very personal—personal to each of the many people who have collaborated with him on publications, and even more, personal to each member of the Society who’s ability to take care of patients has been dramatically improved by his inventions.

—Richard F. Spaide, MD
The Retina Society Fellowship Research Award was established in 1996 to encourage academic pursuit in young vitreoretinal surgeons and to acquaint them with the scientific and social aspects of the Society. The applicant must be sponsored by an active member of The Retina Society. Each paper is judged on originality, quality of investigation methods, and merit of scientific contribution.

**RECIPIENT OF THE 23rd FELLOWSHIP RESEARCH AWARD**

**HARRIS SULTAN, MD**  
*St. Louis, MO*

**SPONSOR:** Cagri Besirli, MD

**CONGRATULATIONS!**

**THE FELLOWSHIP AWARDS SELECTION COMMITTEE:**

PRITHVI MRUTHYUNJAYA, MD, *CHAIR*

RAJENDRA APTE, MD • AMANI FAWZI, MD • DEEBA HUSAIN, MD • ADRIENNE SCOTT, MD

We would like to thank all members who have sponsored applicants and ask that all members continue to support this award.

**PAST AWARD RECIPIENTS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Sponsor</th>
<th>Location</th>
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<tbody>
<tr>
<td>2018</td>
<td>THOMAS WUBBEN, MD, PhD</td>
<td>Cagri Besirli</td>
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<td>2017</td>
<td>SUN YOUNG LEE, MD, PhD</td>
<td>James Folk</td>
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<td>2016</td>
<td>ELAD MOISSEIEV, MD</td>
<td>Susanna Park</td>
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<td>2015</td>
<td>YOSHIHIRO YONEKAWA, MD</td>
<td>Antonio Capone Jr</td>
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<td>FRANCISCO FOLGAR, MD</td>
<td>Emily Chew</td>
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<td>GLENN YIU, MD, PhD</td>
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<td>LEJLA VAJZOVIC, MD</td>
<td>David Abramson</td>
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<td>CAGRI BESIRLI, MD</td>
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<td>2010</td>
<td>BRIAN L. VANDERBEEK, MD, PhD</td>
<td>David Zacks</td>
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<td>2009</td>
<td>SANDRA ROCIO MONTEZUMA, MD</td>
<td>Joan Miller</td>
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<td>2008</td>
<td>MEHRAN TABAN, MD</td>
<td>Peter Kaiser</td>
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<td>SAI CHAVALA, MD</td>
<td>Thomas Lee</td>
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<td>POLLY A. QUIRAM, MD</td>
<td>George Williams</td>
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<td>FRANCISCO MAX DAMICO, MD</td>
<td>Lucy Young</td>
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<td>SEAN S. KO, MD</td>
<td>Shizu Mukai</td>
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<td>2003</td>
<td>SEENU M. HARIPRASAD, MD</td>
<td>William Mieler</td>
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<td>FRANCO M. RECCHIA, MD</td>
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<td>DAVID N. ZACKS, MD</td>
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<td>2000</td>
<td>MAGDALENA KRZYSTOLIK, MD</td>
<td>Evangelos Gragoudas and Enrique Garcia-Valenzuela, MD, PhD</td>
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<td>1999</td>
<td>THOMAS C. LEE, MD</td>
<td>Shizu Mukai</td>
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<td>1998</td>
<td>INGRID U. SCOTT, MD</td>
<td>Timothy Murray</td>
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<tr>
<td>1997</td>
<td>ANDREW CHANG, MD</td>
<td>Lawrence Morse</td>
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THE RAYMOND R. MARGHERIO AWARD

RAYMOND R. MARGHERIO, MD
1939 – 2000
President, The Retina Society, 1996 - 1997

The Raymond R. Margherio Endowed Memorial Fund was established to support research into macular disease and development of new techniques of macular surgery. The Fund supports an award presented annually to a vitreoretinal fellow of an Active Member of The Retina Society. The fellow will present his work at the Annual Meeting of The Retina Society. The winner is selected by the Research Award Committee.

RECIPIENT OF THE 18TH MARGHERIO AWARD

SALLY ONG, MD
Baltimore, MD

SPONSOR: Susanna Park, MD

CONGRATULATIONS!

THE FELLOWSHIP AWARDS SELECTION COMMITTEE:

PRITHVI MRUTHYUNJAYA, MD, CHAIR
RAJENDRA APTE, MD • AMANI FAWZI, MD • DEEBAHUSAIN, MD • ADRIENNE SCOTT, MD

WE WOULD LIKE TO THANK ALL MEMBERS WHO HAVE SPONSORED APPLICANTS AND ASK THAT ALL MEMBERS CONTINUE TO SUPPORT THIS AWARD.

PAST AWARD RECIPIENTS

2018 AMIRFARBOD YAZDANYAR, MD, MPH
Sponsored by Susanna Park, MD

2017 PRETHY RAO, MD, MPH
Sponsored by George Williams

2016 XI CHEN, MD, PhD
Sponsored by Cynthia Toth

2015 DEVON GHODASRA, MD
Sponsored by Thomas Gardner

2014 JOHN B. MILLER, MD
Sponsored by Evangelos Gragoudas

2013 DIMITRA SKONDRA, MD
Sponsored by Joan Miller

2012 ANTHONY B. DANIELS, MD
Sponsored by Ivana Kim

2011 MARC-ANDRE RHEAUME, MD
Sponsored by Shizuo Mukai

2010 DANIEL F. KIERNAN, MD
Sponsored by William Mieler

2009 CATHERINE CUKRAS, MD, PhD
Sponsored by Frederick Ferris

2008 EDWARD F. HALL, MD
Sponsored by David Zacks

2007 STEPHEN J. KIM, MD
Sponsored by Baker Hubbard

2006 JASMINE R. ELISON, MD
Sponsored by Jackson Coleman

2005 MICHAEL D. OBER, MD
Sponsored by Lawrence Yannuzzi

2004 HOWARD S. YING, MD
Sponsored by Morton Goldberg

2003 ANTONIO P. CIARDELLA, MD
Sponsored by Stanley Chang

2002 EUGENE S. LIT, MD
Sponsored by Donald D’Amico
WEDNESDAY, SEPTEMBER 11, 2019

PRESIDING OFFICER: William Mieler, MD
MODERATOR: Anita Agarwal, MD

12:30 pm  WELCOME
            Bernard Doft, MD

12:35  Interesting Case from MSKCC
            David Abramson, MD

12:40  ... And We Did Nothing
            Carol Shields, MD

12:45  Macula Mindbogger
            Mark Johnson, MD

12:50  A Hair-Raising Ocular Complication
            Manjot Gill, MD

12:55  “I am so tired, I think I will die”
            Alice Lyon, MD

1:00  Fever, Jaundice and Visual Loss in a Young Woman
            Lihteh Wu, MD

1:05  Panuveitis in a 48-year-old Myopic Woman
            Anita Agarwal, MD

1:10  “I see red flowers”—Hemorrhage in Henle’s Nerve Fiber Layer
            Caroline Baumal, MD

1:15  New Complication in IRVAN
            Michael Ober, MD

1:20  An Unusual Case of ‘Central Serous Chorioretinopathy’
            Petros Carvounis, MD

1:25  Choroiditis Masquerading as Choroidal Neovascularization
            Stephen Schwartz, MD, MBA

1:30  What’s that in the Choroid?
            Rukhsana Mirza, MD

1:35  Maternally Inherited Diabetes and Deafness Associated Maculopathy Imaged with Optical Coherence Tomography Angiography
            Jaclyn Kovach, MD

1:40  Intravitreal Injection of EPO for Severe Central Vein Occlusion in the Context of Flammer Syndrome (Endothelin Dysfunctioning)
            Claude Boscher, MD

1:45  Adolescent with Familial Mediterranean Fever Presents with Painful Serous Macular Detachment, Pinpoint Dye Leakage and Type A Personality: Atypical CSCR?
            Ahmad Mansour, MD

1:50  A is for Anti-retinal Antibodies
            Glenn Yiu, MD, PhD
<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>1:55</td>
<td>All That Glitters: West African Crystalline Maculopathy</td>
<td>Christina Weng, MD, MBA</td>
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<tr>
<td>2:00</td>
<td>Systemic Capillary Leak Syndrome (Clarkson’s Disease): An Uncommon Cause of Retinal New Vessels and Cystoid Macular Edema</td>
<td>Stefano Piermarocchi, MD</td>
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<td>2:05</td>
<td>Visual Improvement in the Non-implanted Eye after Retinal Prosthesis Surgery</td>
<td>Andre Witkin, MD</td>
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<td>2:10</td>
<td>Can You Get Too Many Optical Coherence Tomographys?</td>
<td>Aleksandra Rachitskaya, MD</td>
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<td>2:15</td>
<td>Resistant Cytomegalovirus Retinitis in a Cardiac Transplant Patient</td>
<td>Alan Palestine, MD</td>
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<td>2:20</td>
<td>Post-injection Intraretinal Hemorrhages</td>
<td>Bernard Doft, MD</td>
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<td>2:25</td>
<td>A Mystery Case of Bilateral Vitritis</td>
<td>Jasmine Francis, MD, FACS</td>
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<td>2:30</td>
<td>And Years Later....</td>
<td>Audina Berrocal, MD</td>
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<td>2:35</td>
<td>Off-label, New-age Therapy for Pediatric Uveitis</td>
<td>Franco Recchia, MD</td>
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<td>2:40</td>
<td>Central Retinal Vein Occlusion in a Pediatric Patient</td>
<td>Cagri Besirli, MD, PhD</td>
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<td>2:45</td>
<td>A Surprising Twist: Not a Melanoma</td>
<td>Jerry Shields, MD</td>
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<td>2:50</td>
<td>When All Else Fails: Molecular Utility of Diluted Vitreous Biopsies for Vitreoretinal Lymphoma with Negative Cytology and Indeterminate Flow Cytometry</td>
<td>Rajesh Rao, MD</td>
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<td>2:55</td>
<td>Subretinal Hemorrhage after Melanoma Tumor Biopsy: Now What??</td>
<td>Prithvi Mruthyunjaya, MD, MHS</td>
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<td>3:00</td>
<td>Resolution of Complete Exudative Retinal Detachment Following V-PDT Treatment</td>
<td>Alan Cruess, MD</td>
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<td>3:05</td>
<td>All That Glisters Is Not Gold...</td>
<td>Anthony Daniels, MD, MSc</td>
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<td>3:10</td>
<td>Anti-VEGF Resistant Macular Edema and Serous Detachment</td>
<td>Gregg Kokame, MD, MMM</td>
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VIDEO PRESENTATIONS

3:15 pm Extreme Retinal Detachment
Arnaldo Bordon, MD, PhD

3:20 Rhegmatogenous Retinal Detachment with Peripheral Retinal Breaks and Macular Hole Treated by Two Consecutive Vitrectomies
Florian Balta, MD, PhD

3:25 Relaxing Membranectomies in the Surgical Management of Tabletop Tractional Retinal Detachments
Maria Berrocal, MD

3:30 Surgical Embolectomy in a Case of a Fovea-involving Branch Retinal Artery Occlusion
Uday Desai, MD

3:35 Surgical Techniques for Epiretinal Prosthesis Removal and Exchange
Lejla Vajzovic, MD

3:40 Nano Subretinal Gateway Device
Tamer Mahmoud, MD, PhD

3:45 REFRESHMENT BREAK
WEDNESDAY, SEPTEMBER 11, 2019

4:20 pm  **WELCOME, INTRODUCTION OF UK HOST COMMITTEE**
Bernard Doft, MD

**DIABETIC RETINOPATHY I**

**PRESIDING OFFICER:** Jennifer Sun, MD  
**MODERATOR:** James Bainbridge, MA, MB, BChir, PhD, FRCOphth

4:25 Randomized Clinical Trial of Initiation with Aflibercept, Focal/Grid Laser Photocoagulation, or Observation for Center-involved DME in Eyes with Good Visual Acuity — Protocol V  
Andrew Antoszyk, MD

4:31 DRCR Retina Network Approach to Observation with Aflibercept for Vision Decrease in Eyes with Center-involved Diabetic Macular Edema and Good Visual Acuity  
Jennifer Sun, MD

4:37 Discussion of above 2 papers

4:41 Visual Acuity Outcomes and Anti-Vascular Endothelial Growth Factor Therapy Intensity in Diabetic Macular Edema: A “Real World” Analysis in 28,456 Eyes  
Thomas Ciulla, MD, MBA

4:47 Two-year Results of Treat-and-Extend Regimen using Aflibercept for Diabetic Macular Edema; VIBIM Study  
Ji Eun Lee, MD, PhD

4:53 Discussion of above 2 papers

4:57 Consistent Improvements in Retinal Thickness Stability with 0.19 mg Fluocinolone Acetonide Implant in DME: Results from FAME, PALADIN and USER Studies  
Christopher Riemann, MD

5:02 DIAbetic Macular Oedema aNd Diode Subthreshold Micropulse Laser (DIAMONDS)  
Noemi Lois, MD, PhD, FRCS(Ed), FRCOphth

5:07 Blood Pressure is Associated with Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Treatment in Patients with Diabetes  
Anjali Shah, MD

5:12 Three-dimensional Analysis of Morphologic Changes and Visual Outcomes in Diabetic Macular Edema  
Hyung Chan Kim, MD, PhD

5:17 Comparisons of Nonperfusion and Ultrawide Diabetic Retinopathy  
Paolo Silva, MD

5:23 Quantification of Diabetic Retinopathy-associated Non-perfusion and Neovascularization on Ultra-widefield Fluorescein Angiography  
Yannis Paulus, MD

5:29 Discussion of above 2 papers
RETINAL VASCULAR DISEASES

PRESIDING OFFICER: Caroline Baumal, MD
MODERATOR: Mark Johnson, MD

5:33 pm The Association of Stroke with Retinal Artery Occlusions
Brian VanderBeek, MD, MPH, MSCE

5:39 Discussion

5:42 Association between the Risk of Central Retinal Artery Occlusion and the Concentration of Environmental Air Pollutants — The Original Study
Andrzej Grzybowski, MD, PhD, MBA

5:48 Discussion

5:51 Long-term Visual Outcome and Its Predictors in Macular Oedema Secondary to Retinal Vein Occlusion Treated with Dexamethasone Implant
Luiz Lima, MD

5:57 Discussion

6:00 Risk of Systemic Adverse Events Following Intravitreal Aflibercept, Ranibizumab, and Bevacizumab for Common Medical Retinal Conditions in Routine Clinical Practice: A Large Propensity-weighted Cohort Study
Andrew Barkmeier, MD

6:06 Vision and Optical Coherence Tomography Outcomes Following the 2018 Aflibercept Recall
Christopher Brady, MD, MHS

6:12 Discussion of above 2 papers

6:16 Active Learning of Contrast Sensitivity Deficits in Maculopathy with Good Acuity
John Miller, MD

6:22 Discussion

6:25 A 20-year Multi-centre Retrospective Review of the Management of Incontinentia Pigmenti
Robert Henderson, BSc, MBBS, MD, FRCOphth

6:30 Tele-ophthalmology Screening in Sickle Cell Retinopathy
Adrienne Scott, MD

6:35 ADJOURN
THURSDAY, SEPTEMBER 12, 2019

AGE-RELATED MACULAR DEGENERATION I

PRESIDING OFFICER: Glenn Jaffe, MD
MODERATOR: Allen Ho, MD

7:30 am
ANNOUNCEMENTS

7:32 RGX-314 Gene Therapy for Neovascular Age-related Macular Degeneration: Interim Results of an Ongoing Phase I/IIa

Allen Ho, MD

7:38 Discussion

7:41 Interim 24-week data from the OPTIC Trial: Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 (AAV.7m8-aflibercept) for Neovascular (Wet) Age-related Macular Degeneration

Szilárd Kiss, MD

7:47 Discussion

7:50 Comparison of the Efficacy and Safety of Brolucizumab versus Aflibercept in Eyes with Polypoidal Choroidal Vasculopathy: 96-week Results from the HAWK Study

Glenn Jaffe, MD

7:56 Discussion

7:59 Time to Dry Analysis of Brolucizumab Versus Aflibercept in Patients with Neovascular Age-related Macular Degeneration: 96-week Data from the HAWK and HARRIER Trials

Pravin Dugel, MD

8:05 Fluid Analysis from the HAWK and HARRIER Studies: Brolucizumab versus Aflibercept for Neovascular Age-related Macular Degeneration

Seenu Hariprasad, MD

8:11 Discussion of above 2 papers

8:15 Dorzolamide-Timolol vs Placebo Drops as an Adjunct to Intravitreal Anti-Vascular Endothelial Growth Factor Injections for Incomplete Responders with Neovascular Age-related Macular Degeneration

Jason Hsu, MD

8:21 Discussion

8:24 Port Delivery System with Ranibizumab (PDS) Phase 2 Ladder Results that Informed Phase 3 Archway Trial Design

Nancy Holekamp, MD

8:30 Discussion

8:33 Dual Inhibition of Ang-2 and VEGF-A with Faricimab in nAMD: Q16-week and Q12-week Dosing in the STAIRWAY Trial

Caroline Baumal, MD

8:39 Discussion
8:42 am  APEX: A Phase II Clinical Trial Evaluating the Safety and Preliminary Efficacy of X-82 Administered Orally in the Treatment of Exudative Macular Degeneration

**Michael Cohen, MD**

8:48  Discussion

8:51  Macular Atrophy in the 5-year Observational Follow-up of the IVAN Trial Cohort

**Clare Bailey, MA, BM, BCh, MD, FRCP, FRCOphth**

8:57  Discussion

### SURGERY I

**PRESIDING OFFICER: Edwin Ryan, MD**

**MODERATOR: Prithvi Mruthyunjaya, MD, MHS**

9:00  Vision Degrading Myodesopsia in Myopia

**Jerry Sebag, MD, FACS, FRCOphth, FARVO**

9:05  Discussion

9:07  Confusions in Retinal and Other Ophthalmic Surgical Procedures: Description, Analysis and Prevention of Errors from 2006 - 2017

**Ravi Parikh, MD, MPH**

9:13  Infusion Occlusion and Pump Confusion: Risk Factors and Intraoperative Management of Acute Hypotony During PPV

**Raymond Iezzi, MD, MS**

9:19  Discussion of above 2 papers

9:23  The ‘Weekend Effect’ in Vitreoretinal Surgery: Retinal Detachment Repair and Outcomes Vary by Day of the Week

**Prithvi Mruthyunjaya, MD, MHS**

9:28  Discussion

9:30  REFRESHMENT BREAK/EXHIBITS

### SURGERY II

**PRESIDING OFFICER: Bill Aylward, MB, BChir, FRCS, MD**

**MODERATOR: David Zacks, MD, PhD**

10:00  Results of a Lamellar Macular Hole (LMH)-associated Epiretinal Proliferation Embedding Technique for the Treatment of Degenerative LMH

**Yuki Morizane, MD, PhD**

10:06  Ectopic Inner Foveal Layers Classification Scheme Predicts Visual Outcomes After Epiretinal Membrane Surgery

**Gerardo González-Saldívar, MD**

10:12  Comparative Assessment of Surgical Outcomes and Ellipsoid Zone Mapping for Epiretinal Membrane Peeling Using Intraoperative Optical Coherence Tomography-guided Membrane Removal in the DISCOVER Study versus Complete Internal Limiting Membrane (ILM) Peeling

**Arjun Sood, MD**
10:18 am  Temporal Changes of Parafoveal Microvasculature after Epiretinal Membrane Surgery: An Optical Coherence Tomography Angiography Study  
Kyu-Hyung Park, MD

10:24  Discussion of above 4 papers

10:29  Evaluation of Iris and Intraocular Lens (IOL) Mobility in Eyes with Scleral-fixated IOL  
Jeremy Wolfe, MD, MS

10:35  Discussion

10:38  High-mobility Group Box 1 (HMGB1) Protein Contributes to Photoreceptor Survival During Retinal Detachment  
David Zacks, MD, PhD

10:44  Discussion

10:47  INNOVATIONS IN RETINA LECTURE  
Simply Cut and Paste—Prospects for Retinal Gene Editing  
James Bainbridge, MA, MB, BCHir, PhD, FRCOphth

11:17  ANNUAL BUSINESS MEETING — MEMBERS ONLY

11:57  ATTENDEE LUNCH — DRAWING ROOM, WINTER GARDEN, GARDEN TERRACE

12:49 pm  POSTER SESSION — EMPIRE ROOM

AGE-RELATED MACULAR DEGENERATION II

PRESIDING OFFICER: SriniVas Sadda, MD
MODERATOR: David Brown, MD

1:39  Injection Intervals in Treatment-Naive Neovascular Age-related Macular Degeneration (nAMD) Patients Who Received Anti-Vascular Endothelial Growth Factor (VEGF) Agents: Intelligent Research in Sight (IRIS®) Registry Analysis  
Mathew MacCumber, MD, PhD

1:45  Discussion

1:48  Prophylaxis Intravitreal Aflibercept against Conversion to Neovascular Age-related Macular Degeneration in High Risk Eyes (PRO-CON): 24 Month Results  
David Brown, MD

1:54  Discussion

1:57  Association Between Early Visual Function Outcomes and Anatomic Dryness in Neovascular Age-related Macular Degeneration  
Rishi Singh, MD

2:03  Discussion

2:06  Ziv-aflibercept Efficacy in Better Regulating AMD: 52-week Results of the ZEBRA Study  
Kapil Kapoor, MD

2:12  Discussion
Relationship Between Subretinal Fluid (SRF) or Intraretinal Fluid (IRF) and Vision Outcomes in Eyes with Neovascular Age-related Macular Degeneration (nAMD) Treated with Ranibizumab in the HARBOR Trial
SriniVas Sadda, MD

Pigment Epithelial Detachments Response to a Single Ranibizumab Injection: A HARBOR Subanalysis
Michael Javaheri, MD

Danger for Patients on the Horizon
Gary Brown, MD, MBA

Submacular Hemorrhage Secondary to Age-related Macular Degeneration in a Treat and Extend Regimen: Clinical Characteristics and Correlations
Douglas Matsunaga, MD

Improved Visual Functional Outcomes in Age-related Macular Degeneration Patients with Oculenz ARwear
Linda Lam, MD, MBA

Safety and Efficacy of Risuteganib in Intermediate Non-exudative (Dry) Age-related Macular Degeneration (AMD)
David Boyer, MD

Introduction to Afternoon Tea Etiquette
Bernie Doft, MD

Real-world Outcomes Can Reflect Clinical-trial Outcomes when Real-world Patients Reflect Clinical-trial Patients
Franco Recchia, MD

Real-world Outcomes for Treat and Extend Treatment Regimen with Anti-VEGF Agents for Neovascular Age-related Macular Degeneration—A Review of 4202 Intravitreal Injections
Geoff Williams, MD, FRCSC

FIDO Study: 10-year Outcomes of Eyes Receiving Continuous, Fixed-interval Dosing of Anti-VEGF Agents for Neovascular Age-related Macular Degeneration
Ivan Suner, MD, MB

Characterization of Eyes Developing Exudative Age-related Macular Degeneration During the Phase 2 FILLY Study
Charles Wykoff, MD, PhD

Discussion of above 3 papers

Discussion
3:59 Elamipretide, A Mitochondria-Targeted Drug, for the Treatment of Vision Loss in Dry Age-related Macular Degeneration: Results of the Phase 1 ReCLAIM Study
Scott Cousins, MD

4:05 Discussion

4:08 Intraocular Device to Trap Complement Factors Associated with Non-Exudative Macular Degeneration
Jeffrey Olson, MD

4:14 Discussion

4:17 Safety and Efficacy of a Single HMR59 Gene Therapy Injection in Advanced Dry Age-related Macular Degeneration and New Onset Wet Age-related Macular Degeneration
Jeffrey Heier, MD

4:23 Discussion

4:26 One Year Results of a Photovoltaic Wireless Subretinal Implant for Advanced Atrophic Dry Age-related Macular Degeneration
Mahi Muqit, PhD, FRCOphth

4:31 Assessment of Eyes with Non-Exudative Age-related Macular Degeneration in US Retina Practices
Andrew Moshfeghi, MD, MBA

4:36 Characterization of the Angiofibrotic Switch in Anti-VEGF Therapy of Neovascular Age-related Macular Degeneration
Ursula Schmidt-Erfurth, MD

4:42 Discussion

SURGERY III

PRESIDING OFFICER: Baker Hubbard, MD
MODERATOR: Antonio Capone, MD

4:45 Optimizing Outcomes for Subretinal Delivery of Gene Therapy and Scaffolds for Stem Cell Transplantation
Elliott Sohn, MD

4:51 Optimization of Implant Insertion Procedure for the Port Delivery System with Ranibizumab (PDS) in the Ladder Phase 2 Trial
John Pollack, MD

4:57 Discussion of above 2 papers

5:01 Topical Therapy as Primary Therapy for Small Secondary Full-thickness Macular Holes
Donald Fong, MD

5:07 Pneumatic Vitreolysis for Resolving Focal Vitreomacular Traction: An Update on Clinical Outcome
Clement Chan, MD, FACS

5:13 Discussion of above 2 papers

5:17 pm Subretinal Fluid Application to Close Persisting Full-thickness
Macular Holes

Carsten Meyer, MD, FEBO, FMH

5:23 Autologous Retinal Transplantation (ART) for Primary and Refractory Macular Holes: The ART Global Consortium

Stavros Moysidis, MD

5:29 Discussion of above 2 papers

5:33 ADJOURN
FRIDAY, SEPTEMBER 13, 2019

DIABETIC RETINOPATHY II

PRESIDING OFFICER: Judy Kim, MD
MODERATOR: Charles Wykoff, MD, PhD

7:00 am
ANNOUNCEMENTS

7:32 Macular Blood Flow Increases on Optical Coherence Tomography Angiography after Panretinal Photocoagulation-results and Mathematical Model
Amani Fawzi, MD

7:37 Treatment of Capillary Nonperfusion Secondary to Retinal Vascular Disease
Thomas Friberg, MD

7:42 Discussion of above 2 papers

7:45 Clinical Outcomes of Eyes Lost to Follow-up with Proliferative Diabetic Retinopathy that Received Panretinal Photocoagulation versus Intravitreal Anti-Vascular Endothelial Growth Factor Injections: A Real World Analysis
Durga Borkar, MD

7:51 Discussion

7:54 Proliferative Diabetic Retinopathy: Outcomes of Combination Therapy in Clinical Practice
Sundeep Dev, MD

7:59 Visual Field Loss Over 5 Years in Patients Treated with Panretinal Photocoagulation or Ranibizumab for Proliferative Diabetic Retinopathy
Dennis Marcus, MD

8:05 Discussion

8:08 Association Between 4-step or Greater Improvement in Diabetic Retinopathy Severity and Patient-reported Visual Function in DRCR.net Protocol S
Michael Singer, MD

8:14 Discussion

SURGERY IV

PRESIDING OFFICER: George Williams, MD
MODERATOR: Jason Hsu, MD, PhD

8:17 The PRO Study—Procedure Preferences and Outcomes for the Primary Repair of Rhegmatogenous Retinal Detachments Based on Training Era
Shaina Rubino, MD

8:23 Retinal Redetachment after 23-gauge Pars Plana Vitrectomy Alone for the Management of Primary Rhegmatogenous Pseudophakic Retinal Detachment
Vicente Martínez Castillo, MD
8:29 am  Discussion of above 2 papers
8:33  Supplemental Scleral Buckle in the Era of Small Incision Vitrectomy and Wide-angle Viewing Systems—Decreasing Trends, Steady Outcomes
   Homayoun Tabandeh, MD, MS
8:39  Factors Associated with the Use of 360-degree Laser Retinopexy During Primary Pars Plana Vitrectomy with or without Scleral Buckle for Rhegmatogenous Retinal Detachment and Impact on Surgical Outcomes
   Jay Wang, MD
8:45  Discussion of above 2 papers
8:49  Macular Edema after Successful Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment: Factors Affecting Edema development and Considerations for Treatment
   Panagiotis Theodosiadis, MD
8:55  Retinal Displacement Detected with Fundus Autofluorescence Imaging Following Pneumatic Retinopexy vs Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment (INTEGRITY STUDY)
   Rajeev Muni, MD, MSc, FRCSC
9:01  Discussion of above 2 papers
9:05  Relaxing Retinectomy for Proliferative Vitreo Retinopathy in Rhegmatogenous Retinal Detachment
   Tom Williamson, MD
9:10  Only Close Surgical Dissection of the Vitreo Retinal Interface Can Prevent/Treat Proliferative Vitreo Retinopathy (PVR) in the Entire Eye In Vivo
   Claude Boscher, MD
9:15  Discussion of above 2 papers
9:18  RAYMOND MARGHERIO AWARD INTRODUCTION
   Prithvi Mruthyunjaya, MD
   Retinal Thickness and Microvascular Changes in Children with Sickle Cell Disease Evaluated by Optical Coherence Tomography and Optical Coherence Tomography Angiography
   Sally Ong, MD
9:33  J. DONALD M. GASS AWARD INTRODUCTION
   Julia Haller, MD
   Understanding Uveal Melanoma and Unlocking the Immune System
   Carol Shields, MD
10:03  REFRESHMENT BREAK/EXHIBITS
AGE-RELATED MACULAR DEGENERATION IV

PRESIDING OFFICER: Joan Miller, MD
MODERATOR: Paul Sternberg, MD

10:33 am An Important Marker for Anti-VEGF Resistance — Subretinal Aneurysmal Neovascularization Diagnostic of the Polypoidal Choroidal Vasculopathy Subtype of Exudative Age-related Macular Degeneration
Gregg Kokame, MD, MMM

10:39 Evaluation of Polyp Morphology during Course of Active Treatment of Polypoidal Choroidal Vasculopathy
Colin Tan, MBBS, FRCSEd (Ophth)

10:45 Discussion of above 2 papers

10:49 What Does Optical Coherence Tomography Angiography Reveal about the Choroidal Neovascularization Response to the Port Delivery System with Ranibizumab Compared with Monthly Ranibizumab Injections?
Nadia Waheed, MD, MPH

10:54 Quantitative Fundus Autofluorescence (qAF) Characterizes Two Pathways and Two Phenotypes of Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD)
Theodore Smith, MD

11:00 Discussion

11:03 Analysis of in Vivo Stimulation of Retinal Pigment Epithelium Regeneration in the Axin2lacZ Knock-in Mouse
Paul Sternberg, MD

11:09 Discussion

11:12 Human Plasma Metabolomics in Age-related Macular Degeneration — Meta-analysis of Two Cohorts
Joan Miller, MD

11:18 Metabolomic Genomic association in Age-related Macular Degeneration
Deeba Husain, MD

11:24 Discussion of above 2 papers

11:28 Plasma Vinculin is Elevated in Advanced Age-related Macular Degeneration
Alan Palestine, MD

11:33 The Frequency of the Age-related Macular Degeneration Risk Alleles, Y402H and A69S, in a Direct-to-Consumer Genetic Database
Theodore Leng, MD, MS

11:39 Discussion

11:42 Association of Age-related Macular Degeneration with Mortality in Patients with AIDS: Role of Systemic Inflammation
Douglas Jabs, MD

11:48 Discussion
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<tr>
<td>11:51</td>
<td>Extended Dual Release of Dexamethasone and Aflibercept from a Single Drug Delivery System</td>
<td>Jennifer Kang-Mieler, PhD</td>
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<td>11:56</td>
<td>Intravitreal Aflibercept Injection for Nonproliferative Diabetic Retinopathy: 52-week Results from the Phase 3 PANORAMA Study</td>
<td>Lloyd Clark, MD</td>
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<td>12:02</td>
<td>Vision-Threatening Proliferative Diabetic Retinopathy (PDR) Events in Diabetic Retinopathy (DR) Patients with Diabetic Macular Edema (DME): A Post Hoc Analysis of the VISTA and VIVID Trials</td>
<td>Chirag Shah, MD, MPH</td>
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<td>12:08</td>
<td>Discussion of above 2 papers</td>
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<td>12:12</td>
<td>Diabetic Retinopathy Improvements with Intravitreal Faricimab in the BOULEVARD Trial</td>
<td>Nathan Steinle, MD</td>
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<td>Discussion</td>
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<td>12:21</td>
<td>TIME-2b Study of AKB-9778 on DRSS in Patients with Moderate to Severe Non Proliferative Diabetic Retinopathy</td>
<td>Victor Gonzalez, MD</td>
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<td>12:27</td>
<td>Discussion</td>
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GENETIC DISEASES, DYSTROPHIES AND DEGENERATIONS

PRESIDING OFFICER: Lucian Del Priore, MD, PhD
MODERATOR: Michel Michaelides, BSc, MB, BS, MD(Res), FRCOphth, FACS

7:30 am

ANNOUNCEMENTS

7:32 Determining the Long-term Progression of Untreated Atrophic Lesions in Age-related Macular Degeneration (AMD) and Stargardt Disease (STGD)
Lucian Del Priore, MD, PhD

7:36 Progression of Stargardt Disease as Measured by Spectral-domain Optical Coherence Tomography (SD-OCT) in the ProgStar Study
Rupert Strauss, MD

7:42 Discussion of above 2 papers

7:46 Month 24 Results from the Scotopic Microperimetric Assessment of Rod Function in Stargardt Disease (SMART) Study
Hendrik Scholl, MD, MA

7:52 Discussion

7:55 Rapid Symmetrical Progression of Retinal Degeneration in Patients with CLN2-associated Batten Disease
Kyle Kovacs, MD

8:00 Suprachoroidal Injection of AAV8 using Microneedles for Ocular Gene Delivery in the Nonhuman Primate
Glenn Yiu, MD, PhD

8:06 Surgical Technique with Intraoperative Optical Coherence Tomography for Subretinal Gene Therapy in Patients with Inherited Retinal Degenerations
Ninel Gregori, MD

8:12 Discussion of above 2 papers

8:16 In Vitro Mutagenesis of RPE65 Protein for Verification of Mutational Pathogenicity Prior to Gene Therapy Surgery
Aaron Nagiel, MD, PhD

8:22 Four-year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation–associated Inherited Retinal Disease
Stephen Russell, MD

8:28 Discussion of above 2 papers

8:32 Gene Therapy for X-linked Retinitis Pigmentosa Caused by Mutations in RPGR
Robert MacLaren, MBChB DPhil FACS

8:38 Discussion

8:41 Safety and Efficacy of rAAVtYF-CB-hRS1 Intravitreal Gene Therapy for X-linked Retinoschisis — One Year Results
Mark Pennesi, MD, PhD
8:46 am  Patient-reported Outcomes in Retinal Degenerations
   Thiran Jayasundera, MD

8:51   Computer Assisted Immersive Visual Rehabilitation in Retinal Prosthesis Recipients
   Aleksandra Rachitskaya, MD

8:56   PDE 5/6 Treatment of Choroidal Ischemia in Macular Degeneration and Dystrophy
   Jackson Coleman, MD

9:01   Multimodal Imaging in Transthyretine Amyloidosis
   Jose Pulido, MD

9:06   Use of a Conjoint Analysis Survey to Understand Patient Preferences in Potential Ocular Stem Cell Therapies
   Rajesh Rao, MD

9:11   FELLOWS RESEARCH AWARD PRESENTATION INTRODUCTION
   Prithvi Mruthyunjaya, MD

   Vitreous Microparticles in Diabetic Eye Disease Signal Hyalocyte Apoptosis Suggesting a Diabetic Vitreopathy
   Harris Sultan, MS, MD

9:26   RETINA RESEARCH FOUNDATION AWARD—CHARLES L. SCHEPENS LECTURE INTRODUCTION
   Richard Spaide, MD

   Optical Coherence Tomography: History, Evolution and Future Prospects
   James Fujimoto, PhD

9:56   REFRESHMENT BREAK / EXHIBITS

IMAGING

PRESIDING OFFICER: Richard Spaide, MD
MODERATOR: Richard Rosen, MD, ScD

10:26  Optical Coherence Tomography Angiography (OCTA) Quality in DRCR Retina Network Multicenter Clinical Studies
   Brandon Lujan, MD

10:32  Microaneurysm Imaging in Diabetic Retinopathy using Multiple En Face Optical Coherence Tomography Angiography Image Averaging
   Shintaro Nakao, MD

10:38  Discussion of above 2 papers

10:42  Nonperfusion and Reperfusion Following Anti-VEGF Treatment Using Reference-based Optical Coherence Tomography Angiography Perfusion Density Mapping
   Richard Rosen, MD, ScD

10:48  Discussion

10:51  Measurable Aspects of the Retinal Neurovascular Unit in Diabetes, Glaucoma and Controls
   Richard Spaide, MD
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<tr>
<th>Time</th>
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<tr>
<td>11:00</td>
<td>Advanced Technical Development in Diagnostic B-Scan Ultrasound</td>
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<td><strong>Yale Fisher, MD</strong></td>
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<td>11:05</td>
<td>Longitudinal Ellipsoid Zone Mapping on Spectral Domain Optical</td>
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<td>Coherence Tomography in Eyes with Hydroxychloroquine Use to</td>
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<td>Evaluate for Subclinical Outer Retinal Alterations</td>
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<td><strong>Katherine Talcott, MD</strong></td>
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<td>11:10</td>
<td>Comparing OCTA Density Measurements of Eyes with and without</td>
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<td>Radiation Retinopathy after I-125 Plaque Brachytherapy and</td>
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<td>Non-irradiated Fellow Eyes</td>
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<td><strong>Talisa De Carlo, MD</strong></td>
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**ARTIFICIAL INTELLIGENCE AND THE RETINA**

**PRESIDING OFFICER:** Carl Regillo, MD  
**MODERATOR:** Jennifer Lim, MD

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<th>Time</th>
<th>Artificial Intelligence Screening for Diabetic Retinopathy: Analysis</th>
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<td>Deep Learning Systems for Detecting Age-related Macular</td>
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<td><strong>Daniel Ting, MD, PhD</strong></td>
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<td>Machine Learning Analysis of SD-OCT Features Predicting Short-</td>
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<td>term Progression of Intermediate Age-related Macular Degeneration</td>
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<td>(AMD) to Geographic Atrophy (GA)</td>
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<td><strong>Eleonora Lad, MD, PhD</strong></td>
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**PEDIATRIC RETINAL DISEASES**

**PRESIDING OFFICER:** Audina Berrocal, MD  
**MODERATOR:** Mary Elizabeth Hartnett, MD

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<th>Time</th>
<th>Quantitative Analysis of Vascular Severity in Patients Diagnosed</th>
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<td>with Plus Disease in the Imaging and Informatics in Retinopathy of</td>
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<td>Prematurity Study</td>
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<td><strong>Rene Choi, MD, PhD</strong></td>
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<td>11:40</td>
<td>Regression Patterns after Ranibizumab Treatment of Retinopathy of</td>
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<td>Prematurity (ROP): An Anti-VEGF Class Effect</td>
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<td></td>
<td><strong>Darius Moshfeghi, MD</strong></td>
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<td>11:51</td>
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<td>11:54</td>
<td>Reactivation of Previously Stable Retinopathy of Prematurity (ROP)</td>
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<td><strong>Baker Hubbard, MD</strong></td>
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<td>12:00 pm</td>
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<td>Presentation</td>
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| 12:03 | Ocular and Neurodevelopmental Outcomes Among Infants Treated for Retinopathy of Prematurity (ROP)  
Michael Blair, MD |
| 12:09 | Discussion                                                                  |
| 12:12 | Protective Effects of Erythropoietin in Oxygen-induced Retinopathy           
Mary Elizabeth Hartnett, MD |
| 12:18 | Discussion                                                                  |
| 12:21 | Early Gut Microbiome Profile in High-risk Preterm Infants with and without Retinopathy of Prematurity  
Dimitra Skondra, MD, PhD |
| 12:27 | Discussion                                                                  |
| 12:30 | Retinal Vascular Abnormalities are More Common than Previously Reported in Incontinentia Pigmenti  
Peter Campbell, MD, MPH |
| 12:36 | Discussion                                                                  |
| 12:39 | Ocular Histopathologic Findings of Congenital Zika Syndrome                  
Sander Dubovy, MD |
| 12:44 | Serous Macular Detachment Due to Congenital Optic Disk Abnormalities: A Comparative Study  
Arnaldo Bordon, MD, PhD |
| 12:49 | Optical Coherence Tomography Angiography of Pediatric Choroidal Neovascular Membranes  
Lejla Vajzovic, MD |
| 12:54 | ADJOURN                                                                     |
SCIENTIFIC PROGRAM

SUNDAY, SEPTEMBER 15, 2019

RETINAL POTPOURRI
PRESIDING OFFICER: Gaurav Shah, MD
MODERATOR: Timothy Jackson, PhD, FRCOphth

7:30 am
ANNOUNCEMENTS
7:32 From Helmholtz to Optos: A Brief History of the Ophthalmoscope
Ian McAllister, MD, PhD
7:37 Release of Silicone Oil and the Off-label use of Syringes in Vitreoretinal Diseases: Understanding this Public Health Problem
Mauricio Maia, MD, PhD
7:42 Variable Risk of Silicone Oil Microdroplets Following Multiple Bevacizumab, Ranibizumab and Aflibercept Intravitreal Injections
John Thompson, MD
7:47 Mishandling of Syringes and the Risks to the Eye
Gustavo Melo, MD, PhD
7:52 Discussion of above 4 papers
7:56 Ranibizumab and Aflibercept Levels and their Impact on Vascular Endothelial Growth Factor in Human Breast Milk Following Intravitreal Injection
Verena Juncal, MD

8:01 Process Mapping and Activity-based Costing of the Intravitreal Injection Procedure
Christina Weng, MD, MBA
8:06 The Retina as a Window to Understanding Sub-types of Alzheimer’s Disease
Tunde Peto, MD, PhD
8:11 Analysis of Emergent Non-hospital Based Retina Consultation Requests In an Academic Non-hospital Associated Retina Practice
Gaurav Shah, MD
8:16 NAD+ Based Therapeutic Development
Rajendra Apte, MD, PhD

TUMORS
PRESIDING OFFICER: Carol Shields, MD
MODERATOR: Timothy Murray, MD, MBA, FACS

8:21 Prospective Evaluation of Genomic Prognostic Risk Factors in 921 Uveal Melanomas: Report from the Collaborative Ocular Oncology Group Study Number 2
Thomas Aaberg, MD
8:27 Discussion
8:30 am Intravitreal Bevacizumab to Prevent or Delay Radiation Maculopathy after Transfoveal Plaque Radiotherapy for Choroidal Melanoma: The PRELAY Study
  Brittany Powell, MD

8:35 Targeted Treatment of Uveal Melanoma: Increased Survival AND Enhanced Visual Function
  Timothy Murray, MD, MBA, FACS

8:41 Discussion

8:44 Proton Irradiation of Uveal Melanomas Involving the Iris and Ciliary Body without Surgical Localization (Light Field)
  Evangelos Gragoudas, MD

8:50 Discussion

8:53 Outcomes of Intravitreal Methotrexate to Salvage Eyes with Relapsed Primary Intraocular Lymphoma.
  Mandeep Sagoo, MB, PhD, FRCS (Ed), FRCOphth

8:59 Discussion

9:02 Choroidal Nevus Risk Factors for Transformation into Melanoma Using Multimodal Imaging in 3806 Cases
  Carol Shields, MD

9:08 Focal Aggregates of Normal Choroidal Melanocytes (Choroidal Melanocytic Clusters): A Distinct Clinical Entity
  James Augsburger, MD

9:14 Discussion of above 2 papers

9:18 Fine Needle Aspiration Biopsy for Cytopathologic Diagnosis of Posterior Segment Tumors in 494 Consecutive Patients
  Basil Williams, MD

9:24 Discussion

9:27 Universal Reflex Referral to VHL Comprehensive Clinical Care Center of Patients Presenting to Ophthalmologists Leads to Dramatic Improvement in Guideline-concordant Screening: Results of a Pilot Study
  Anthony Daniels, MD, MSc

9:32 USA Health Policy Directions: A single payer like the UK’s NHS?
  David Parke II, MD

9:42 REFRESHMENT BREAK/EXHIBITS

OTHER MACULAR DISEASES
  PRESIDING OFFICER: David Sarraf, MD
  MODERATOR: Shlomit Schaal, MD, PhD

  Adam Hanif, MD
10:18 am Strength of Association Between Pentosan Polysulfate Exposure and a Newly Described Maculopathy among Patients with Interstitial Cystitis
Nieraj Jain, MD

10:24 Novel Multi-modal Image Analysis to Quantify Pentosan Polysulfate Sodium (Elmiron) Retinal Toxicity Demonstrates an Exponential Dose-response Curve
Shlomit Schaal, MD, PhD

10:30 Discussion of above 3 papers

10:35 Outer Hemorrhagic Henle Maculopathy (OHHM): Clinical Features and Pathogenesis of a New Syndrome
David Sarraf, MD

10:41 Discussion

10:44 TGF-β-SNAIL Axis Induces Müller Glial-Mesenchymal Transition in the Pathogenesis of Idiopathic Epiretinal Membrane
Susumu Ishida, MD, PhD

10:49 Primary Retinal Vascular Abnormalities in Neurofibromatosis Type 1 (NF1): a NF1 Related Capillary Hemangioma
Edoardo Midena, MD, PhD

LATE BREAKING PRESENTATIONS

PRESIDING OFFICER: Jose Pulido, MD
MODERATOR: Mark Blumenkranz, MD

Anthony Daniels, MD, MSc

10:59 Discussion

11:01 Results of a Phase 1/2 Trial of an Optimized Gene Therapy in Adults and Children with Retinal Dystrophy Associated with Bi-allelic Variants in RPE65
Michel Michaelides, BSc, MB, BS, MD(Res), FRCOphth, FACS

11:06 Discussion

11:08 Novel Anti-VEGF Antibody Biopolymer Conjugate KSI-301 with Potential for Extended Durability in Retinal Vascular Diseases: Late-Breaking Results from a Phase 1b Study in Patients with wAMD, DME and RVO
David Brown, MD

11:13 Discussion

11:15 Results of a Phase 1, Open-label, Dose-escalation Study of THR-149 for the Treatment of Diabetic Macular Oedema (DME)
Pravin Dugel, MD

11:20 Discussion
INFLAMMATION

PRESIDING OFFICER: Douglas Jabs, MD
MODERATOR: Thomas Albini, MD

11:22 am  Suprachoroidal Injection of CLS-TA in Uveitis Maintains Efficacy Outcomes Through 48-weeks: Results of the MAGNOLIA Phase 3 Extension Study
Sumit Sharma, MD

11:28  Suprachoroidal Triamcinolone Acetonide Suspension (CLS-TA) and Intraocular Pressure: Results from the Phase 3 PEACHTREE Clinical Trial for Uveitis
Pauline Merrill, MD

11:34  Discussion of above 2 papers

11:38  Duration of Effect for Long-acting Injectable Fluocinolone Acetonide Implant for Noninfectious Uveitis
Cindy Cai, MD

11:44  The Use of Adjunctive Anti-inflammatory Medications: Results from a 3 Year Study of a Fluocinolone Acetonide Intravitreal Insert in Chronic Non-infectious Uveitis Affecting the Posterior Segment
Dilraj Grewal, MD

11:50  Discussion of above 2 papers

11:54  Minimizing Uveitic Recurrences: Results from a 36M Study of Fluocinolone Acetonide Intravitreal Insert in Subjects with Chronic Non-infectious Uveitis Affecting the Posterior Segment
Thomas Albini, MD

12:00 pm  Discussion

12:03  Patient Comfort and Antimicrobial Efficacy of Aqueous Chlorhexidine Compared to Povidone Iodine as an Ocular Surface Disinfectant Prior to Intravitreal Injection: A Randomized Clinical Trial
Thomas Jenkins, MD

12:08  Toxic Posterior Segment Syndrome: Clinical Characteristics of 48 Eyes
Ashkan Abbey, MD

12:14  Discussion

12:15  Real-world Rates of Suspected Endophthalmitis Following Intravitreal Injections in the United States
Dilsher Dhoot, MD

12:22  Endogenous Endophthalmitis: Empiric Antibacterial and Antifungal Management
Mallika Doss, MD

12:27  Domination of Enterococcal Isolates in Postoperative Endophthalmitis associated with Selection Pressure of Fluoroquinolone: 10-year Multicenter Study and Co-culture Experimental Study
Sang Joon Lee, MD
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<tr>
<td>12:32 pm</td>
<td>Discussion of above 3 papers</td>
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| 12:36  | PCR versus Conventional Culture for Detection of Endophthalmitis Pathogens  
Scott Walter, MD, MSc |
| 12:41  | ADJOURN                                                              |
POSTER SESSION

THURSDAY, SEPTEMBER 12 • 12:49 - 1:39 PM • EMPIRE ROOM

RETINAL VASCULAR DISEASE

POSTER 1 Short-term Outcomes of Eyes Switched from Intravitreal Aflibercept (IVA) to Ranibizumab (IVR)
Michael Klufas, MD

POSTER 2 Peripapillary Vascular Loops — A Collaborative Study
Ahmad Mansour, MD

POSTER 3 Optical Coherence Tomography Angiography Findings in Purtscher-like Retinopathy in Systemic Lupus Erythematosus
Ryoji Yanai, MD

AGE-RELATED MACULAR DEGENERATION

POSTER 4 Survey of Intravitreal Injection Practice Patterns among Retina Specialists
Stephen Smith, MD

POSTER 5 Delayed Onset Retinal Detachment in Patients Receiving Chronic Anti-Vascular Endothelial Intravitreal Injection Therapy
Judy Chen, MD

SURGERY

POSTER 6 Outcomes and Complications of In-office Laser Demarcation of Peripheral Rhegmatogenous Retinal Detachments
David Xu, MD

POSTER 7 Optimizing the Visual Performance of a 3D Viewing System
David Chow, MD, FRCS(C)

POSTER 8 Chandelier Assisted Scleral Buckling for Primary Uncomplicated Rhegmatogenous Retinal Detachment
Jose Roca, MD

POSTER 9 Clinical Characteristics Predictive of Successful Pneumatic Retinopexy for Rhegmatogenous Retinal Detachment
Michelle Peng, MD

POSTER 10 Biocompatibility of Silicone Oils: The Role of Exogenous and Endogenous Surfactants
Mario Romano, MD, PhD

POSTER 11 Utilizing Spectral Domain Optical Coherence Tomography to Identify Posterior Vitreous Detachment in Patients with Retinal Detachment: Analysis of the Primary Retinal Detachment Outcomes (PRO) Study
Sushant Wagley, MD

POSTER 12 Full Thickness and Basement Membrane-only Transplant of Dehydrated Amniotic Membrane for Macular Holes, Penetrating Trauma and Retinal Detachments
Xihui Lin, MD
POSTER SESSION

POSTER 13  Retinal Detachment after TASER Trauma
Nicole Koulisis, MD

POSTER 14  Vitrectomy with the Inverted ILM Flap Technique in Eyes with Full-thickness Macular Hole Coexisting with Dry Age-related Macular Degeneration
Zofia Michalewska, MD, PhD

POSTER 15  A Case of Macular Hole with Multiple Recurrences and Spontaneous Closures; A Condition Behind the Disease
Yoko Ozawa, MD, PhD

POSTER 16  Grid Deformation Analysis of the Macula and Postoperative Metamorphopsia after Macular Hole Surgery
Hwa Yeong Kim, MD

POSTER 17  Surgical Outcomes of Traumatic Retinal Detachment Repair in Patients with Self-injurious Behavior
Elizabeth Rossin, MD, PhD

DIABETIC RETINOPATHY

POSTER 18  Identifying Gaps in Patient Access to Diabetic Screening Eye Examinations in Ontario: A Provincially Representative Cross-sectional Study
David Wong, MD FRCSC

POSTER 19  Morphofunctional Analysis of the Retina in Type 1 Diabetic Patients without Complications after 30 Years of Disease
Giuseppe Querques, MD, PhD

POSTER 20  Alteration in the Number of Microaneurysms in Diabetic Macular Edema after Anti-Vascular Endothelial Growth Factor Therapy
Shigeo Yoshida, MD, PhD

GENETIC DISEASES, DYSTROPHIES AND DEGENERATIONS

POSTER 21  Retinal Degeneration in Oguchi Disease
Mineo Kondo, MD, PhD

POSTER 22  Verscian Canonical Splice Site Mutation is associated with Vitreoretinal Degeneration and Disrupts a Matrix Metalloproteinase Proteolytic Site
Peter Tang, MD, PhD

POSTER 23  Genotypic Profile and Phenotype Correlations of ABCA4-associated Retinopathy in Koreans
Kwangsic Joo, MD, PhD

POSTER 24  Multimodal Imaging of Macular Neovascularization in Stargardt Disease
Jorge Orellana-Rios, MD

IMAGING
POSTER SESSION

POSTER 25  Effect of Intravitreal Bevacizumab on the Retinal Ganglion Cell Layer
            Uday Desai, MD

            Akitoshi Yoshida, MD

POSTER 27  Optical Coherence Tomography Angiography Redefining Rare Retinal Disease
            Jaclyn Kovach, MD

ARTIFICIAL INTELLIGENCE

POSTER 28  An AI-assisted Decision Support Tool for Retinal Video Angiography
            Saad Shaikh, MD, MBA

PEDIATRICS

POSTER 29  Inner Retinal Fenestration for Pediatric Optic Disc Pit Maculopathy
            Nicole Scripsema, MD

POSTER 30  Ocular Manifestations of Cutis Marmorata Telangiectatica Congenita (CMTC)
            Vaidehi Dedania, MD

POSTER 31  Pediatric Gene Therapy Experience at the Bascom Palmer Eye Institute
            Audina Berrocal, MD

POSTER 32  Bevacizumab or laser for Aggressive Posterior Retinopathy of Prematurity
            Sidney Schechet, MD

RETINAL POTPOURRI

POSTER 33  Adopting Contrast Sensitivity Screening in a Driver’s License Program: Results from a Pilot Study of 352 Subjects
            Asad Durrani, MD

POSTER 34  Cellular Automata: A Conceptual Framework for Perfect Drusen Symmetry
            Edward Chaum, MD, PhD

POSTER 35  Opioid Prescribing Patterns Among Retina Specialists in the United States
            Cindy Ung, MD

POSTER 36  Distribution and Practice Patterns of Retina Providers Across the United States
            Ravi Pandit, MD, MPH
POSTER SESSION

TUMORS

POSTER 37 Choroidal Circulation in Radiation Retinopathy
Satoru Kase

POSTER 38 Retinal Vascular Abnormalities in Phakomatosis Pigmentovascularis; Implications for G-protein Involvement in Retinal Vascular Development
Aristomenis Thanos, MD

POSTER 39 Intra-operative Cytology on Choroidal Tumors
James Bolling, MD

POSTER 40 Whole Genome Sequencing of Circulating Cell-free DNA in Patients with Uveal Melanoma
Ivana Kim, MD

OTHER MACULAR DISEASES

POSTER 41 Central Serous Chorioretinopathy Treated with Targeted Navigated Laser Photocoagulation
James Major Jr, MD, PhD, FACS

POSTER 42 Experience in Initial Management of Central Serous Retinopathy with Spironolactone
Alexander Kuley, MD

INFLAMMATION

POSTER 43 Use of Alcohol Swabs and Nonsterile Gloves in Preparation of Anti-VEGF Medication for Intravitreal Injestion
Kathleen Regan, MD

POSTER 44 Staphylococcus Warneri Endophthalmitis following Intravitreal Anti-VEGF Injection
Tamara Vrabec, MD

POSTER 45 A Case of Poor Visual Acuity due to Iridocyclitis and Choroiditis associated with Past Langerhans Cell Histiocytosis
Kazuhiro Kimura, MD

POSTER 46 Oculocardiac Reflex during Intravitreal Injection
Hugo Quiroz-Mercado, MD
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Randomized Clinical Trial of Initiation with Aflibercept, Focal/Grid Laser Photocoagulation, or Observation for Center-involved DME in Eyes with Good Visual Acuity—Protocol V

Andrew Antoszyk, MD
Charlotte, NC
DRCR Retina Network

**PURPOSE:** To compare 2-year vision loss among eyes with center-involved diabetic macular edema (CI-DME) and good visual acuity (VA, 20/25 or better) when initiating one of three management strategies: intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (aflibercept), focal/grid laser photocoagulation, or observation.

**METHODS:** Two-year DRCR Retina Network randomized clinical trial conducted at 91 United States and Canadian sites. Participants (n = 702) were adults with type 1 or 2 diabetes who had one study eye with CI-DME confirmed on optical coherence tomography (OCT) and VA 20/25 or better (>79 letters). Aflibercept injections were given to the laser and observation groups if vision decreased from baseline due to CI-DME by >10 letters at 1 visit or >5 letters at 2 consecutive visits.

**RESULTS:** At 2 years, there was no significant difference in the primary outcome of >5-letter VA decrease in the aflibercept 16% (33 of 205), laser 17% (36 of 212) or observation 19% (39 of 208) groups [relative risk (95% confidence interval): aflibercept vs. laser photocoagulation = 0.88 (0.57-1.35), P = 0.79; aflibercept vs. observation = 0.83 (0.55-1.27), P = 0.79; laser photocoagulation vs. observation = 0.95 (0.64-1.41), P=0.79]. There was also no significant difference in mean change in VA [mean difference (95% confidence interval): aflibercept vs. laser photocoagulation = 1.0 (-0.4 to 2.5), P = 0.21; aflibercept vs. observation = 1.3 (-0.3 to 2.8), P = 0.14; laser photocoagulation vs. observation = 0.2 (-1.0 to 1.5), P = 0.70]. Mean visual acuity was 20/20 in all three groups at 2 years. The percentage of eyes with VA 20/20 or better at 2 years was 77% (158 of 205), 71% (151 of 212) and 66% (137 of 208) with aflibercept, laser, and observation, respectively [relative risk (95% confidence interval): aflibercept vs. laser photocoagulation = 1.11 (0.97-1.27), P = 0.15; aflibercept vs. observation = 1.18 (1.01-1.37), P = 0.03; laser photocoagulation vs. observation = 1.06 (0.93-1.20), P = 0.40]. Aflibercept was given for vision decrease in 25% (60 of 240) and 34% (80 of 236) of eyes in the laser and observation groups, respectively.

**CONCLUSIONS:** Given the cost and risks associated with intravitreous anti-VEGF injections or laser, observation with initiation of aflibercept if vision decreases may be a reasonable strategy for eyes that present with CI-DME and good VA. Support Statement: National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (UGIEY014231 and UGIEY023207). Regeneron provided aflibercept for the study and funds to DRCR Retina Network to defray the study’s clinical site costs. The DRCR Retina Network had complete control over the design of the protocol, ownership of the data, all editorial content of presentations and publications related to the protocol, and the decision to submit for publication.
DRCR Retina Network Approach to Observation with Aflibercept for Vision Decrease in Eyes with Center-involved Diabetic Macular Edema and Good Visual Acuity

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PURPOSE: A randomized clinical trial of eyes with center-involved diabetic macular edema (CI-DME) and good visual acuity (VA) showed no difference in rates of > 5 letter VA loss whether eyes were initially treated with aflibercept versus laser or observation and given aflibercept only if VA decreased. The purpose of this study is to outline the DRCR Retina Network approach of observation with subsequent addition of aflibercept only if VA decreases.

METHODS: Exploratory analyses of Protocol V, a randomized clinical trial of 702 adults (236 randomly assigned to observation) with type 1 or 2 diabetes, one study eye with CI-DME confirmed on optical coherence tomography, and VA > 79 letters (20/25 or better), followed for 2 years. Aflibercept was initiated in the observation group only if VA decreased from baseline by > 10 letters at any follow-up visit or by > 5 letters at 2 consecutive follow-up visits.

RESULTS: Among 236 eyes assigned to initial observation, 44 (19%) initiated aflibercept injections due to > 10-letter VA loss at a single visit and 34 (14%) initiated aflibercept injections due to 5 to 9-letter VA loss at consecutive visits. Ninety-two eyes experienced a 5-9 letter VA loss at least once prior to the last visit; 29 of these eyes (32%) had sustained VA loss at the next visit and met protocol criteria for aflibercept initiation; 20 eyes (22%) later received aflibercept for VA loss; 42 (46%) never received aflibercept. When baseline OCT central subfield thickness (Zeiss-Stratus equivalent) was > 300 µm, eyes were more likely to receive aflibercept than when CST was < 300 µm (43% vs. 27%, P = .009). Initiation of aflibercept was also more likely among participants with a non-study eye receiving DME treatment within 4 months of randomization (52% vs. 25%, P < .001), a pre-specified randomization stratification factor.

CONCLUSIONS: Using this approach of initial observation with subsequent aflibercept only if vision decreases, the majority of eyes did not require aflibercept injections through 2 years of follow-up. Eyes with greater CST at baseline and participants with a fellow eye receiving treatment for DME were more likely to need anti-vascular endothelial growth factor therapy for vision worsening.
Visual Acuity Outcomes and Anti-Vascular Endothelial Growth Factor Therapy Intensity in Diabetic Macular Edema: A “Real World” Analysis in 28,456 Eyes

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PURPOSE: This study assessed anti-vascular endothelial growth factor (VEGF) therapy intensity, as well as the relationship between treatment intensity and visual acuity (VA) outcomes, in “real world” diabetic macular edema (DME) patients, using a demographically diverse sample of U.S. retina specialists’ electronic medical records (EMR). In DME, few studies have investigated the translatability of randomized clinical trials (RCTs) to the “real world”, in which patients often do not meet RCT eligibility criteria, because of minimal or extensive systemic or ocular disease severity or both.

METHODS: Analysis was performed on a large database of aggregated, longitudinal EMR from a demographically diverse sample of U.S. retina specialists. The HIPAA-compliant Vestrum Health Retina Database was used retrospectively. Treatment naïve DME patients who underwent anti-VEGF injections between January 2013 and October 2017 were eligible if follow up data was available through October 2018. VA outcomes were assessed at 1 year and stratified based on number of injections received over 1 year.

RESULTS: This analysis included 28,456 eyes. The mean age at initial presentation was 62.5 years. At 1 year, the mean number of letters gained was 4 letters after a mean of 5.8 injections, with no significant trends in these figures between 2013-2017. There were no meaningful differences in injection frequency or visual outcomes based on choice of initial anti-VEGF agent. Between 4 and 13 yearly injections, there was a linear relationship between number of injections over 1 year and mean letters gained. The mean change in VA at 1 year was +1.9, +4.2, +5.7, and +7.4 letters in those 2870, 3102, 2447, and 620 patients who received a mean of 3, 6, 9, and 12 injections respectively.

CONCLUSIONS: “Real world” DME patients are under-treated with resulting visual outcomes following anti-VEGF therapy less than those seen in randomized controlled trials. This analysis also demonstrates that treatment intensity in the “real world” correlates with visual outcomes over the first year of treatment.
Two-year Results of Treat-and-Extend Regimen using Aflibercept for Diabetic Macular Edema; VIBIM Study

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PURPOSE: To investigate the efficacy of treat-and-extend regimen (TER) using aflibercept for diabetic macular edema.

METHODS: This was a prospective multi-center single-arm study planned for two years. The eyes received five consecutive intravitreal injections of 2mg aflibercept every 4 weeks and then the injection interval was adjusted by 2 weeks based on changes of central subfield macular thickness (CSMT). If CSMT was worse, stable or better, the interval was shortened, extended and maintained, respectively. The primary outcome was the change in best-corrected visual acuity (BCVA) from baseline at 104 weeks, and the secondary outcomes include the change in BCVA at 52 weeks.

RESULTS: Of enrolled 48 patients, 46 completed one-year visit. BCVA increased significantly by 8.9 letters from 52.5 letters at baseline (P<0.001), and CSMT decreased by -171.7 from 489.4 to 317.7 µm (P<0.001). Proportion of eyes having 20/40 or better vision increased from 17.4% to 41.3%, and proportion of eyes gained 15 letters or more was 28.3%. The mean number of injections was 8.5 times for 52 weeks. Worsening of macular edema did not occur in 76.1% during the extension period, and the injection interval was extended to 12 weeks in 73.9% at 52 weeks.

CONCLUSIONS: The TER of the current study showed one-year efficacy comparable to the fixed dosing regimen of the pivotal trials, and its flexible dosing would avoid overtreatment. The two-year results will be presented in the meeting.
Consistent Improvements in Retinal Thickness Stability with 0.19 mg Fluocinolone Acetonide Implant in DME: Results from FAME, PALADIN and USER Studies

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PURPOSE: Randomized controlled trials and real-world studies have shown the 0.19 mg fluocinolone acetonide (FAc) implant effectively reduces (CST) in patients with DME. As alternate measures of edema control, the RTA (Retinal Thickness Amplitude) and standard deviation of CST over time define CST stability. We explore these measures in pivotal datasets (FAME, PALADIN and USER).

METHODS: Three studies (643 eyes) with DME patients treated with the FAc implant were included. 1) Prospective cohort of 324 eyes from the FAME trial with 3 years follow-up (phase III RCT); 2) 199 eyes from the PALADIN study with 526 days follow-up (phase IV study); and, 3) 124 eyes from USER with over 403 days of follow-up. RTA, expressed in microns, was calculated as the maximum range of retinal thickness fluctuation based on the difference between minimum and maximum CST for each eye receiving the FAc implant. Standard deviations (SD) of CST over time were also further explored for each eye. RTA value across subgroups including lens status, baseline visual acuity and last DME treatment were assessed. Values are reported as mean’s throughout.

RESULTS: In FAME, RTA in the FAc implant treated patients was significantly reduced compared to sham. (186.8 µm versus 239.7 µm respectively, p<0.001). In PALADIN, RTA decreased from 245.5 µm in the pre FAc period to 132.4 µm post-FAc (p<0.001). In USER, RTA decreased from 230.9 µm to 96.4 µm pre- to post-FAc implant (p<0.001). Subgroup analyses of lens status, baseline visual acuity and last DME treatment showed statistically significant improvements in all studies. Across the real-world studies, the least fluctuation in retinal thickness as measured by RTA occurred in eyes with VA 20/40 or better at baseline (p<0.001).

CONCLUSIONS: Across all datasets analyzed, RTA and standard deviation analyses showed consistent improvements in edema stability over time post FAc implant. Patients with better vision had the most stable CST measures over time. Assessments of CST stability over time may be an important measure of DME and other retinal disease state treatment success - especially in the setting of longer acting treatment modalities.
**PURPOSE:** To present baseline characteristics of participants enrolled in DIAMONDS.

**METHODS:** DIAMONDS, a pragmatic, multicentre, allocation-concealed, randomised, equivalence, double-masked clinical trial, aims at determining clinical effectiveness and cost-effectiveness of subthreshold micropulse laser, compared with standard threshold laser, for the treatment of Diabetic Macular Oedema (DMO) with central subfield thickness (CST) of < 400 µm, for which the National Institute for Health and Care Excellence advises this therapeutic option. Primary outcome is mean change in best-corrected visual acuity (BCVA) in the study eye from baseline to month 24. Secondary outcomes at 24 months include change in binocular BCVA; CST; mean deviation of Humphrey 10–2 visual field; change in percentage of people meeting driving standards; EQ-5D, NEI-VFQ 25 and VisQoL scores; incremental cost per quality-adjusted life year gained; side effects; laser sessions received and use of additional therapies. Based on a mean (standard deviation; SD) of 0.08 (0.23) logMAR for BCVA change from baseline for the standard laser and a permitted maximum difference of 0.1 logMAR (5 ETDRS letters) between groups, 113 participants per group would be required to have 90% power at 0.05 level of significance. Allowing for 15% dropout, 266 participants were needed. Eligible participants have centre-involving DMO, which in the opinion of the investigator requires and is suitable for macular laser in one or both eyes. The study eye is that with better BCVA and, if vision the same in both eyes, less CST.

**RESULTS:** Participants (n=266) have an average age of 62 years (range 24-88), the majority (70%) are males, white (77%), with type 2 diabetes (86%) of, on average, 16 years standing and mean HbA1c of 68.7 mmol/mol (SD 19.4). In 8% of participants, fellow eyes had eligible DMO. Most eyes included were phakic (83%). Previous laser and/or anti-VEGF therapies were used in 24% and 15% of study eyes, respectively, with a mean number of injections received of 9.1. Mean BCVA at presentation was 80 ETDRS letters (SD 8.4) (~20/25 Snellen Equivalent) and mean CST 329 µm.

**CONCLUSIONS:** DIAMONDS will provide strong evidence to guide laser selection for people with DMO.
Blood Pressure is Associated with Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Treatment in Patients with Diabetes

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PURPOSE: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are commonly used in the treatment of diabetic retinopathy (DR), but the need for treatment and frequency of administration varies considerably among patients. There is no way to predict which patients will require treatment, and how frequently injections will be needed. This study aims to identify factors associated with receiving anti-VEGF injections and the number of treatments received in an 18-month period in patients with diabetes.

METHODS: Retrospective analysis was performed with IRB approval using data collected from 2916 patients with diabetes who presented to the Kellogg Eye Center Retina Clinic from June 1, 2016 to December 31, 2017. Logistic regression was used to identify demographic and medical factors associated with receiving at least one injection. Negative binomial regression was used to model the number of anti-VEGF injections. Main outcome measures were receiving at least one anti-VEGF injection and number of anti-VEGF injections received during the study period.

RESULTS: Of 2916 patients with diabetes, 21.1% received an anti-VEGF injection. An average of 5.75 injections were performed per patient in at least a 12-month period. Systolic blood pressure and a diagnosis of diabetic retinopathy were significantly associated with receiving an injection. A history of kidney disease was positively associated with the number of injections received. Type 1 diabetes was negatively associated with receiving an injection and the number of injections. Current hemoglobin A1c was not associated with either receiving an injection or number of injections.

CONCLUSIONS: Using data collected in a real-world setting, elevated blood pressure is significantly associated with need for treatment with anti-VEGF injections in patients with diabetes, and a diagnosis of type 1 diabetes is negatively associated with both receiving treatment and number of injections. Of note, current glycemic control is not significantly associated with either outcome measure. This, to our knowledge, is the first study to report such associations, implying that factors that confer risk for development of DR may not be the same that confer risk for treatment.
Three-dimensional Analysis of Morphologic Changes and Visual Outcomes in Diabetic Macular Edema

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PURPOSE: To investigate the association of retinal fluid volume with visual and anatomical outcome in diabetic macular edema (DME) after bevacizumab treatment.

METHODS: We retrospectively analyzed 65 eyes of 58 DME patients treated with bevacizumab. Volumes of intraretinal fluid (IRF) in inner nuclear layer (INL), outer plexiform layer (OPL)/outer nuclear layer (ONL) and subretinal fluid (SRF) were calculated. The correlation of the baseline fluid volumes with the best-corrected visual acuity (BCVA) at baseline and after 1 year was analyzed. In addition, the correlation of the baseline fluid volume with the anatomical outcomes including the area of disorganization of retinal inner layers (DRIL), disrupted external limiting membrane (ELM) and disrupted ellipsoid zone (EZ) was assessed.

RESULTS: Baseline IRF volume in INL positively correlated with the logarithm of the minimal angle of resolution (logMAR) BCVA at final visit (r=0.524, p<0.001), whereas the IRF volume in OPL/ONL and SRF volume did not (r=0.227, p=0.069 and r=0.065, p=0.608). The improvement of BCVA correlated with the reduction of the IRF volume in INL and OPL/ONL (r=0.254, p=0.041 and r=0.361, p=0.003), not with the SRF volume (r=-0.068, p=0.591). The baseline volume of IRF in INL positively correlated with the area of DRIL and the disrupted ELM at final visit (r=0.557, p<0.001 and r=0.246, p=0.048). This relationship was sustained in each quadrant of macula (p<0.005 in all quadrants).

CONCLUSIONS: The baseline IRF volume in INL correlated with the poor visual outcome and the DRIL after the bevacizumab treatment in DME.
Comparisons of Nonperfusion and Ultrawide Diabetic Retinopathy

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**PURPOSE:** To evaluate the association of retinal nonperfusion (NP) on ultrawide field (UWF) fluorescein angiography (FA) with diabetic retinopathy (DR) severity and the presence of predominantly peripheral retinal lesions (PPL).

**METHODS:** This was a predefined exploratory analysis from an ongoing multicenter longitudinal observational study involving 386 participants with at least 1 eye with nonproliferative DR (NPDR) without center-involved diabetic macular edema. Both 200° UWF images and UWF-FA were acquired at the same visit using standardized protocols. UWF color and UWF-FA grading was performed at a central reading center. Standardized ETDRS photo templates were digitally overlaid onto stereographically projected UWF images. All images were evaluated for the presence or absence of PPL, defined as presence of more than 50% of the graded lesion located outside the ETDRS field in any of the 5 extended fields. UWF-FA images at peak fluorescence were evaluated for extent of retinal NP area (NPA) and NP index (nonperfused/total gradable area: NPI). NP on each image was evaluated within concentric zones corresponding to the estimated anatomic location of the posterior pole (15mm).

**RESULTS:** A total of 664 eyes with gradable UWF and UWF-FA images were reviewed. The DR distribution by UWF images masked to ETDRS fields was: no DR or mild NPDR 33.7% (224); moderate NPDR 39.6% (263), severe or very severe NPDR 22.7% (151) and proliferative DR (PDR) 26 (3.9%). In eyes without PDR (N=638), increasing NPI was associated with worsening DR severity was associated with increasing overall (p<0.001), posterior pole (p<0.001) and mid-periphery (p=0.002). Retinal nonperfusion was most commonly seen in the mid-periphery (49%) followed by the posterior pole (28%) and far periphery (23%). Retinal NP most commonly appeared in the temporal and superotemporal periphery. PPL were identified in 265 eyes (39.7%). Eyes with PPL did not have significantly greater NPA or NPI (PPL, NPA 105.9 ± 117.7, vs no PPL, NPA: 83.2 ± 107.7, p=0.82).

**CONCLUSIONS:** The use of UWF FA allows assessment of NP in retinal mid-peripheral and far peripheral zones that are not covered by standard ETDRS FA imaging. These findings suggest that over 70% of NP in diabetic eyes is located outside the posterior pole, potentially suggesting that UWF-FA may enable more sensitive and specific methods to identify nonperfusion and predict future DR worsening than are currently available with standard FA.
Quantification of Diabetic Retinopathy-associated Non-perfusion and Neovascularization on Ultra-widefield Fluorescein Angiography

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PURPOSE: This study evaluates the association between diabetic retinopathy (DR) related non-perfusion (NP) and neovascularization (NV) observed using ultra-widefield (UWF) fluorescein angiography (FA) and variables including age, sex, and race.

METHODS: A retrospective chart review of patients diagnosed with DM evaluated at the University of Michigan Kellogg Eye Center who underwent UWF FA imaging between January 2009 and May 2018 was conducted after IRB approval. Demographic and clinical data were acquired. Trained, masked graders segmented regions of NP and NV within one FA image acquired between 40 and 90 seconds. Eyes with severe media opacities and/or panretinal photocoagulation were excluded. UWF FA research software was used to determine the surface area (SA) of the segmented regions for a nominal eye diameter of 24mm. A linear mixed model was used to evaluate univariate associations and to account for inter-eye correlation. Compound symmetry was chosen for the variance structure, and all independent variables were treated as categorical.

RESULTS: 573 eyes from 349 patients were included. The mean age of the cohort was 57.7 years, and 42.4% of patients were female. 65.0% of patients were white, 24.4% were African American, 4.6% were Asian, and 6.0% were unknown/other. 81.7% of patients were diagnosed with type II DM, 17.8% had type I DM, and 0.6% were unknown. Sex and race both significantly impacted the NP SA in the mid-periphery (p=0.046 and p=0.047, respectively) and the far-periphery (p=0.007 and p=0.01, respectively). Additionally, sex had a significant impact on the total NP SA (p=0.006) with men having more NP. Age had a significant impact on the total NP SA (p=0.04) and far-periphery NP SA (p=0.001). Race significantly impacted both the total SA of NV (p=0.02) and the far-periphery NV SA (p=0.002) with African Americans having more NV. Age significantly impacted the total SA of NV (p=0.04) and the SA of NV in the mid-periphery (p=0.03).

CONCLUSIONS: Age, race, and sex all had significant impacts on the quantified extent of NP and NV on UWF FA. Further studies are needed to determine how these variables associate with the clinical progression of DR.
The Association of Stroke with Retinal Artery Occlusions

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PURPOSE: To determine if the occurrence of a retinal artery occlusion increases the near-term risk of having a stroke.

METHODS: The risk of stroke was assessed in two manners; first a self-controlled case series (SCCS) was performed followed by a propensity score matched cohort study using data from a large national US medical claims database. For the SCCS, all patients who had an incident retinal artery occlusion diagnosis were assigned the date of diagnosis as the index date. Serving as their own controls, patients had various time periods around the index compared for new diagnoses of strokes. The primary analysis compared 90-60 days pre-index date to the 30-day period immediately following the index date to create an incident rate ratio (IRR). The second portion of the study created cohorts from new RAO patients or hip fracture patients discharged from the hospital. The index was assigned to the date of RAO or discharge, respectively. A greedy matching algorithm was performed based on the propensity score for having an RAO. All patients analyzed had to have 2+ years of data in the dataset prior to their index date. Exclusion occurred for any previous diagnosis of stroke. A Cox proportional hazard regression was run to assess the hazard for incident stroke. All demographic and numerous comorbidities were included in the propensity score. Patients were censored at 1 year of observation, had an event to qualify for the comparison group or when they left the plan.

RESULTS: The SCCS study included 38185 RAO patients had a new RAO. 68 and 157 new strokes occurred in the 90-60 days pre-index and 30 days immediately following, respectively, for an IRR of 2.31 (95% CI:1.74-3.07, p<0.001). The cohort study, 40940 patients in both the RAO and hip fracture groups. After propensity score matching, the HR for having a stroke associated with having an RAO compared to a hip fracture was 1.85 (95% CI: 1.73-1.98, p<0.001).

CONCLUSIONS: Having an RAO is associated with a significant risk of stroke in the days following the RAO. Recent guidelines for immediate referral to the emergency room upon RAO presentation should be followed.
Association between the Risk of Central Retinal Artery Occlusion and the Concentration of Environmental Air Pollutants — The Original Study

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PURPOSE: The purpose of the population-based study was to assess the relationship between the risk of central retinal artery occlusion (CRAO) and the level of air pollutants as well as with the air temperature in the days preceding the diagnosis of the disease.

METHODS: The study authors included all registered cases, in the given time interval, diagnosed with a central retinal artery occlusion in Poland. The data received from the NHS contained the exact date of diagnosis of CRAO and was divided into voivodships as to where these cases occurred. CRAO was defined in accordance with the ICD-10 as diagnostic code H34.1. A total of 2,762 cases of CRAO were analyzed. The study authors gathered hourly ambient concentrations of particulate matter — PM 2.5, PM 10, benzene, carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide from pollution monitoring stations. Data on average daily temperature and atmospheric pressure were also obtained. The study calculated the average air pollution with individual particles on the 6th, 4th, 2nd, and 1st day before the registration of the disease, on the day of the registration of the disease, and during the week preceding the registration of the disease. For the statistical analyses, single- and multi-factor Poisson negative binomial regression models, controlling also for ambient temperature and atmospheric pressure were carried out. The seasonality was set at a level of 4 due to immanent characteristics of the natural environment in Poland’s latitude.

RESULTS: Using a multi-factor regression analysis, controlling for ambient temperature and atmospheric pressure, the authors determined the statistically significant relationship (p < 0.05) between the occurrence of CRAO and the increase in PM 10, CO, SO2 concentration on the day of CRAO diagnosis, the increase in NO2 concentration on the 6th day, 4th day prior to the onset of CRAO, and on the day of CRAO diagnosis, and the increase in O3 concentration on the 4th day, 2nd day, 1st day, and the cumulative 7-day period prior to the onset of CRAO. Multi-factor analysis has shown the statistically significant negative interaction between the occurrence of CRAO and NO2 concentration on the 1st day prior to the onset of CRAO and O3 concentration on the day of CRAO onset and air temperature on the 6th, 4th, 1st, and the cumulative 7-day period prior to the onset of CRAO.

CONCLUSIONS: This study has shown the positive association between CRAO onset and short-term, daily changes in PM 10, NO2, SO2, O3, and CO concentrations, as well as with air temperature in the days preceding the diagnosis of the disease. Knowing the aforementioned risk factors, we should strive to reduce them in order to minimize the risk of vision-threatening diseases, such as CRAO. This study points out that air pollution may cause blindness, therefore, the fight against pollution should be extremely important, especially for developing countries struggling with high levels of air pollutants.
Long-term Visual Outcome and Its Predictors in Macular Oedema Secondary to Retinal Vein Occlusion Treated with Dexamethasone Implant

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PURPOSE: To evaluate the functional long-term outcome in patients with macular oedema (MO) secondary to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) treated with dexamethasone implant (DEX implant) and to identify its clinical predictors.

METHODS: A 24-month, retrospective, multinational, real-world study. Chart review of patients with either naïve or recurrent MO secondary to CRVO/BRVO treated with DEX implant, including best-corrected visual acuity (BCVA), central subfield thickness (CST), demographic baseline characteristics and details of any additional treatment during follow-up.

RESULTS: A total of 155 eyes (65 CRVO, 90 BRVO) from 155 patients were included. At 24 months, mean BCVA did not change significantly in CRVO (-2.1 ± 24.5 letters, p=0.96) and BRVO patients (1.3 ± 27.0 letters, p=0.07). A worse baseline BCVA (p<0.001), visual acuity (VA) gain of 5 letters or more at 2 months (p=0.006) and no need for adjunctive intravitreal therapy after first DEX implant (p=0.001) were associated with a better final BCVA gain. Treatment-naïve patients (p=0.006, OR: 0.25, 95% CI: 0.11 to 0.57) and those with a baseline CST of 400 µm or less (p=0.02, OR: 0.25, 95% CI 0.10 to 0.63) were identified as being less likely to need additional intravitreal therapy.

CONCLUSIONS: Clinical baseline characteristics and the early treatment response were identified as possible predictors for long-term outcome and the need of adjunctive intravitreal therapy in MO secondary to BRVO/CRVO treated by DEX implant.
Risk of Systemic Adverse Events Following Intravitreal Aflibercept, Ranibizumab, and Bevacizumab for Common Medical Retinal Conditions in Routine Clinical Practice: A Large Propensity-weighted Cohort Study

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Purpose: Intravitreal anti-VEGF pharmacotherapy plays a central role in the management of neovascular age-related macular degeneration (nAMD), diabetic retinopathy-related complications (DR), and retinal venous occlusion (RVO). Reported rates of systemic adverse events (SAEs) following anti-VEGF treatment within clinical trials have been low. However, comparative systemic safety analyses involving routine clinical use of aflibercept are lacking. We use a large claims database to compare the safety of aflibercept, bevacizumab, and ranibizumab in routine clinical practice.

Methods: Using Optum Labs Warehouse, a large U.S. administrative claims database, we compared cohorts of 50,628 patients receiving initial anti-VEGF injections for nAMD, DR, and RVO between 1/1/2007 and 7/31/2017 (38,401 bevacizumab, 6,940 ranibizumab, 5,287 aflibercept). Primary outcomes were acute myocardial infarction (MI), acute cerebrovascular disease (CVD), major bleeding, and all-cause hospitalization occurring within 6 months of the initial anti-VEGF injection. Patients were censored if treatment switched to a different anti-VEGF medication or health plan coverage ended. Outcomes were compared between treatment groups using propensity score weighted Cox proportional hazards models.

Results: The post-injection hazards of bevacizumab and aflibercept were similar for MI (hazard ratio [HR] 1.23 [95%CI 0.79,1.91], p=0.36), CVD (HR 1.05 [95%CI 0.70,1.58], p=0.80), major bleeding (HR 1.24 [95%CI 0.69,2.22], p=0.48), and hospital admission (HR 1.08 [95%CI 0.97,1.19], p=0.17). The post-injection hazards of aflibercept and ranibizumab were similar for MI (HR 0.68 [95%CI 0.40,1.17], p=0.17), CVD (HR 1.28 [95%CI 0.78,2.12], p=0.33), major bleeding (HR 0.98 [95%CI 0.51,1.89], p=0.95), and hospital admission (0.97 [95%CI 0.85,1.10], p=0.62). The post-injection hazard of bevacizumab vs. ranibizumab was similar for MI (1.02 [95%CI 0.74,1.40], p=0.91), CVD (1.07 [95%CI 0.76,1.51], p=0.69), major bleeding (1.02 [95%CI 0.69,1.51], p=0.91), and hospital admission (1.05 [95%CI 0.97,1.14], p=0.22). Subgroup analyses of patients receiving treatment for nAMD (n=25,411), DR (n=17,129), and RVO (n=8,088) also revealed similar post-injection outcome hazards between anti-VEGF agents (all p>0.05), as did subgroup analyses of patients with baseline moderate/severe renal disease (n=8,820, all p>0.05), prior MI (n=2,249, all p>0.05), or prior CVD (n=7,005, all p>0.05).

Conclusions: We identified no differences in the risk of myocardial infarction, cerebrovascular disease, major bleeding, or all-cause hospitalization following initiation of intravitreal aflibercept, ranibizumab, or bevacizumab pharmacotherapy during routine clinical practice.
Vision and Optical Coherence Tomography Outcomes Following the 2018 Aflibercept Recall

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PURPOSE: A voluntary recall of aflibercept was instituted on 2/28/18 due to increased post-injection inflammation observed in 8 manufacturing lot. At our practice, affected vials were used in 320 patients without any known cases of inflammation. Bevacizumab was recommended as an alternative to aflibercept immediately following the recall. Non-recalled lots of aflibercept were also available for patients who preferred not to switch. By 4/1/2018, planned aflibercept injections were resumed and patients were offered to transition back to aflibercept from bevacizumab. For this study we sought to characterize the impact of switching medication on visual acuity (VA) and central subfield thickness (CST) on Optical Coherence Tomography (OCT).

METHODS: Charts were reviewed for all patients who received an intravitreal injection with University of Vermont Ophthalmology between 3/1–3/31/2018. Patients that had an intravitreal injection with aflibercept between 10/31/2017–2/28/2018 at their last visit prior to 3/1/2018, had an intravitreal injection with either aflibercept or bevacizumab between 3/1–3/31/2018 (index period), and had at least one office visit between 3/31/2018–1/1/2019 were included. Visual acuity and CST data were extracted for each visit and compared for patients who were switched at the following visit to bevacizumab from aflibercept and those who were maintained on aflibercept.

RESULTS: During the index period, 184 injections were performed in eligible patients. Bevacizumab was used in 117 (63.6%) and aflibercept was used in 49 (36.4%). There were no significant differences between groups in terms of follow-up interval before and after the index visit. At the next visit (median of 49 days), 99 (84.6%) patients who had received bevacizumab transitioned back to aflibercept. In both switched and maintained patients, the median change in visual acuity at the visit immediately after switching was 0 letters (p=0.276). Approximately 5% of patients lost more than 10 letters in each group (p=0.844). The median change in CST was +1 microns for switched and -6 for maintained (p=0.152). There were, however, more than double the number of switched patients who had >50 microns increased CST (13.4%) as compared with maintained patients (29.1%; p=0.016).

CONCLUSIONS: A voluntary recall of aflibercept allowed us to study the effect of changing anti-VEGF agent in our patients with retinal vascular disorders. Given there was no median change in vision, we felt this switch did not have an overall deleterious effect on our patients. Assuming a difference in Medicare allowable cost between the 2 medications of approximately $1900, by replacing 117 aflibercept injections with bevacizumab at a single visit, $222,300 was theoretically saved by the healthcare system overall during this period. The fact that the change in CST favored the group who maintained on aflibercept is worth further exploration.
Active Learning of Contrast Sensitivity Deficits in Maculopathy with Good Acuity

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PURPOSE: Traditional letter acuity does not always adequately describe a patient’s visual limitations or pathologic changes in macular disease. Herein, we evaluate active learning of contrast sensitivity function (CSF) as a measure of vision loss in eyes with good letter acuity.

METHODS: Prospective, observational, IRB-approved study of CSF. Patients were tested using the Manifold Contrast Vision Meter (Adaptive Sensory Technology, SD, CA) and SD-OCT at their regularly scheduled visits. Exclusion criteria was cataract status >2+ or VA. This active learning approach estimates a CSF curve using an information-gain strategy with 2D sampling of optotype size and contrast to provide a summary vision metric via the area under the CSF (AULCSF).

RESULTS: 103 eyes were tested with various maculopathies. Compared to 62 age-matched controls, there was a significant reduction in AULCSF (mean deficit= .41; p<.000001).

A secondary analysis was performed on 62 eyes with good letter acuity, VA >20/32: RVO (N=22), mac-off RD (N=7), dry AMD (N=16), and wet AMD (N=17). Relative to controls, mean VA deficits ranged from .07-.11 logMAR (p>.05 for dry AMD). In comparison, AULCSF deficits ranged from .18 to .28 (p<.03 for dry AMD; p<.005 for others). At intermediate frequencies of 3, 6, and 12 cpd, CS deficits ranged from .25 to .37 logCS, which corresponds to contrast reductions of 44-54%.

In RVO, the presence of macular edema significantly reduced contrast sensitivity relative to eyes with RVO but NO macular edema (p<.04), but did not reduce acuity (p>.05).

For a small set of eyes (n=4), the therapeutic effect of a single anti-VEGF injection was measured: mean pre- vs post-changes for AULCSF=.44 (sd=.21;p<.03) and .083 (sd=.08) for VA.

CONCLUSIONS: qCSF testing confirms reduced contrast thresholds in patients with maculopathies and demonstrates the potential for measuring large treatment effects. Even in maculopathies with VA losses of 1 line, contrast can be reduced by 50% at multiple frequencies. Current testing of VA and CS using ETDRS and Pelli-Robson uses a limited set of test items (14 sizes and 15 contrasts) with coarse resolution (.10 logMAR and .15 logCS). Using active, intelligent sampling of size-contrast combinations can reveal meaningful contrast deficits underexplored with current testing methods.
A 20-year Multi-centre Retrospective Review of the Management of Incontinentia Pigmenti

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PURPOSE: To investigate the management and outcomes of patients with Incontinentia Pigmenti in 3 national paediatric centres in the UK over a 20 year period.

METHODS: This is a multi-centre retrospective case note review of children with genetically confirmed IP, identified between 1989 and 2017, at Great Ormond Street Hospital (London), John Radcliffe Hospital (Oxford) and Manchester Royal Infirmary. The primary end point was incidence of retinal complications. The utility of FFA in determining the presence of disease and the differences in outcome between those who had FFA guided laser pan-retinal photocoagulation and those who did not have FFA or did not receive PRP were examined.

RESULTS: 45 children with a clinical diagnosis of IP were identified of whom 30 had genetic confirmation. 7/60 eyes (12%) presented with total retinal detachment. 14/60 eyes (23%) had clinical evidence of retinal abnormalities at the primary exam. 34 eyes (56%) had subsequent fluorescein angiography; 57% of these had angiographic abnormalities. 18/60 eyes were treated with laser. Patients treated with laser for retinal ischaemia developed normal visual acuity for age. One patient developed late onset retinal detachment after treatment.

CONCLUSIONS: The peripheral retinal non perfusion in IP is variable, even between eyes, but can be severe; early diagnosis is important. Fluorescein Angiography is vital for making this diagnosis and clinical examination is insufficient to diagnose retinal ischaemia. The use and timing of laser for what is non-VEGF mediated disease requires further study.
Tele-ophthalmology Screening in Sickle Cell Retinopathy

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**PURPOSE:** Ultra-wide field (UWF) fundus photography has proven successful in screening for diabetic retinopathy, however, ophthalmic imaging protocols for sickle cell retinopathy (SCR) screening remain poorly defined. Proliferative sickle cell retinopathy (PSR) is primarily a peripheral retinopathy, and even patients with potentially vision-threatening PSR lesions can be asymptomatic. This proof of concept study evaluates feasibility of non-mydriatic UWF fundus images in sickle cell retinopathy screening.

**METHODS:** Consecutive SCD patient were enrolled from the Johns Hopkins Hospital hematology clinics. Non-mydriatic UWF-F images were obtained by the study team (non-professional photographers with minimal training in image acquisition) with the a UWF Primary camera. De-identified images were evaluated by two masked retina specialist graders who evaluated images for quality, the presence/absence of sickle cell retinopathy, and to determine if retinal lesions consistent with PSR were present, absent, or indeterminate. If PSR lesions are present, the graders indicated whether the neovascular lesion appears active or regressed, and made recommendations for retinal evaluation and/or treatment. Agreement between the observers’ grades of image quality was assessed via concordance correlation coefficient analysis. Study participants underwent their standard of care annual retinal examinations, and the results of their dilated fundus examinations were compared to the sickle cell retinopathy retinal image adjudication by the JHMI masked study graders.

**RESULTS:** UWF fundus images were obtained from patients with SCD of sufficient quality such that a determination of PSR could be made with a high correlation between masked graders. UWF fundus images displayed a high sensitivity in detecting PSR as compared to the patients’ standard of care dilated fundus examination. Data collection and analysis are ongoing.

**CONCLUSIONS:** Non-mydriatic UWF fundus images are feasible to obtain in hematology clinics by personnel with minimal training. These images can be of sufficient quality to determine which patients with SCD are most in need of surgical referral to a retinal specialist for closer monitoring of or treatment for PSR.
BIG BEN AND WESTMINSTER BRIDGE
RGX-314 Gene Therapy for Neovascular Age-related Macular Degeneration: Interim Results of an Ongoing Phase I/IIa

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PURPOSE: Optimal treatment for neovascular age-related macular degeneration (nAMD) often requires frequent intravitreal injections. Gene therapy delivering a transgene for an anti-VEGF protein has the potential for continuous anti-VEGF therapy after a one-time administration. The RGX-314 Phase I/IIa study is underway to evaluate the safety and signals of efficacy of an AAV8 vector encoding for a soluble anti-VEGF Fab protein, in previously-treated subjects with nAMD.

METHODS: Phase I/IIa trial is evaluating five doses of RGX-314 (3 x 10^9, 1 x 10^10, 6 x 10^10, 1.6 x 10^11, and 2.5 x 10^11 genome copies/eye) administered via subretinal delivery. Assessments of safety and efficacy are being conducted with the Primary Endpoints at week 26 and continued assessments to week 106. Measurements include: ocular and systemic adverse events, RGX-314 aqueous protein level, vision, central retinal thickness (CRT), and additional anti-VEGF injections needed post-RGX-314.

RESULTS: As of February 27, 2019, cohorts 1–4 have completed enrollment (n=30). As of December 2018, RGX-314 has been well-tolerated with no drug-related serious adverse events (SAEs) reported for 24 subjects with nAMD (Cohort 1–4) that had been enrolled into the dose-escalation trial. Six non-drug-related SAEs had been reported among four subjects. Dose dependent protein production was observed in cohorts 1-3. Cohort 3 showed sustain RGX-314 protein production at one month and six months with stability in vision and anatomy despite few to no injections. Three subjects (50%) in Cohort 3 (6 x 10^10GC/eye) have not received any additional anti-VEGF injections for nine months following RGX-314 administration, with anatomic stability (CRT -37 µm) and improved vision (+13 ETDRS letters) from baseline at nine months. For the first six subjects enrolled in Cohort 4, mean aqueous protein levels were higher than Cohort 3 at one month post-RGX-314 administration.

CONCLUSIONS: In the 24 subjects with nAMD, subretinal administration of RGX-314 has been well-tolerated and initial results show potential for a one-time administration of RGX-314 to provide sustained treatment of nAMD.
**Interim 24-week Data from the OPTIC Trial: Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 (AAV.7m8-aflibercept) for Neovascular (Wet) Age-related Macular Degeneration**

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**PURPOSE:** To assess the safety and tolerability of a single intravitreal injection of ADVM-022 in patients with neovascular age-related macular degeneration (nAMD).

**METHODS:** ADVM-022 is a gene therapy product that utilizes a novel vector capsid (AAV.7m8) carrying an aflibercept coding sequence under the control of a proprietary expression cassette and is administered as a single intravitreal injection. ADVM-022 is designed to provide long-term therapeutic levels of aflibercept following a single intravitreal injection for the treatment of retinal and choroidal neovascularization disorders. An open-label, multicenter, dose-escalation study in 18 subjects with active choroidal neovascularization secondary to AMD is underway. Subjects requiring frequent anti-VEGF treatment who have demonstrated a clinical response to anti-VEGF therapy are eligible for enrollment. The primary outcome measure for this study is the nature, severity and incidence of ocular and systemic adverse events. Secondary outcomes include change in best-corrected visual acuity (BCVA), change in central retinal thickness (CST) and number of rescue anti-VEGF treatments received during the study period.

**RESULTS:** Enrollment and dosing of anti-VEGF treatment experienced patients (n=6) in the first cohort of the OPTIC trial has been completed. Safety data from this first cohort of patients has shown no serious adverse events or dose-limiting toxicities following a single intravitreal injection of ADVM-022 at the initial dose of $6 \times 10^{11}$ vg/eye. Baseline characteristics, safety, BCVA, CST and rescue treatment data through week 24 will be presented.

**CONCLUSIONS:** ADVM-022 is designed to provide sustained therapeutic levels of aflibercept, and subsequently minimize the burden of frequent anti-VEGF injections, and improve real-world vision outcomes for patients with nAMD. Interim 24-week safety and efficacy data from the first cohort of this multicenter Phase 1 study will be presented for the first time.
Comparison of the Efficacy and Safety of Brolucizumab versus Aflibercept in Eyes with Polypoidal Choroidal Vasculopathy: 96-week Results from the HAWK Study

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**PURPOSE:** HAWK (NCT02307682) was a prospective Phase III study investigating the efficacy and safety of brolucizumab versus aflibercept in the treatment of neovascular age-related macular degeneration (nAMD). Polypoidal choroidal vasculopathy (PCV) is a common subtype of nAMD, particularly prevalent among Asians. Here, the 96-week results from Japanese participants enrolled in the HAWK trial who were diagnosed with PCV are reported.

**METHODS:** Participants were randomized 1:1:1 to brolucizumab 3 mg (n=358), 6 mg (n=360) or aflibercept 2 mg (n=360). Indocyanine green videoangiography was performed at screening on all participants from Japanese sites. After three loading doses, brolucizumab participants received 12-week dosing (q12w) with an option to adjust to 8-week dosing (q8w) at predefined disease activity assessment visits; aflibercept was dosed q8w.

**RESULTS:** Of the 154 Japanese participants in HAWK, PCV was present at screening in 89 (58.6%). Mean change in BCVA (±SE) from baseline to Week 48 for brolucizumab 3 mg (n=20), 6 mg (n=39) and aflibercept (n=30) was 11.4 (2.6), 10.4 (1.5), and 11.6 (1.4) EDTRS letters, respectively. The BCVA gains were maintained to Week 96 for brolucizumab 3 mg (12.8±2.5 letters) and 6 mg (11.4±1.6 letters), and for aflibercept (11.1±1.9 letters). Most eyes with PCV treated with brolucizumab 6 mg were maintained exclusively on a q12w dosing interval immediately following a loading phase through Weeks 48 (76%) and 96 (68%). Eyes with PCV had decreased central subfield thickness at Week 96. Compared with aflibercept, fewer eyes with brolucizumab 6 mg had fluid (intraretinal and/or subretinal) at Weeks 48 and 96, and fewer eyes given brolucizumab 6 mg had subretinal pigment epithelium (RPE) fluid. No new safety findings were observed.

**CONCLUSIONS:** In the cohort of 89 Japanese participants diagnosed with PCV in the HAWK trial, robust and consistent BCVA gains were observed with brolucizumab treatment across 96 weeks that were comparable with aflibercept treatment and the majority of eyes treated with brolucizumab 6 mg were maintained on a q12w interval immediately after loading. Fewer brolucizumab 6 mg-treated eyes had fluid (intraretinal and/or subretinal or sub-RPE) compared with aflibercept. Brolucizumab has a beneficial effect on visual acuity in eyes with PCV.
Time to Dry Analysis of Brolucizumab Versus Aflibercept in Patients with Neovascular Age-related Macular Degeneration: 96-week Data from the HAWK and HARRIER Trials

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PURPOSE: HAWK (NCT02307682) and HARRIER (NCT02434328) are two Phase III, 96-week, prospective double-masked, active-controlled, multicenter studies that investigated the efficacy and safety of brolucizumab compared with aflibercept in patients with neovascular age-related macular degeneration (nAMD). Here, we analyze the time to achieving sustained dryness (absence of fluid for \( \geq 2 \) or \( \geq 3 \) consecutive visits) with brolucizumab versus aflibercept.

METHODS: Patients were randomized 1:1:1 to brolucizumab 3mg (n=358), 6 mg (n=360) or aflibercept 2mg (n=360) in HAWK, and 1:1 to brolucizumab 6mg (n=370) or aflibercept 2mg (n=369) in HARRIER. After three monthly loading doses, brolucizumab patients were treated every 12 weeks, with an option to adjust to 8-week dosing (q8w) at predefined disease activity assessment visits; aflibercept was dosed in a fixed q8w regimen after the loading dose as per label.

RESULTS: In HAWK and HARRIER, brolucizumab was non-inferior to aflibercept in mean BCVA change from baseline at Week 48 (primary endpoint) and the visual gains were maintained to Week 96. The cumulative incidence rate (%) in study eyes with sustained dryness was greater for brolucizumab compared with aflibercept at Week 48 (\( \geq 2/\geq 3 \) visits: HAWK [brolucizumab 3mg, 82.9/77.1; brolucizumab 6mg, 86.4/79.1; Afl, 76.4/67.6]; HARRIER [brolucizumab 6mg, 91.5/85.9; Afl, 81.2/72.7]). The 50th percentile for sustained dryness was achieved earlier for patients receiving brolucizumab (\( \geq 2/\geq 3 \) visits by Week 8/8 for both brolucizumab 3mg and 6mg in HAWK and Week 4/4 in HARRIER) compared with Afl (\( \geq 2/\geq 3 \) visits: HAWK, Week 8/12; HARRIER: Week 8/8), as was the 75th percentile (\( \geq 2/\geq 3 \) visits: HAWK [brolucizumab 3mg, Week 24/40; brolucizumab 6mg, Week 16/32; aflibercept, Week 40/not achieved]; HARRIER [brolucizumab 6mg, Week 8/20; aflibercept, Week 20/not achieved]). The rates of sustained dryness and incidence rates through Week 96 will also be presented.

CONCLUSIONS: In HAWK and HARRIER, patients treated with brolucizumab were more likely to achieve sustained dryness than those treated with aflibercept. Brolucizumab also achieved better fluid control faster than aflibercept. These data inform the new head-to-head TALON study that will investigate superiority in the length of treatment interval of brolucizumab compared with aflibercept using a treat-to-control regimen in patients with nAMD.
**Purpose:** Post-hoc exploratory evaluation of the anatomic outcomes of brolucizumab vs aflibercept for nAMD from two phase III, 2-year, randomized, double-masked, multicenter trials (HAWK & HARRIER).

**Methods:** Patients aged greater than or equal to 50 years with treatment naive, choroidal neovascularization lesions secondary to AMD, with a presence of subfoveal intraretinal and/or subretinal fluid (IRF/SRF) as assessed on spectral domain optical coherence tomography (OCT) and BCVA between 78 and 23 ETDRS letters and no fibrosis or atrophy affecting the central subfield were eligible to enter the trials. Eligible patients were randomized 1:1:1 to brolucizumab 3 mg or 6 mg or aflibercept 2 mg (HAWK) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg (HARRIER). After the loading phase, brolucizumab patients received q12w dosing with an option to adjust to q8w at predefined disease activity assessment visits; aflibercept was dosed q8w.

**Results:** Brolucizumab was non-inferior to aflibercept in mean BCVA change from baseline at 48 weeks (primary endpoint) and at 96 weeks. A greater proportion of brolucizumab 6 mg-treated patients were fluid-free [absence of IRF/SRF and sub-retinal pigment epithelial (sub-RPE) fluid] compared to aflibercept 2 mg at Week 16 [end of matched phase; brolucizumab 6 mg, 58.9% vs aflibercept, 39.1% (HAWK); brolucizumab 6 mg, 60.3% vs aflibercept 45.5% (HARRIER)], Week 48 [brolucizumab 6 mg, 64.1% vs aflibercept, 49.5% (HAWK); brolucizumab 6 mg, 65.2% vs aflibercept 47.7% (HARRIER)] and Week 96 [brolucizumab 6 mg, 71.3% vs aflibercept, 58.8% (HAWK); brolucizumab 6 mg, 64.8% vs aflibercept 52.4% (HARRIER)] (P<0.001). Once becoming fluid-free, more brolucizumab-treated patients were fluid-free for greater than or equal to 2 and greater than or equal to 3 consecutive visits versus aflibercept up until Week 48 and Week 96. Brolucizumab achieved better fluid control with more patients remaining fluid free at week 96 compared with aflibercept.

**Conclusions:** This exploratory post-hoc analysis of the HAWK and HARRIER studies demonstrate that compared to aflibercept, more patients treated with brolucizumab achieved fluid-free status which was sustained for consecutive visits. Taken together, the results demonstrate superior anatomic outcomes with brolucizumab over aflibercept in patients with nAMD.
Dorzolamide-Timolol vs Placebo Drops as an Adjunct to Intravitreal Anti-Vascular Endothelial Growth Factor Injections for Incomplete Responders with Neovascular Age-related Macular Degeneration

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PURPOSE: To evaluate the effect of topical dorzolamide-timolol vs placebo on anatomic and functional outcomes in neovascular age related macular degeneration (AMD) eyes with an incomplete response to anti-vascular endothelial growth factor (VEGF) injections.

METHODS: This prospective, multicenter randomized clinical trial enrolled patients with neovascular AMD and persistent macular edema despite frequent fixed-interval intravitreal anti-VEGF therapy. Eyes were randomized to receive topical dorzolamide-timolol twice daily or artificial tears twice daily for the duration of the study. At each visit, anti-VEGF injections were continued with the same fixed interval and agent as before the addition of drops. Visual acuity, intraocular pressure, central subfield thickness (CST), maximum subretinal fluid height (SRF), and maximum pigment epithelial detachment (PED) height were measured at baseline and for the subsequent three visits.

RESULTS: The primary analysis population was 46 patients with 25 in the dorzolamide-timolol arm and 21 in the placebo arm. The mean age was 78.4 years (range, 65 – 94 years). Patients received a mean of 20.5 anti-VEGF injections (range, 4 – 58) of the same medication prior to randomization. The mean time between enrollment and final follow up was 99.4 days (time range, 84 – 126 days). At final follow up, mean (SE) change in CST from baseline in the dorzolamide-timolol group was -40.67 (11) µm compared to -0.75 (13) µm for the placebo group (mean difference, 39.9; 95% CI 5.25 – 74.59; P=0.025). Mean (SE) change in maximum PED from baseline in the dorzolamide-timolol group was -18.87 (11) µm compared to +4.60 (5) µm for the control group (mean difference, 23.47; 95% CI -2.33 – 49.27; P=0.073). Mean (SE) change in maximum SRF from baseline in the dorzolamide-timolol group was -36.30 (11) µm compared to -19.55 (13) µm for the control group (mean difference, 16.75; 95% CI -18.70 – 52.21; P=0.346). The mean change (SE) in logarithm of the minimum angle of resolution (logMAR) visual acuity from baseline in the dorzolamide-timolol group was 0.037 (0.031) compared to 0.017 (0.036) for the control group (P=0.679).

CONCLUSIONS: Topical dorzolamide-timolol appears to reduce macular edema in eyes with persistent exudation despite consistent, fixed-interval intravitreal anti-VEGF treatment for neovascular AMD.
Port Delivery System with Ranibizumab (PDS) Phase 2 Ladder Results that Informed Phase 3 Archway Trial Design

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PURPOSE: The PDS consists of a refillable, indwelling implant that provides continuous intravitreal release of ranibizumab. Results from the phase 2 Ladder trial of the PDS for neovascular age-related macular degeneration (nAMD) that informed the randomized phase 3 Archway trial design are presented.

METHODS: In Ladder (NCT02510794), eyes with nAMD were randomized to PDS with 1 of 3 customized ranibizumab formulations or monthly intravitreal ranibizumab 0.5 mg injections. Key outcomes: time to first implant refill (per protocol-specified criteria), best-corrected visual acuity (BCVA), central foveal thickness (CFT), adverse events (AEs). The Archway (NCT03677934) trial comparing PDS 100 mg/mL with fixed 24-week refills versus monthly intravitreal ranibizumab 0.5 mg is ongoing.

RESULTS: In Ladder, 220 patients (primary analysis population) were randomized 3:3:3:2 to PDS 10, 40, and 100 mg/mL or monthly intravitreal ranibizumab 0.5 mg. For PDS 10, 40, and 100 mg/mL arms, respectively, median time to first refill was 8.7, 13.0, and 15.0 months; 63.5%, 71.3%, and 79.8% of patients did not meet refill criteria until ≥ 6 months. Adjusted mean changes from baseline in visual and anatomic outcomes for PDS 100 mg/mL were comparable with monthly intravitreal ranibizumab 0.5 mg at month (M) 9 (BCVA, 5.0 vs 3.9 letters; CFT, –1.7 vs –6.3 µm). In a new subanalysis, mean BCVA gains from baseline to M6 were comparable between PDS 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg regardless of presence or absence of macular fluid at either baseline or M6. More ocular AEs were observed with the PDS than monthly intravitreal ranibizumab 0.5 mg, particularly during the perioperative period (as expected given the surgical nature of the study).

CONCLUSIONS: In Ladder, 80% of patients in the PDS 100 mg/mL arm did not require an implant refill until ≥ 6 months. Vision and anatomic outcomes were comparable at M9 with PDS 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg. Macular fluid presence or absence (at baseline or M6) was not observed to have an impact on vision outcomes at M6. Overall, Ladder results support phase 3 Archway trial design of PDS 100 mg/mL with fixed 24-week refill for anti-VEGF responsive nAMD.
Dual Inhibition of Ang-2 and VEGF-A with Faricimab in nAMD: Q16-week and Q12-week Dosing in the STAIRWAY Trial

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PURPOSE: Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) are key drivers of angiogenesis, leakage, and inflammation. Owing to the role of the Ang-2/Tie signaling pathway in vascular destabilization, it is hypothesized that dual Ang-2/VEGF-A inhibition may provide increased durability over anti-VEGF monotherapy. Faricimab, the first bispecific antibody for intraocular use, binds and neutralizes both Ang-2 and VEGF-A. Evidence from preclinical and phase 1 trials on faricimab supported its efficacy, safety, and potential for extended durability. The phase 2 STAIRWAY trial (NCT03038880) further evaluated the durability of faricimab in patients with nAMD.

METHODS: STAIRWAY was a phase 2, 52-week study that enrolled treatment-naïve patients aged >/= 50 years with subfoveal choroidal neovascularization and nAMD. Patients were randomized 2:2:1 to: intravitreal 6.0 mg faricimab, dosed at fixed 16- (q16w) and 12-week (q12w) intervals after q4w loading, or 0.5 mg ranibizumab q4w. The primary objective was to evaluate the efficacy of faricimab administered at q16w and q12w intervals, assessed by best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letter score). Following disease assessment at week 24, faricimab q16w- assigned patients without protocol-defined disease activity continued fixed q16w.

RESULTS: Preclinical and phase 1 data supported a potential role for faricimab in the treatment of patients with nAMD. In STAIRWAY, faricimab-treated patients achieved robust BCVA gains after the initial loading phase that were sustained throughout the study with q16w and q12w dosing. At week 24, 12 weeks after the last loading dose, 65% (36/55) of faricimab-treated patients had no disease activity. At week 52, q16w flex faricimab-, q12w faricimab-, and q4w ranibizumab–treated patients gained 11.4, 10.1, and 9.6 letters, respectively, with 46.4%, 33.3% and 37.5% of patients, respectively, gaining >/=15 letters from baseline. No new or unexpected safety signals were identified.

CONCLUSIONS: Faricimab q16w and q12w resulted in robust initial BCVA gains that were sustained throughout the study and comparable with ranibizumab q4w, with no new or unexpected safety signals. Combined Ang-2/VEGF inhibition shows potential for better outcomes for patients with nAMD through extended durability. Two large, global, phase 3 trials (TENAYA: NCT03823287; LUCERNE: NCT03823300) to further investigate these results are currently underway.
APEX: A Phase II Clinical Trial Evaluating the Safety and Preliminary Efficacy of X-82 Administered Orally in the Treatment of Exudative Macular Degeneration

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PURPOSE: Systemic toxicities have prevented long-term use of early generation oral VEGF/PDGF inhibitors in patients with exudative macular degeneration, but the creation of a newer generation of drugs, with a more tolerated side effect profile, might allow for potent blockage of VEGF and PDGF via an oral route. After promising results of a phase 1 trial, showing reduction in anti-VEGF treatment burden of those on X-82 with limited side effects, this trial was conducted whose goal was to evaluate the safety and preliminary efficacy of X-82 administered orally in the treatment of exudative macular degeneration.

METHODS: This was a phase 2, randomized, double-masked, placebo-controlled trial that enrolled 157 patients in 39 sites across the United States. Subjects with exudative macular degeneration, diagnosed at least six months prior to study enrollment and who had received at least two intravitreal injections of anti-VEGF therapy were randomized into four equally represented groups receiving either 50 mg, 100 mg, or 200 mg tablets of X-82, or a matching placebo tablet, daily. During each visit, which occurred at four-week intervals, the assessment was made if rescue treatment was needed with anti-VEGF therapy. The trial was scheduled to take place for 56 weeks total (52 weeks of treatment with one month of follow up) but was stopped prematurely (after the second interim analysis, which was conducted after 90% of patients had reached week 36) based on concern for gastrointestinal and hepatobiliary toxicity.

RESULTS: Overall, the intention-to-treat population started with a mean visual acuity of 71.0 (n=157) and ended with a mean of 72.3 (n= 81) at week 52. Broken down by group, those in the 50 mg group started at a visual acuity of 72.3 (n=40) and ended at 73.0 (n=23), those in the 100 mg group started at 71.2 (n=39) and ended at 73.0 (n=19), those in the 200 mg group started at 71.9 (n=39) and ended at 74.2 (n=17), and those in the placebo group started at 68.8 (n=39) and ended at 69.5 (n=22). Statistical modeling demonstrated a non-inferiority of visual acuity at the week 52 visit in all groups receiving X-82 when compared with placebo. The per-protocol population started with a mean visual acuity of 71.7 (n=192) and ended with a mean of 71.2 (n= 68) at week 52. Further broken down by group, those in the 50 mg group started at a visual acuity of 73.4 (n=27) and ended at 72.2 (n=19), those in the 100 mg group started at 73.2 (n=19; Snellen 20/40) and ended at 73.7 (n=16), those in the 200 mg group started at 71.5 (n=18) and ended at 71.1 (n=12), and those in the placebo group started at 69.3 (n=28) and ended at 68.6 (n=21). Statistically significant non-inferiority of visual acuity was demonstrated in all groups receiving X-82 when compared with placebo. Patients who completed the study in the ITT population (n=81) required an average of 6.4 intravitreal injections over a 52 week period, with the 50 mg (n=23), 100 mg (n=19), 200 mg (n=17), and placebo (n=22) group requiring 7.5, 5.4, 4.3, and 7.9 injections respectively. In the PP population (n=92), an average of 6.3 injections were required per year, with the 50 mg (n=27), 100 mg (n=19), 200 mg (n=18), and placebo (n=28) group requiring 6.4, 5.1, 4.8, and 8.1 injections respectively. There were several instances in which patients did not require another
anti-VEGF injection after the initial screening treatment to document a response. This was more common in those receiving X-82 (7.5% (3/40), 10.3% (4/39), and 20.5% (8/39) in the 50 mg, 100 mg, and 200 mg groups respectively) when compared to placebo (2.6%; 1/39) but this was not analyzed for statistical significance.

**CONCLUSIONS:** Patients receiving X-82 plus PRN anti-VEGF injections demonstrated statistically significant non-inferiority in visual acuity compared to those receiving placebo plus PRN anti-VEGF injections. Patients receiving X-82 had a dose-dependent decrease in anti-VEGF injection burden compared to those on placebo. Patients also displayed dose-dependent elevations in liver enzymes which ultimately required premature termination of the trial.
Macular Atrophy in the 5-year Observational Follow-up of the IVAN Trial Cohort

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PURPOSE: To describe frequency, and risk factors for development, of macular atrophy after release from protocol (exit) during the extended follow up period in participants in the IVAN clinical trial.

METHODS: Of the 610 participants in the IVAN trial, 408 agreed to take part in the follow up evaluation. Passive data collection occurred for participants who had died during extended follow-up (n=124). Any available imaging modality (color, OCT, FA and autofluorescence) at the most recent routine visit or from a final study visit (in those who agreed to attend) were graded by trained graders at netWORC UK. The primary outcome was the development (incident) or expansion of the area (worsened) intralesional macular atrophy (ILMA) and extralesional macular atrophy (ELMA). Logistic regression was used to assess the effects of demographic, morphological characteristics, and randomized allocations, on the incidence/worsening of ILMA and ELMA in the study eye.

RESULTS: The median length of follow-up (FU) from IVAN exit to date of imaging was 4.7 years with a median follow-up of 3.7 years including those who deceased. ILMA was present in 9.4% of study eyes at entry to IVAN study, 32.4% at study exit and 73.9% at the observational follow-up assessment. ELMA was present in 2.8% of study eyes at entry to IVAN study, 4.1% at IVAN exit and 34% at extended follow-up. Age and absence of PED at the final visit were associated with increased rates of both ILMA and ELMA. The protective associations found for SRF and classic CNV at IVAN exit were reduced and not significant but remained in the same direction.

CONCLUSIONS: ILMA is frequent at extended follow-up. Age and absence of PED at the final visit were associated with increased rates of both ILMA and ELMA. We found no evidence to suggest that more compared to less frequent anti-vascular endothelial growth factor treatment is associated with incident or worsened ILMA or ELMA.
Vision Degrading Myodesopsia in Myopia

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**PURPOSE:** To evaluate vitreous structure and visual function in myopic eyes with and without posterior vitreous detachment (PVD), since it is not known whether opacities in the central vitreous from myopic vitreopathy are associated with reduced contrast sensitivity function (CSF), and if PVD further degrades CSF. Increased axial length is hypothesized to correlate with increased vitreous echodensity and worse CSF.

**METHODS:** PVD was diagnosed by ultrasonography, also employed to measure axial length (AL) and quantify vitreous echodensity (QUS, arbitrary units (AU); IOVS 56:1611–7, 2015; AJO 172:7-12, 2016; Ophthalmol Retina 2:881-7, 2018). Visual function was evaluated with best-corrected visual acuity (BCVA, logMAR) and CSF measured with Freiburg Acuity Contrast Testing (Weber Index, %W: lower score = better CSF). 38 myopic eyes with vitreous floaters (20 with PVD, 18 without) were compared to 24 age-matched controls (11 PVD, 13 without). Statistical comparisons were myopic vs. non-myopic eyes, with and without PVD.

**RESULTS:** BCVA was the same in myopic and non-myopic eyes, both with and without PVD. However, CSF in myopic eyes without PVD (3.03±1.47%W) was 62% worse than controls without PVD (1.87±0.71%W; p=0.0001). Furthermore, CSF in myopic eyes with PVD (3.74±1.11 %W) was 80% worse than controls with PVD (2.08±0.59 %W; p<0.0001) and 23% worse than myopic eyes without PVD (3.03 ±1.47 %W; P<0.01). AL was similar in myopic eyes with/without PVD (26.53 vs. 26.35mm; p=0.35) and controls (23.56 vs. 22.95mm; p=0.25). In myopic eyes, greater AL was correlated with increasing vitreous echodensity (r=0.60, p<0.001) and more degradation in CSF (r=0.67, p<0.01). There was 67% greater vitreous echodensity in myopic eyes with PVD (831±201 AU) than myopic eyes without PVD (499±138 AU; p=0.034).

**CONCLUSIONS:** Eyes with increased AL have greater vitreous echodensity (r=0.60, p<0.001), probably due to vitreous collagen aggregation. Resultant increased light scattering degrades CSF proportionally (r=0.67, p<0.01). Further, myopic eyes with vitreous floaters have worse CSF than controls. That myopic eyes with PVD have even worse CSF and QUS than eyes with only myopic vitreopathy suggests that PVD in myopic eyes additionally increases light scattering with 23% more CSF degradation, although the majority (62%) of effects appear to be due to myopic vitreopathy alone.
Confusions in Retinal and Other Ophthalmic Surgical Procedures: Description, Analysis and Prevention of Errors from 2006–2017

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PURPOSE: To characterize surgical confusions in retina and other fields of ophthalmology in order to determine their incidence, root causes, and impact on patients and physicians as well as preventability via the Universal Protocol.

METHODS: A retrospective cohort study of errors in ophthalmic surgical procedures between January 1, 2006 and December 31, 2017. Cases were identified by the Ophthalmic Mutual Insurance Company (OMIC) from closed case files and by the New York State Health Department from the New York Patient Occurrence Reporting and Tracking (NYPORTS) program.

RESULTS: Of the 143 cases of surgical confusions identified, only 11 (7.69%) were related to retinal procedures of which 2 were injections (1 intravitreal and 1 subtenons) and 9 involved pars plana vitrectomy (PPV) or other retinal detachment repair. Both injections were wrong eye. Among the PPV or other retinal detachment repair 2 involved wrong eye blocks, 1 involved an incorrect lens calculation (not accounting for silicone oil) in a combined PPV/oil removal/lens implantation, 1 involved retinal toxicity from tobramycin leaking through unsutured sclerotomies, 1 involved PPV on the wrong eye, and 4 involved incorrect gas dilution. The majority of the retinal errors were deemed not preventable by the current Universal Protocol (6/11; retinal toxicity, incorrect lens calculation, and incorrect gas dilutions). Approximately two-thirds of all errors, 95 cases (66.4%), were wrong implants during cataract surgery (CE/IOL), and 36 cases (38%) were not preventable by the Universal Protocol. The most common root cause of error among all ophthalmic errors was an inadequately performed Universal Protocol, which was responsible for nearly one-third of all surgical confusions, 46 cases (32.2%). The average legal indemnity for wrong implant during cataract surgery was US$57,514 compared to the indemnity from wrong gas concentration was US$220,844.

CONCLUSIONS: Across all subspecialties, the majority of surgical confusions could have been prevented by following the Universal Protocol properly; however this is not the case for many retinal procedures, specifically wrong gas concentration. Errors originating in the clinic before surgery as well as from intraoperative decision-making and ineffective communication during time-outs suggest need for additions along with adherence to the current Universal Protocol.
**Infusion Occlusion and Pump Confusion: Risk Factors and Intraoperative Management of Acute Hypotony During PPV**

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**PURPOSE:** Modern vitrectomy systems that dynamically control intraocular pressure (IOP) adjust the infusion pump flow according to an IOP setpoint. These systems do not measure IOP directly, however. Rather, they measure flow through the infusion pump and compute IOP using Ohm’s law because the resistance of the infusion circuit is assumed. While these systems may keep IOP within a range of values, several intraoperative scenarios may lead to failure of these control systems and paradoxical pump behavior during acute intraoperative hypotony. The purpose of this work is to describe how automated IOP control systems work and actions that surgeons may take to avoid worsening hypotony.

**METHODS:** A test platform was created using a model eye and a stopcock valve to simulate a partially occluded infusion line. Intraocular pressure was measured to demonstrate the relationship between infusion occlusion and difference between actual IOP and IOP setpoint. Clinical cases that involved infusion occlusion with pump confusion were reviewed.

**RESULTS:** A case in which vitreous incarceration within the infusion line caused hypotony with pump confusion. Automatic pressure control was turned off and the bottle was raised. Incarcerated vitreous was removed from the infusion line using the vitreous cutter. Another case was reviewed in which vitrectomy of a synergetic vitreous led to transient hypotony. A thin and highly compliant sclera in this patient allowed the infusion line to change angle, becoming flatter and thus caused the tip of the infusion line to become partially occluded by cortical vitreous adjacent to the patient’s lens. This was associated with further hypotony and compression of the vitreous into the infusion line. Infusion occlusion led to pump confusion in this case. The infusion line prolapsed through the lens into the posterior chamber.

**CONCLUSIONS:** Pump confusion during infusion occlusion may be minimized by taking the following steps. 1) After cannula placement, begin PPV adjacent to the infusion line ostium to minimize the risk of infusion occlusion by vitreous. 2) If hypotony is detected during PPV, immediately assess the angle of the infusion line, determine if there is an infusion occlusion and consider disabling IOP control and raising the IOP setting on the machine.
The ‘Weekend Effect’ in Vitreoretinal Surgery: Retinal Detachment Repair and Outcomes Vary by Day of the Week

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**PURPOSE:** Variation in patient management and patient outcomes by day of the week has been identified in many medical specialties, but no study has investigated the presence of a so-called “weekend effect” in ophthalmology. We use a large cohort of patients with newly diagnosed rhegmatogenous retinal detachment (RRD) to determine whether surgeons’ choice of repair technique for RRD is associated with the day of the week that the diagnosis is made or the repair is conducted.

**METHODS:** We selected all patients in a large commercial insurance database with a new diagnosis of RRD and with a subsequent procedural code for laser barricade, cryotherapy, pneumatic retinopexy (PR), scleral buckle (SB), or pars plana vitrectomy (PPV). Multinomial logistic regression models were used to estimate the association between likelihood of repair with each type of procedure and the day of the week that the procedure was performed. Logistic regression models were used to estimate the likelihood of re-operation within 30-days. All models controlled for patients’ ocular comorbidities, demographics, year of repair, and type of insurance plan.

**RESULTS:** We identified 42,543 patients with incident RRD. Detachments were repaired with PPV (59%), laser barricade (17%), PR (13%), SB (10%), or cryotherapy (1%). Approximately 95% of repairs occurred during weekdays. Proportions of repairs accounted for by each procedure type were stable over different days of the week for most procedures (compared PPV as reference category), but odds of repair by PR were higher when detachments were diagnosed or repaired on weekends. These differences were most dramatic when detachments were diagnosed on Fridays (OR 1.39, p<0.001), Saturdays (OR 1.78, p<0.001), or Sundays (OR 1.68, p=0.002), and when repairs were conducted on Fridays (OR 1.58, p<0.001), Saturdays (2.11, p<0.001), Sundays (2.45, p<0.001), and Mondays (1.63, p<0.001). Patients who underwent PR on Sundays had higher odds of re-operation within the next 30 days (OR 1.51, p=0.046).

**CONCLUSIONS:** The use of PR in repairing RRD is associated with both day of diagnosis and procedure date: preferentially on weekends and with higher odds of reoperation. This is the first study to identify variation in care associated with day of the week in vitreoretinal surgery.
Results of a Lamellar Macular Hole (LMH)-associated Epiretinal Proliferation Embedding Technique for the Treatment of Degenerative LMH

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PURPOSE: To investigate the outcomes of embedding lamellar hole-associated epiretinal proliferation (LHEP) into retinal cleavage for the surgical treatment of degenerative lamellar macular hole (LMH).

METHODS: We retrospectively reviewed the medical records of 34 consecutive eyes of degenerative LMH patients who underwent LHEP embedding and who were followed up for at least 12 months. Best corrected visual acuity (BCVA), central retinal thickness (CRT), and macular structure before surgery and at the final follow-up appointment were compared.

RESULTS: The mean (±SD) follow-up period was 30.0±17.7 months. Twelve patients (35.3%) were men, and the mean age was 69.6±10.1 years. Twenty-three eyes (67.6%) underwent simultaneous cataract surgery. BCVA and CRT were significantly improved at the final visit, from 0.31±0.25 logarithm of the minimum angle of resolution units, Snellen equivalent 20/40, and 123.2±42.6 µm, respectively, preoperatively to 0.10±0.25, 20/25, and 191.2±42.6 µm, respectively (both P<0.001). External limiting membrane and ellipsoid zone defects were detected in 17 (50.0%) and 15 (44.1%) eyes, respectively, but these were resolved in 10 (58.8%) and 7 (46.7%) eyes, respectively, at the final visit. No intraoperative or postoperative complications were observed.

CONCLUSIONS: Embedding LHEP may be an effective and safe procedure to treat degenerative LMH.
Ectopic Inner Foveal Layers Classification Scheme Predicts Visual Outcomes After Epiretinal Membrane Surgery

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PURPOSE: To evaluate the ectopic inner foveal layer (EIFL) staging scheme as a visual prognostic factor for patients undergoing epiretinal membrane surgery.

METHODS: Retrospective study of 88 pseudophakic patients with diagnosis of idiopathic ERM who underwent ERM surgery with a minimum follow-up of 12 months. Preoperative and postoperative EIFL staging scheme was correlated with the final best corrected visual acuity (BCVA). As secondary outcome, evaluation of the proportion of patients achieving final BCVA ≥20/40 at each stage, and anatomical evolution on SD-OCT was assessed.

RESULTS: Based on the EIFL staging scheme, out of 88 pseudophakic eyes preoperatively analyzed, 24 (27.4%) were diagnosed as stage 2, characterized by ERM and loss of foveal depression; 45 (51.1%) as stage 3, characterized by ERM, loss of the foveal depression and continuous inner nuclear layer and inner plexiform layer across the fovea (EIFL); and 19 (21.5%) as stage 4, characterized by ERM, and lost anatomy of the EIFL layers. By final follow-up visit (12-months), 70.8% of eyes at stage 2 showed an improvement in EIFL staging scheme to stage 1, with foveal depression reappearance; while 68% of eyes in stage 3 and 4 remained with EIFL. Final BCVA significantly improved at all EIFL stages (p= stage 3> stage 4 p≥20/40 was reached in 91.7% of eyes at stage 2, contrary to only a 42.3% at stage 3 and 5.2% at stage 4.

CONCLUSIONS: The EIFL staging scheme is an easy, fast, and reproducible method to evaluate visual prognosis for ERM surgery. Surgery on stage 2 ERM results in significantly better final visual outcomes and a greater chance of reversibility in anatomic changes. Patients at stage 3 and 4 EIFL are less likely to show anatomical improvement and although vision improves final visual outcomes are compromised.
Comparative Assessment of Surgical Outcomes and Ellipsoid Zone Mapping for Epiretinal Membrane Peeling Using Intraoperative Optical Coherence Tomography-guided Membrane Removal in the DISCOVER Study versus Complete Internal Limiting Membrane (ILM) Peeling

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PURPOSE: To compare surgical outcomes and ellipsoid zone architecture changes in patients undergoing intraoperative OCT-guided membrane peeling versus complete ILM peeling for the removal of ERM.

METHODS: The DISCOVER study is an IRB-approved prospective consecutive case series evaluating the impact of iOCT on ophthalmic surgery. In this analysis, a case-control retrospective comparative assessment was performed between eyes in the DISCOVER study undergoing surgery for ERM and a cohort of eyes with that underwent traditional vitrectomy with ILM/ERM removal. In the iOCT cohort, initial staining with indocyanine green (ICG) was performed with removal of ERM+/-ILM. After the initial peel, iOCT was performed and if complete ERM removal was confirmed, no additional peeling/staining was performed. In the ILM/ERM cohort, initial staining was performed. Following initial peel, additional ICG staining was performed after ERM removal and any residual ILM was removed at that time. Outcomes for visual acuity, ERM recurrence on OCT, and reoperation rates were assessed. Preoperative and postoperative quantitative OCT assessments were performed using a novel EZ algorithm to assess the EZ-RPE central area, EZ-RPE volume and en-face EZ integrity.

RESULTS: The iOCT group included 151 eyes and the ILM/ERM cohort included 111 eyes. Baseline mean VA in the iOCT group was 20/55 and 20/50 in the ILM/ERM group (p=0.41). At 6-month follow-up, mean VA was 20/32 in iOCT and 20/31 for ILM/ERM (p=0.480). Baseline mean EZ-RPE volume (mm3) was 1.37 for iOCT and 1.23 in ILM/ERM cohort (p 3) was 1.4 in the iOCT group and 1.27 in the ILM/ERM group (p=0.001). The anatomic significant ERM recurrence rate was 2% in the iOCT group and 0% in the ILM/ERM group (p=.14). There were no visually significant recurrent ERM in either group and no patients required reoperation for ERM (0%).

CONCLUSIONS: Intraoperative OCT-guided ERM peeling demonstrated similar visual acuity, ellipsoid zone mapping and anatomic improvements without the need for sequential ILM peeling. Furthermore, no patients had visually significant ERM that required reoperation. A future multi-center randomized comparative trial is being designed to further evaluate the differences and potential benefits of iOCT in vitreoretinal surgery.
Temporal Changes of Parafoveal Microvasculature after Epiretinal Membrane Surgery: An Optical Coherence Tomography Angiography Study

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PURPOSE: To evaluate the temporal changes of parafoveal microvascular architecture in patients with ERM surgery and to analyze the correlations between parafoveal capillary displacement, fractal geometries (fractal dimension & lacunarity), foveal thickness and visual outcome.

METHODS: We retrospectively analyzed the records of 71 eyes of 71 patients with idiopathic ERM. Ophthalmic evaluation included best-corrected visual acuity (BCVA), spectral domain-OCT and swept-source OCTA before surgery and 1 week, 1 month, 4 month and 10 months after the surgery. OCTA images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were obtained for each eye. The length from the foveola to the vessel branching point (FBP) in SCP and fractal geometries of DCP, such as fractal dimension (FD) and lacunarity, were measured using ImageJ and FracLac. Correlations between FBP, FD, lacunarity, foveal thickness and visual outcomes were assessed before and after ERM surgery.

RESULTS: The FBP in SCP, representing tangential traction of ERM, was significantly increased postoperatively. FD of DCP gradually increased and lacunarity decreased during 10 months follow up after surgery. Most of the microvascular changes reached a plateau after 1 months postoperatively. The FBP difference of SCP was significantly correlated with preoperative BCVA (P=0.01). The FD of DCP was significantly correlated with preoperative and postoperative 1 week, 1 month, 4 month follow up. However, in multiple regression analysis, the correlations between fractal parameters and BCVA were not significant.

CONCLUSIONS: This study shows that fractal characteristics, such as FD and lacunarity of parafoveal microvasculature undergo gradual improvement after ERM removal. OCTA may serve as a tool to quantify the changes of distortions in inner foveal layers due to tractional forces in patients undergoing ERM surgery.
Evaluation of Iris and Intraocular Lens (IOL) Mobility in Eyes with Scleral-fixated IOL

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PURPOSE: To assess 1) the mobility of scleral-fixated intraocular lenses (IOLs) compared to PCIOL, and 2) iris mobility in eyes with scleral-fixated IOLs compared to eyes with PCIOL.

METHODS: This is a retrospective, consecutive case series. Ultrasound biomicroscopy (UBM) was performed on eyes with scleral-fixated IOLs early in the post-operative period and again approximately 2 months later. The UBM was performed with the patient’s head in the seated and reclined positions. Additionally, UBM was performed at the time of blink to assess iris mobility.

RESULTS: Thirty-six eyes of 29 patients were included in the analysis, with 25 eyes having scleral-fixated IOL and 11 having PCIOL. Lens position relative to the cornea did not change with head position, upright 4.87 (0.42) mm vs reclined 4.93 (0.46)mm (p=0.653). Scleral-fixated IOLs are positioned more posterior in the eye compared to PCIOL, 4.87 (0.42) mm from the cornea vs. 4.11(0.39)mm (p<0.001). The iris is more mobile in eyes with a scleral-fixated IOL compared to eyes with PCIOL, 2.58 (0.57) vs 1.15 (0.35) (p<0.001).

CONCLUSIONS: Sutureless intrasceral fixated IOLs are positioned more posterior in the eye compared to PCIOL. The scleral-fixated lenses are stable with changes in head position. The iris in eyes with a scleral-fixated IOL appears more mobile, thereby increasing the risk for pigment dispersion and pupil/IOL capture. Additional studies are ongoing, but one should consider placement of a peripheral iridectomy to mitigate this risk.
High-mobility Group Box 1 (HMGB1) Protein Contributes to Photoreceptor Survival During Retinal Detachment

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PURPOSE: Retinal detachment (RD) disrupts the nutritional support and oxygen delivery to photoreceptors (PRs), causing stress and ultimately cell death. High-mobility group box 1 (HMGB1), a chromatin-associated nuclear protein, can serve as an extracellular alarmin when released from stressed and dying cells. PR cells release HMGB1 after RD; however, the relationship between HMGB1 and PR cell survival remains unknown. The purpose of this study was to investigate the relationship between HMGB1 and PR cell survival after RD.

METHODS: Acute RD was created by the injection of hyaluronic acid (1%) into the subretinal space in C57BL/6 mice and a mouse with rhodopsin promoter-Cre-mediated conditional knockout (cKO) of HMGB1 in rod PRs (HMGB1ΔRod). Immunofluorescence (IF) in retinal sections was used to localize HMGB1 and rhodopsin proteins. Optical coherence tomography (OCT) and electroretinography (ERG) were used to record retinal thickness and function, respectively. The morphology of the retina was assessed by H&E staining.

RESULTS: HMGB1 protein was localized to the nuclei of all retinal cell types, including PRs, with cones staining more intensely than rods. HMGB1 protein was also detected in the inner and outer segments of cones, but not rods. After creation of RD, there was a dramatic increase in HMGB1 staining in rods. In addition, RD resulted in translocation of HMGB1 from the nucleus to the cytoplasm and subsequent secretion into the extracellular space. This translocation and secretion was also seen in the fellow (non-detached) eye, but with a temporal delay. Deletion of HMGB1 from the rods did not result in any anatomic or functional deficits in the retina. However, when RD was created in the HMGB1ΔRod mouse, there was a significantly more rapid degeneration of the PR cells. Interestingly, ERGs were decreased in the fellow eye of HMGB1ΔRod mice after creation of RD, as compared to littermate controls.

CONCLUSIONS: Increased HMGB1 expression in stressed PR cells may represent an intrinsic signal essential for PR survival after RD. Further work is required to confirm these results and elucidate the mechanism by which HMGB1 contributes to PR function and survival.
Conventional gene therapy compensates for specific genetic deficiencies by supplementation with copies of the normal gene. This simple strategy can be highly effective but its application can be limited by the capacity of vectors to deliver large genes and by the ability to achieve physiological expression in target cells. Gene defects resulting in the expression of harmful proteins can be addressed by therapeutic strategies to block the consequences. How ART graft dislocation (4.9%), ever this must be achieved while sparing the critical function of the normal allele or simultaneously providing a resistant version. While both supplementation and silencing strategies act downstream of a gene defect to compensate for the harmful effects, novel strategies now offer the opportunity to correct the gene defect itself. By exploiting an ancient bacterial immune system evolved to detect and destroy viral DNA, the defective sequence of a gene can be excised specifically and replaced with the normal sequence. This powerful technology offers new opportunities to understand mechanisms of disease and to accelerated the development of gene therapies for a wide range of retinal disorders.
Injection Intervals in Treatment-naive Neovascular Age-related Macular Degeneration (nAMD) Patients Who Received Anti-Vascular Endothelial Growth Factor (VEGF) Agents: Intelligent Research in Sight (IRIS®) Registry Analysis

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PURPOSE: The purpose of this analysis was to evaluate real-world injection intervals in nAMD eyes treated with anti-VEGF agents in the United States.

METHODS: Using the IRIS® Registry (1,705,936 unique patients who received ≥1 anti-VEGF injection; 48% with a nAMD diagnosis before or on the day of the first injection), we studied nAMD eyes receiving ≥1 anti-VEGF injection from 7/1/13 to 12/31/16 (date of earliest injection = index date). Patients were ≥50 years old on the index date and did not have a record of another condition that could be treated with an anti-VEGF agent on or within 6 months prior to the index date. Injection intervals were determined based on the last injections at Months (M) 12 and 24 (+/- 2 M if no injection exactly at the time point).

RESULTS: Among patient eyes with ≥1.5 years of follow-up, there were 31,292 unique patients with 32,006 unique eyes. The mean patient age at baseline was 80 years (standard deviation [SD] = 9) and 60% of patients were female. 68% of eyes (21,658) initiated and maintained anti-VEGF treatment up to M12; in contrast, 21% of eyes (6,758) discontinued treatment (i.e., no additional injection for ≥180 days) by M12 and 11% of eyes (3,590) had a gap in treatment but resumed after M12. Among the 21,658 eyes on treatment at M12, 40% received an injection less than every 8 weeks (<q8W), 33% received an injection q8W to <q12W, and 27% received an injection ≥q12W. 9,750 eyes also initiated and maintained anti-VEGF treatment up to M24 among those eyes at M24, 39% received an injection <q8W, 33% received an injection q8W to <q12W, and 29% received an injection ≥q12W.

CONCLUSIONS: The percentages of patients with nAMD who received an anti-VEGF injection at <q8W intervals at 12 and 24 months of treatment are substantial and consistent. More effective therapies that allow for less frequent dosing are needed to ease management burden for this patient population.
Prophylaxis Intravitreal Aflibercept against Conversion to Neovascular Age-related Macular Degeneration in High Risk Eyes (PRO-CON): 24 Month Results

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PURPOSE: To evaluate intravitreal aflibercept (IAI) 2 mg as prophylaxis against the conversion to neovascular age-related macular degeneration (AMD) in high-risk eyes at 24 months.

METHODS: Prospective, single-masked study evaluating IAI versus sham as prophylaxis treatment against conversion to nAMD in patients with intermediate AMD in one eye (study eye), defined as presence of >10 intermediate sized drusen (≥ 63 and >1 large drusen (≥125 µm), and/or retinal pigmentary changes with nAMD in the fellow eye. Patients were randomized 1:1 to receive either IAI or sham quarterly for 24 months. The primary endpoint is proportion of patients converting to nAMD at Month 24 characterized by development of choroidal neovascularization (CNV) assessed by leakage on FA and fluid on SD-OCT by an independent masked reading center. Planned interim analysis was performed at Month 12.

RESULTS: Of the 128 patients enrolled in the study, 116 completed the Month 12 visit. Baseline best-corrected visual acuity (BCVA) was 78.4 and 79.2 letters in the IAI and sham groups respectively. By Month 12, 4/63 (6.3%) and 6/64 (9.4%) eyes in the IAI and sham groups, respectively, converted to nAMD. The rate of conversion between the two groups was not significant (p=0.50). In patients with non-exudative CNVs at any point prior to the Month 12 visit as determined by OCT-Angiography, 2/7 (25%) and 3/10 (30%) eyes in the IAI and sham groups, respectively, converted to nAMD (p=0.18 for rate of conversion). No new safety events were identified.

CONCLUSIONS: Interim analysis at Month 12 did not demonstrate a benefit of IAI as a prophylactic treatment against conversion to nAMD in high risk eyes. Primary results at Month 24 will be presented that will provide additional information in the management of these patients.
Association Between Early Visual Function Outcomes and Anatomic Dryness in Neovascular Age-related Macular Degeneration

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PURPOSE: Previous studies have suggested that the presence of fluid subtypes may affect final visual outcomes in patients with neovascular age-related macular degeneration (AMD). However, early anatomical restoration and its effect on visual outcomes has not been explored. In this post hoc analysis of the phase 3 VIEW 1 (NCT00509795) and VIEW 2 (NCT00637377) trials, we assessed the relationship between early best-corrected visual acuity (BCVA) outcomes and anatomic dryness response to treatment by fluid location.

METHODS: Observed data from the integrated VIEW 1 and VIEW 2 datasets were included for eyes with known retinal fluid status (assessed using time-domain optical coherence tomography) at baseline through week 12 that were treated with ranibizumab 0.5 mg q4 weeks (Rq4, n=595), intravitreal aflibercept injection (IAI) 2 mg q4 weeks (2q4, n=613), and IAI 2 mg q8 weeks after three initial monthly doses (2q8, n=607). Eyes were categorized as persistent dry (PD; no fluid at weeks 4, 8, and 12) or not persistent dry (NPD; fluid at any visit during weeks 4 to 12).

RESULTS: In the combined treatment group, 511 eyes (28%) were PD, and 1304 eyes (72%) were NPD at week 12. The difference (95% confidence interval [CI]) in BCVA gains between eyes categorized as PD versus NPD with intraretinal fluid (IRF) was 1.7 letters (0.6, 2.8) at week 24. Across treatment groups, more eyes treated with 2q4 (188 [30.7%]) and 2q8 (182 [30.0%]) were PD versus eyes treated with Rq4 (141 [23.7%]; P<0.05 for both) at week 12. The difference (95% CI) in BCVA gains within each treatment group between eyes categorized as PD versus NPD with IRF was 3.4 (1.6, 5.2) letters for Rq4, -0.3 (-2.1, 1.5) letters for 2q4, and 2.2 (0.1, 4.3) letters for 2q8 at week 24. In both the combined treatment group and within each treatment group, BCVA gains were similar for eyes categorized as PD versus NPD with total retinal or subretinal fluid.

CONCLUSIONS: IRF, but not total retinal or subretinal fluid, was associated with differential visual function outcomes. Neovascular AMD patients with IRF early in their treatment course sustained lower BCVA gains.
Ziv-aflibercept Efficacy in Better Regulating Age-related Macular Degeneration: 52-week Results of the ZEBRA Study

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PURPOSE: To determine the efficacy of ziv-aflibercept compared to other anti-VEGF agents in neovascular AMD (nAMD).

METHODS: This is a prospective, randomized, IRB-approved study. Inclusion criteria were active nAMD, prior anti-VEGF treatment, and BCVA <20/200. The treatment group received 1.25 mg/0.05 mL intravitreal ziv-aflibercept. The control group maintained their current anti-VEGF regimen.

RESULTS: 56 patients have enrolled in the study. At one year, mean baseline BCVA was 1.58±0.42 and 1.76±0.32 logMAR in the control and treatment groups respectively. Mean change in BCVA was 0.07 and 0.01 logMAR (p=0.56). Baseline CFT was 261±81 and 242±79 µm, and mean change in CFT was 7 and -3 µm (p=0.64). There were no adverse events.

CONCLUSIONS: Ziv-aflibercept is effective in treating nAMD and non-inferior to bevacizumab and aflibercept with respect to anatomy and function. It may be a cost-effective alternative to aflibercept and second-line therapy for eyes resistant to bevacizumab.
Relationship Between Subretinal Fluid (SRF) or Intraretinal Fluid (IRF) and Vision Outcomes in Eyes with Neovascular Age-related Macular Degeneration (nAMD) Treated with Ranibizumab in the HARBOR Trial

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PURPOSE: To evaluate the relationship between residual SRF or IRF and best-corrected visual acuity (BCVA) in a post hoc analysis of patients with nAMD treated with ranibizumab over 24 months (HARBOR study; NCT00891735).

METHODS: Treatment-naïve patients with nAMD were randomized to ranibizumab 0.5 mg or 2.0 mg administered monthly or pro re nata. This analysis included eyes with SRF and/or IRF at baseline (defined as screening, baseline, or week 1) and SD-OCT data at month 12 (M12) and 24; all treatment arms pooled. The primary analysis outcome was change from baseline BCVA in the study eye at follow-up visits. Outcomes were evaluated independently as well as combined for SRF and IRF status. All post baseline analyses were adjusted for baseline BCVA. IRF cyst severity graded as mild, moderate, or severe based on numbers of B-scans involved.

RESULTS: At baseline, 86% (785/917) and 63% (577/914) of eyes had SRF or IRF, respectively. Adjusted mean improvement in BCVA from baseline was significantly greater at M12 and M24 in eyes with residual SRF (11.9 and 11.7 letters, respectively) versus resolved SRF (9.5 and 8.6 letters, respectively). In contrast, adjusted mean improvement in BCVA from baseline was significantly lower at M12 and M24 in eyes with residual IRF (6.3 and 5.7 letters, respectively) versus resolved IRF (9.8 and 9.1 letters, respectively), and lowest in eyes with severe cysts (3.3 and 1.4 letters, respectively). At M24, adjusted mean improvement in BCVA from baseline was 3.6 in eyes with IRF present (n=193), 8.5 in eyes with both IRF and SRF present (n=53), 10.0 in completely dry eyes (n=539), and 13.2 in eyes with SRF only (n=110).

CONCLUSIONS: In HARBOR, residual SRF was associated with better vision outcomes compared with resolved SRF. In contrast, residual IRF was associated with lower vision gains. These results suggest that the presence and type of retinal fluid may impact vision outcomes in patients with nAMD treated with ranibizumab. The implications of residual fluid are nuanced. All residual fluid is not bad (as long as eye is being treated) and a dry retina does not necessarily correlate with the best vision gains.
Pigment Epithelial Detachments Response to a Single Ranibizumab Injection: A HARBOR Subanalysis

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PURPOSE: The phase 3 HARBOR trial (NCT00891735) enrolled 1098 treatment naïve patients with subfoveal wet age-related macular degeneration (wAMD). Of these, 53% had pigment epithelial detachment (PED) at baseline. We examined the changes in PED status after one ranibizumab injection.

METHODS: In HARBOR, patients received 3 consecutive monthly loading injections of RBZ 0.5 or 2.0 mg, then as-needed (PRN) or monthly treatment through month (M)24. This study examines 586 eyes from HARBOR with PED at baseline (BL), noting PED response after 1 loading dose (0.5/2.0 mg pooled). BL PED height was examined for flat vs present PEDs after a single injection. PEDs were grouped into quartiles based on height at BL, and mean thickness was evaluated. PED status (present/absent) was assessed at M1 and M2. Patient characteristics including drusen status, RBZ dose regimen, and total number of injections were examined.

RESULTS: After only one ranubizumab injection, 35.5% (208/586) of patients with PED at BL had PED flattened. Importantly, 92.3% (191/208) of these patients maintained a flat PED through M2. Of the patients with PED present at M1, an additional 17.3% (64/378) had flat PED after receiving a second injection. PED thickness at BL was significantly different between subjects with PED present (319.9 µm) or flat (206.0 µm) at M1 (P < 0.0001). Of 208 eyes with flat PED at M1, 38.9% (81) were from the small PED quartile (35–164 µm) vs 31.7%, 19.2%, and 10.1% in the medium (164.5–233 µm), large (233.25–351 µm), and X-large (352–1395.5 µm) quartiles, respectively. Drusen characteristics (soft/hard and number) were not associated with PED response at M1. Of patients with flat PED at M1, 57.7% (120/208) were in the RBZ 2.0 mg arm and 42.3% (88/208) in the 0.5 mg arm. In the PRN arms, patients with PED present at M1 required a greater mean number of RBZ injections (14.2) vs those with flat PED at M1 (11.0) by M24 (P < 0.0001).

CONCLUSIONS: The present study shows that most patients achieving a flat PED after a single RBZ injection maintained flat PEDs through M2. Smaller PED thickness at BL and higher RBZ dose were associated with PED flattening at M1, however, drusen characteristics (soft/hard and number) were not associated with PED response.
**Danger for Patients on the Horizon**

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**PURPOSE:** To assess how Second Panel on Cost-Effectiveness in Health and Medicine recommendations affect the cost-effectiveness (cost-utility) of VEGF-inhibitor therapy for neovascular age-related macular degeneration (NVAMD).

**METHODS:** The base case analysis on ranibizumab and bevacizumab therapy for NVAMD integrated the Value-Based Medicine® criteria of: 1) time tradeoff utilities, 2) patient utility respondents, 3) average national Medicare costs, 4) a 3% discount rate, 5) a lifetime model, 6) a combined-eye model, and 7) CATT data. A second analysis employed Second Panel recommendations (cross-sectional, community respondent utilities and limiting post-treatment vision utilities to the 0.70 general systemic utility).

**RESULTS:** Base case and Second Panel analyses data (Table) include: 1) substituting public for ophthalmic patient utilities, 2) limiting post-therapy vision utility to 0.70, and 3) integrating both changes. Table. Cost-Utility Analyses of CATT Data with and Without Second Panel Recommendations (both eyes included)* Analysis Input Variables Drug QALY gain Patient value gain Cost $/QALY QALY loss vs. base case Base case: patient utilities Ranibizumab 1.23 23.1% $106,582 $86,794 0% Base case: patient utilities Bevacizumab 1.23 23.1% $14,772 $12,029 0% Public utilities* Ranibizumab 0.89 11.7% $106,582 $120,143 -27.5% 2) 0.7 utility limit* Ranibizumab 0.38 6.3% $106,582 $277,950 -68.8% 2) 0.7 utility limit + public utilities* Ranibizumab 0.28 4.6% $106,582 $383,388 -77.4% 3) 0.7 utility limit + public utilities* Bevacizumab 0.28 4.6% $14,772 $53,137 -77.4% (QALY = quality-adjusted life-year, * = Second Panel recommendations) The cost-effectiveness (cost-utility) of each drug depends upon QALY outcomes, which Second Panel recommendations decrease. Cost-utility ratios reflect QALY loss similarly. Thus, instituting Second Panel changes could decrease both QALY gain and cost-effectiveness by 77.4%.

**CONCLUSIONS:** Adherence to Second Panel recommendations could result in a 77.4% decrease in the cost-effectiveness of VEGF-inhibitor therapy for NVAMD. These recommendations discriminate against the elderly and disabled, and employ utilities from individuals with negligible appreciation of visually-impaired quality-of-life. They could result in less NVAMD patients treated, restrictions upon select intravitreal NVAMD drugs, and decreased resources for NVAMD therapy and research.
Submacular Hemorrhage Secondary to Age-related Macular Degeneration in a Treat and Extend Regimen: Clinical Characteristics and Correlations

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PURPOSE: To characterize severe submacular hemorrhage (SMH) secondary to neovascular age-related macular degeneration (AMD) in a treat and extend regimen.

METHODS: Retrospective case series of 46 eyes of 46 patients diagnosed with SMH due to neovascular AMD requiring pars plana vitrectomy (PPV) with subretinal tissue plasminogen activator (TPA). Patient charts were reviewed to identify baseline clinical characteristics and anti-VEGF treatment details such as number of prior injections and treatment interval at time of SMH. OCT was used to further evaluate pigmented epithelial detachments (PED), SMH and subretinal fluid pre- and post-SMH.

RESULTS: The mean age of our study population was 82 years with 61% on anticoagulation or antiplatelet therapy. Mean LogMAR visual acuity prior to SMH was 0.48 declining to 1.80 after SMH, and 1.60 and 1.65 at 3 and 6 months post-operatively, respectively. SMH occurred in 15 (32%) patients who were treatment naïve. In patients treated with anti-VEGF, 19 (41%) were on a stable treatment interval, 9 (17%) had recently extended their interval, and 3 (6%) had shortened their interval. The average treatment interval at the time of SMH was 6.8 weeks with a median 7 total injections prior to SMH. Seven (23%) of treated patients had a SMH on a 4-week dosing interval. The average time between last injection and SMH was 34.2 days. OCT analysis found mean PED height increased from 440 to 682 micrometers after SMH though 20% of eyes had a PED that was smaller than before SMH. SMH was observed to have an average height of 682 micrometers.

CONCLUSIONS: A large proportion of patients with neovascular AMD complicated by severe SMH were on relatively short anti-VEGF dosing intervals without recent interval extension or were treatment naïve. This suggests that when utilizing an individualized treat and extend approach to neovascular AMD, actively extending appropriately selected patients’ anti-VEGF dosing interval does not increase the risk of severe SMH.
A Novel Augmented Reality headset Improves Visual Functional Outcomes in Age-related Macular Degeneration (AMD) Patients

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PURPOSE: A novel Augmented Reality (AR) Heads-Up Display headset was designed to enhance distance and near vision in Advanced AMD patients with central scotoma(s). The study investigated in AMD patients, capabilities and efficacy of Self-Calibration Visual Field Edge Detection (SCVFED) test and resulting Modified Real-Time Streaming Video (MRTSV), when performing tasks such as reading logMAR chart, reading paragraphs from Contemporaneous Near Eye Chart (CNEC), and recognizing faces. Efficacy was measured in functional vision outcomes with logMAR and CNEC.

METHODS: A single arm, crossover study included five subjects with advanced AMD. Headset self-Calibration was performed via SCVFED test, which identified the subject’s scotoma that correlated non-vision area with the MRTSV. Results of SCVFED test was compared to fundus autofluorescence of each eye prior to testing. Reading performance was evaluated per eye using logMAR chart both before and after wearing the AR headset. CNEC was used to test reading skills before and after wearing the device.

RESULTS: All five subjects improved functional vision in reading logMAR chart, in reading paragraphs in CNEC, and in recognizing faces. Mean age was 68. The BCVA was less than 20/200 improving to 20/63 with the AR headset without any magnification. Mean critical print size improved from 0.96 logMar to 0.58 logMAR with the AR headset. Vision improved up to 5 lines on logMAR chart. All subjects improved reading ability and speed. Findings suggest that with neuroadaptation subjects learned to comprehend the entire modified view and ignore the blind spot while reading.

CONCLUSIONS: The AR device improved the ability of AMD patients with central scotomas to read small letters and print at far and near viewing distances, when compared to their baseline vision. This study demonstrated that this AR headset method of pixel manipulation can provide enhanced functional vision for those with severe AMD scotomas. While the technique does not remove the scotoma, by moving letters and words outside of affected area to adjacent sighted areas of the retina, the patient can see all letters of a focused word. The headset provides a “perceived de-emphasis” of the scotoma and enhanced reading of text, and enhanced recognition of faces and features of individuals.
Safety and Efficacy of Risuteganib in Intermediate Non-exudative (Dry) Age-related Macular Degeneration (AMD)—Primary Results from a Phase 2 Study

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PURPOSE: Oxidative stress at the level of the retinal pigment epithelial (RPE) is one cause of non-exudative (dry) age-related macular degeneration (AMD) eventually leading to RPE and photoreceptor degeneration. Risuteganib is a novel anti-integrin that downregulates the oxidative stress response in the retina. This study evaluates safety and efficacy of risuteganib for the treatment of dry AMD.

METHODS: Prospective, randomized, double-masked, placebo-controlled multi-center US Phase 2 study in eyes with intermediate dry AMD presenting with best-corrected visual acuity (BCVA) between 20/40-20/200 and reasonably well-preserved area of RPE by clinical examination and well-defined RPE and outer segment ellipsoid line by OCT in the central 1mm of the macula as confirmed by the reading center were enrolled. Patients were randomized to receive either intravitreal 1.0mg risuteganib or sham injection at baseline (BSL). At week 16, patients in the risuteganib group received a second dose and the sham group could cross over and receive a single dose of 1.0mg risuteganib. The primary endpoint is the percentage of population with >8 letters ETDRS BCVA gain from baseline to week 28 in 1.0mg risuteganib vs baseline to week 12 for sham. Other visual function and anatomic outcomes will also be evaluated.

RESULTS: Forty-five patients were enrolled in the study between August 2017 and July 2018. The mean age of patients at time of enrollment was 77.8 and 76.0 years in the sham and risuteganib groups, respectively. The mean baseline BCVA was 67.1 and 64.4 letters in the sham and risuteganib groups, respectively. The primary endpoint was met with 48% of patients in the risuteganib group at week 28 and 7% of patients in the sham group at week 12 gaining > 8 letters from baseline (p=0.013). Additional secondary endpoints will be presented.

CONCLUSIONS: Risuteganib is a novel integrin inhibitor that downregulates the oxidative stress response with a potential role for the treatment of dry AMD. Risuteganib showed significant benefit over sham in patients with dry AMD with respect to proportion of patients gaining > 8 letters of BCVA from baseline. Additional safety and efficacy data from the Phase 2 study will be presented.
Real-world Outcomes Can Reflect Clinical-trial Outcomes When Real-world Patients Reflect Clinical-trial Patients

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PURPOSE: Accurate knowledge of real-world outcomes is indispensable for clinical trial design, health policy, and practice management. Growing conventional wisdom holds that “real-world” patients are under-treated and achieve inferior clinical outcomes. The treatment patterns and clinical outcomes reported from registry searches or insurance-claims data may differ from those expected from Phase 3 clinical trials, however, because of underlying discrepancies between “real-world” patients and clinical trial participants. This study was performed to compare the treatment and clinical outcomes of real-world patients with nvAMD who would have qualified for registration trials with the clinical outcomes of real-world patients who would have been trial-ineligible.

METHODS: Clinical records and imaging data of consecutive patients with ICD-10 coding consistent with a new diagnosis of active nvAMD from a community-based retina practice were reviewed. Protocols from the HARBOR, VIEW-1, CATT, and LUCAS trials were applied to determine whether these patients would have been eligible. Primary outcome measures were visual acuity (VA) at 12 months following diagnosis and number of anti-VEGF injections received over 12 months.

RESULTS: Of 755 consecutive eyes, clinical data and angiograms were available in 676. Only 297 eyes (44%) would have been eligible for CATT; 43% for LUCAS; 34% for HARBOR, and only 33% eligible for VIEW-1. Commonest reasons for ineligibility were fibrosis or atrophy involving the fovea and prior anti-VEGF therapy. Trial-eligible eyes were significantly younger and had better presenting VA. At 12 months, trial-eligible eyes had better median VA (20/45 versus 20/55, P < 0.00001), were more likely to show improvement in VA (65% versus 49%, P = 0.0001), gained more Snellen lines (mean 1.16 versus 0.52, P=0.0001), were more likely to achieve 20/40 or better (52% versus 43%, P<0.0001) and less likely to have 20/200 or worse (15% versus 38%, <0.0001). Trial-eligible eyes received significantly more anti-VEGF injections (10.2 versus 8.5, P<0.00001).

CONCLUSIONS: Most real-world nvAMD patients would not qualify for the clinical trials that inform standard care. Real-world outcomes may differ from those in clinical trials due to the inclusion of trial-ineligible patients, many of whom have VA-limiting conditions at presentation. Real-world outcomes approach expected outcomes when only trial-eligible patients are analyzed.
Real-world Outcomes for Treat and Extend Treatment Regimen with Anti-VEGF Agents for Neovascular Age-related Macular Degeneration—A Review of 4202 Intravitreal Injections

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PURPOSE: The frequency of anti-VEGF treatment for neovascular age-related macular degeneration (nAMD) must balance dosing required to achieve optimal visual outcomes while simultaneously balancing the burden of long-term, frequent treatment. Treatment regimens employed in clinical practice typically do not reflect those reported in clinical trials. Treat and extend has been used by retina specialists to minimize the treatment burden to their patients. This review of 4202 intravitreal injections presents real world evidence on the utilization and outcomes of treat and extend with anti-VEGF intravitreal injections in nAMD.

METHODS: This retrospective cohort study of 4202 intravitreal injections from a single centre and single vitreoretinal specialist in Calgary, Alberta included treatment naive nAMD patients who started anti-VEGF treatment between December 2007 and May 2012. Patients were included if they received two or more intravitreal injections of anti-VEGF agents ranibizumab or bevacizumab during the review period.

RESULTS: Two hundred eighty-two eyes of 241 treatment naïve patients that had >12 months of follow-up received 4202 intraocular anti-VEGF injections. Mean visual acuity (VA) prior to first injection was LogMAR 0.645 ~20/90, mean visual acuity at 12 months was LogMAR 0.615 ~20/80. One hundred fifty-seven eyes (55.7%) were able to extend to 12-week intervals, after a mean of 7.85 injections (median 7). Of these, 89 eyes (58.6%) did not maintain 12-week intervals and returned to injections at 4-8-week intervals. After 12 months of treatment, 22 eyes (7.8%) lost >5 lines of visual acuity, 232 eyes (82.3%) gained or lost 5 or fewer lines, 28 eyes (10%) gained more than 5 lines. Eyes losing vision tended to be those with baseline visual acuity of 20/200 or poorer.

CONCLUSIONS: Findings suggest the variability, but also the effectiveness of an anti-VEGF treat and extend regimen in a real-world setting. A treat and extend regimen is beneficial to patients and resource burden in clinical practice. This data would represent a historical baseline to compare to newer agents claiming longer treatment intervals.
FIDO Study: 10-year Outcomes of Eyes Receiving Continuous, Fixed-interval Dosing of Anti-VEGF Agents for Neovascular Age-related Macular Degeneration

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PURPOSE: To report the 10-year visual acuity outcomes of our cohort of patients receiving continuous, fixed-interval dosing of Anti-VEGF agents for neovascular age-related macular degeneration.

METHODS: Retrospective, single center (Retina Associates of Florida) consecutive case series of patients receiving continuous, fixed-interval dosing (every 4-8 weeks) of anti-VEGF agents (ranibizumab, aflibercept, and/or bevacizumab) for 10 years. Last observation carried forward (LOCF) was used for patients not completing 10 years of observation. Seasonal patients (snowbirds) with irregular injection intervals were not included in the analysis. Changes in BCVA from baseline were calculated at yearly intervals. The primary outcome measure was mean change in ETDRS letter score (converted from Snellen acuity); secondary outcome measures included the percentage of patients with ≥ 20/40 vision, percentage of patients with improvement from baseline, percentage of patients with loss ≥3 lines of visual acuity from baseline.

RESULTS: 145 eyes of 133 patients treated with continuous, fixed-interval dosing beginning in 2006–2008 were identified. 48% completed the full 10 years, 48% were deceased during the study, and 4% moved to a different location. The mean change in letter score at year 2 was +14.5 letters, and was relatively well maintained at year 10 at +11.1 letters from baseline. Patients received a mean of 10 injections per year for the 10-year study period. Driving vision (20/40 or better) was achieved in 39% of eyes at 10 years, compared to 8% of eyes at baseline. At 10 years, vision was stable or improved from baseline in 84% of eyes, and declined by < 3 lines in 25% of eyes.

CONCLUSIONS: This is the largest dataset of consecutive patients receiving continuous, fixed-interval dosing with anti-VEGF agents for neovascular AMD for 10 years. The results demonstrate favorable long-term preservation of early visual acuity gains out to 10 years. This suggests that there is a greater risk of vision loss by undertreatment than by continuous treatment with anti-VEGF agents.
Characterization of Eyes Developing Exudative Age-related Macular Degeneration During the Phase 2 FIlLY Study

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PURPOSE: Describe characteristics and outcomes of eyes developing investigator-determined exudative age-related macular degeneration (E-AMD) during the FILLY trial.

METHODS: Post-hoc analysis of the phase 2, multicenter, single-masked trial investigating APL-2 for the treatment of geographic atrophy (GA) in which eyes were randomized equally to sham, APL-2 every other month (EOM), or APL-2 monthly (M). Patients received active treatment for 12 months and were followed through month 18 (M18).

RESULTS: Of 246 enrolled eyes, 26 (10.6%) developed E-AMD, including 1 (1%), 7 (9%) and 18 (21%) in sham, EOM and M arms respectively. Mean time to E-AMD diagnosis was 256 days. History of fellow eye E-AMD was more common among patients who developed study eye E-AMD, 18/26 (69%) vs. 72/217 (33%). Baseline non-exudative neovascular AMD indicated by a “double-layer sign” on optical coherence tomography was more common among eyes that developed E-AMD: 19/26 (73%) eyes vs. 70/216 (32%). Mean best-corrected visual acuity (BCVA) at baseline, visit prior to E-AMD, at E-AMD diagnosis and M18 was 64, 58, 57 & 54 letters respectively; corresponding mean central retinal thickness (CRT) was 146, 144, 201 & 140 microns. In comparison, among eyes that did not develop E-AMD, baseline and M18 BCVA, CRT were 59, 53 letters; 125 & 113 microns. As assessed by the masked reading center at baseline, E-AMD diagnosis, and M18 was 64, 58, 57 & 54 letters respectively; corresponding mean central retinal thickness (CRT) was 146, 144, 201 & 140 microns. In comparison, among eyes that did not develop E-AMD, baseline and M18 among eyes that did not develop E-AMD, 18% & 12% had intraretinal cysts; 5% and 3% had subretinal fluid. Fluorescein angiography (FA) at time of E-AMD diagnosis was performed in 17/26 (65%) eyes and identified occult choroidal neovascularization (CNV) in 10 eyes. The remaining 7 eyes had no CNV on FA. There was no difference in the mean slope of GA growth before or after E-AMD diagnosis.

CONCLUSIONS: A majority of eyes developing E-AMD during the FILLY phase 2 trial had a history of fellow eye E-AMD and a DLS prior to exudation. Onset of E-AMD in these eyes did not lead to significant visual or anatomical impact.
Elamipretide, a Mitochondria-targeted Drug, for the Treatment of Vision Loss in Dry Age-related Macular Degeneration: Results of the Phase 1 ReCLAIM Study

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PURPOSE: Report results from the ReCLAIM study, open-label, phase 1 clinical trial to evaluate safety and efficacy of elamipretide, mitochondria-targeted drug, in patients with dry age-related macular degeneration (AMD).

METHODS: Dry AMD patients were enrolled into one of two disease cohorts: 1) noncentral geographic atrophy (NCGA); or 2) high-risk drusen without geographic atrophy (HRD). One eye of each participant was eligible if best-corrected visual acuity (BCVA) was ≥ 55 ETDRS letters with low luminance VA (LLVA) deficit > 5 letters. LLVA was measured as BCVA through a log 2 neutral density filter. All participants received daily subcutaneous elamipretide (40 mg), with outcomes assessed at week 24.

RESULTS: Subcutaneous elamipretide was safe and well tolerated with no treatment-related serious adverse events. In the NCGA cohort (n=19, mean age 76.0, 57.9% female), mean BCVA at baseline was 73.7 ± 9.5 letters, with mean increase of 4.6 ± 5.1 letters (p=0.003). Mean baseline LLVA was 44.0 ± 19.8 letters, with mean increase of 5.4 ± 7.9 letters (p=0.025). Mean best-corrected reading acuity (BCRA) under standard lighting conditions was logMAR 0.15 ± 0.25 at baseline, with mean change in BCRA of -0.02 ± 0.13 (p=0.55). Mean low luminance reading acuity (LLRA) was logMAR 1.28 ± 1.07 at baseline, with mean increase in LLRA of -0.52 ± 0.75 (p<0.017), approximately 5-line gain. Mean change in NCGA area (SQ RT) was 0.13 ± 0.14 mm by OCT. In the HRD subgroup (n=21, age 70.9, 61.9% female), mean BCVA at baseline was 79.4 ± 7.4 letters, with mean increase of 3.6 ± 6.4 letters (p=0.025). Mean baseline LLVA was 63.7 ± 10.0 letters, with mean increase of 5.6 ± 7.8 letters (p=0.006). Mean BCRA at baseline was logMAR 0.01 ± 0.18, with mean increase of -0.11 ± 0.15 (p=0.005), approximately 1-line gain. Mean LLRA at baseline was logMAR 0.39 ± 0.23, with mean increase of -0.28 ± 0.17 (p=0.0001), approximately 3-line gain.

CONCLUSIONS: Elamipretide is safe and well-tolerated in patients with dry AMD and may improve visual function, especially low luminance vision. A Phase 2b, placebo-controlled clinical trial of subcutaneous elamipretide in patients with dry AMD and NCGA (ReCLAIM-2) is underway.
Intraocular Device to Trap Complement Factors Associated with Non-exudative Macular Degeneration

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PURPOSE: Age-related macular degeneration (AMD) is a leading cause of blindness and will become an ever-increasing burden on economic resources as the percentage of patients over age 55 grows. Currently there are no treatments for non-exudative disease which is thought to be mediated by complement factors (CF) causing chronic low-grade inflammation. We have developed a protein adsorbing device to trap and remove CF proteins from aqueous and vitreous media.

METHODS: Prototype devices comprised of microdialysis membranes with a strong binding affinity for complement proteins C3, C3a, C5, C5a, and CFD were designed and built. Devices were tested in vitro with a saline slurry of both normal and pathologic proteins, ex vivo with freshly harvested human vitreous, and in vivo in normal (Brown Norway rats) and AMD model (CFH deficient mice) models. The main outcome measure was the difference in the initial and final CF concentration and the two groups were compared using a paired t-test. This testing strategy was repeated ex vivo and in vivo with serial electroretinography (ERG), optical coherence tomography (OCT), and histology.

RESULTS: We obtained Colorado Multiple Institutional Review Board approval for retrieval of human vitreous at the time of routinely scheduled vitrectomy at the University of Colorado Health Eye Center. Freshly harvested human vitreous was incubated for 30 minutes with membrane devices. Vitreous samples had an average CF concentration of 586.0 ± 18.4 ng/mL. After 30 minutes exposure to the device, the average concentration dropped to 19.7 ± 3.1ng/mL, indicating that over 96% of the CF had been adsorbed (p-value = 0.0003). Similar results with statistically significant differences were obtained in vitro and in vivo as well, with the devices demonstrating stability and biocompatibility 12 months status post implantation in both Brown Norway rats and CFH deficient mice.

CONCLUSIONS: These results are consistent with the hypothesis that CF proteins can be trapped and removed from the vitreous. Further in vivo testing is needed, but such a device implanted intraocularly may prove useful in retinal diseases mediated by complement factor inflammation such as non-exudative AMD.
Safety and Efficacy of a Single HMR59 Gene Therapy Injection in Advanced Dry Age-related Macular Degeneration and New Onset Wet Age-related Macular Degeneration

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PURPOSE: Evaluate the safety and efficacy of a single intravitreal HMR59 (AAVCAGsCD59) gene therapy injection (3.56x10¹¹vg) blocking membrane attack complex (MAC) in the complement cascade to reduce both geographic atrophy (GA) growth in eyes with advanced dry AMD and reduce anti-VEGF burden in eyes with new onset wet AMD in two separate phase 1 trials.

METHODS: In HMR-1001, intravitreal HMR59 was administered once at enrollment to 11 eyes with advanced dry AMD and GA measuring 5-20mm² (mean, 11.12mm²). In HMR-1002, 18 eyes with new onset wet AMD were treated with intravitreal bevacizumab at Day 0, intravitreal HMR59 at Day 7, then as needed anti-VEGF monthly based on prespecified criteria.

RESULTS: HMR59 given once at enrollment reduced GA growth 22.9% compared to natural history. On an ETDRS chart, vision gained 0.1 letters at Month 12. At day 30, two HMR59 treated eyes (18.2%) experienced mild, self-resolving vitritis and one eye mild panuveitis requiring treatment with topical corticosteroids. In HMR-1002, 12 eyes of 12 patients were followed ≥3 months (mean, 4.4 months) with 6 eyes (50%) not requiring anti-VEGF retreatment a mean 4 months after receiving HMR59. Out of 56 possible monthly anti-VEGF retreatments in 12 eyes, 7 anti-VEGF injections in 6 eyes were administered (12.5% retreatment rate). Mild panuveitis occurred in one eye at day 60 treated with oral and topical corticosteroids.

CONCLUSIONS: In two separate phase 1 clinical trials, intravitreal HMR59 administered once reduced GA growth compared to natural history at 12 months in HMR-1001. In HMR-1002, eyes with new onset wet AMD received bevacizumab at enrollment followed by intravitreal HMR59 seven days later had only a 12.5% anti-VEGF retreatment rate with a mean 4.4 months follow-up. The absence or presence of fluid on OCT at day 7 and 30, following bevacizumab at enrollment, may provide insight into the response to HMR59. Other than mild inflammation in 4 eyes no additional adverse and no serious adverse events related to HMR59 occurred. One-year data in all dry AMD patients, and 6-month data in all wet AMD patients will be presented.
One Year Results of a Photovoltaic Wireless Subretinal Implant for Advanced Atrophic Dry Age-related Macular Degeneration

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PURPOSE: The wireless subretinal microchip, is designed for restoration of central vision in patients blinded by retinal degeneration without compromising residual peripheral field.

METHODS: A prospective single-center study of feasibility and safety in 5 patients suffering from geographic atrophy. The implant is 2x2mm in size, 30 microns in thickness, containing 378 pixels. Each pixel converts pulsed near-infrared light projected from video glasses into electric current to stimulate the nearby inner retinal neurons.

RESULTS: In all patients, the device was successfully implanted under the macula and remains stable. All 5 patients perceive white-yellow patterns with adjustable brightness, in retinotopically correct locations within previous scotoma. The best visual acuity was measured to be 20/460, which is close to the theoretical limit of the implant. Without the system, all patients had the same visual acuity as in their preoperative vision.

CONCLUSIONS: This photovoltaic wireless chip can be safely implanted under the atrophic macula and restore useful central visual perception, while preserving peripheral vision. Improvements of computer vision-processing software can be integrated to further improve the image resolution and overall combined natural and prosthetic visual perception.
Assessment of Eyes with Non-exudative Age-related Macular Degeneration in US Retina Practices

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PURPOSE: To evaluate epidemiology of eyes with non-exudative (dry) age-related macular degeneration (AMD) in US retina practices.

METHODS: Retrospective study of electronic medical records obtained from Vestrum Health Retina Database, a geographically diverse sample of US retina providers. Eyes with a diagnosis of dry AMD based on the associated ICD-10 diagnosis codes between 2017 and 2018 were included. Only the first encounter where the primary disease diagnosis was identified per patient eye is included. The primary aim of the study was to identify proportion of eyes categorized with early, intermediate, advanced (geographic atrophy) and unspecified dry AMD. For those eyes that could have at least one year of follow-up, disease progression between the different categories, conversion to neovascular AMD and proportion of eyes with vision loss were noted.

RESULTS: Of a total of 866,952 eyes, 142,151 (16%) were deemed with dry AMD of which 45,898 (32%), 65,711 (46%), 13,979 (10%), 16,563 (12%) were identified as early, intermediate, advanced, and unspecified dry AMD, respectively. Of the eyes that could have >1 year of follow-up, the majority of the eyes (58% - 65%) remained stable. The rate of conversion to neovascular AMD was 2%, 6%, and 6% in eyes originally diagnosed with early, intermediate and advanced dry AMD, respectively. 32% of the eyes did not have a follow-up visit within the year. Proportions of eyes losing >1 line of vision during the first year of follow-up were 21%, 26%, and 36% in eyes with early, intermediate and advanced dry AMD.

CONCLUSIONS: A large retrospective review of data from multiple US retina practices indicates that majority of eyes with dry AMD are diagnosed with intermediate dry AMD at these sites. Most eyes remained stable during the first year of follow-up and proportion of eyes with vision loss increased with severity level.
Characterization of the angiofibrotic switch in anti-VEGF therapy of neovascular Age-related Macular Degeneration

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PURPOSE: To identify and describe morphological and functional changes during the transition from active macular neovascularization (MNV) to fibrotic scarring, i.e. the angiofibrotic switch, in anti-VEGF therapy of neovascular AMD by multimodal imaging.

METHODS: Thirty treatment-naïve eyes of 30 patients with neovascular AMD, who received standard treat&extend anti-VEGF therapy after a loading dose of 3 monthly injections, were included. Patients were imaged by color fundus photography (CFP), fluorescein angiography (FA), spectral-domain optical coherence tomography (SD-OCT), swept source OCT angiography (SS-OCTA) as well as polarization-sensitive OCT (PS-OCT) selectively detecting collagen. For analysis of retinal function visual acuity was tested and fundus-guided microperimetry (MP) was performed.

RESULTS: At baseline, all eyes presented with an active macular neovascularization (MNV) without a fibrotic component. During 3 and 6 months, a progressive angiofibrotic switch was observed in the majority of treated eyes, most of which had type 2 MNV. In CFP, a clear differentiation of lesion components such as confluent drusen, exudation, subretinal hyperreflective material (SHRM) or subretinal fibrosis was not possible. Functional mapping using microperimetry distinctly identified absolute scotoma in areas harboring fibrosis based on tissue-specific contrast consistent with collagen in PS-OCT. SS-OCTA imaging revealed persistent MNV nets within the area of fibrosis in all cases and a predilection of fibrosis to form in the center of MNV surrounding the medium to large sized vessels rather than capillaries. Retinal pigment epithelium (RPE) in the area of fibrosis, selectively imaged by PS-OCT, was missing in most cases, with few areas showing sub-RPE fibrosis and preserved RPE.

CONCLUSIONS: In neovascular AMD, an angiofibrotic switch occurs early during the course of anti-VEGF therapy. While the MNV component consistently persists throughout the lesion, fibrosis forms progressively in areas of mature vessels. Loss of the adjacent RPE layer suggests transdifferentiation of RPE cells to myofibroblasts. Deposition of yellow-white AMD-associated material may resemble subretinal fibrosis, but can be identified selectively by multimodal imaging such as PS-OCT or functional mapping.
Optimizing Outcomes for Subretinal Delivery of Gene Therapy and Scaffolds for Stem Cell Transplantation

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PURPOSE: Photoreceptor and RPE cell loss are end stage features of RP and LCA as well as GA from AMD. Best practices for bleb creation for gene therapy are unclear. Although scaffolds designed to transplant retinal cells increase cellular survival and integration, tools and procedures for reliable delivery of stem cell grafts are lacking. We describe evidence-based recommendations for gene therapy injections and outcomes for implanting a biodegradable scaffold designed to deliver photoreceptor cells subretinally.

METHODS: Pigs aged 2-6.5 months old underwent PPV. 61 eyes underwent subretinal injection of buffer or iPSC derived-RPCs using either 31G or 41G cannulas. Morphological analysis, immunofluorescence, and cytokine quantification were performed on postmortem eyes. For scaffold insertions (51 pig eyes), a BSS bleb was made under the posterior retina, diathermy was applied and a linear retinotomy was created for the biodegradable polymer (PCL) to be subretinally implanted. 25 eyes were implanted with porous polymers capable of incorporating cells for transplantation. Control animals had sham (n=24) or no surgery (n=16). OCT was performed at sacrifice (1-6 months post-op) followed by extensive histologic characterization.

RESULTS: 96.4% of all eyes demonstrated spontaneous retinal reattachment after simple bleb injection. Clinical and histological RPE abnormalities were seen more frequently in eyes receiving injections via 31G cannula (vs 41G). Significant RPE65 signal loss occurred in ex vivo cadaver retinas from vitrectomized eyes injected at a higher rate. For eyes administered polymers, exam, fundus and OCT imaging revealed retinal reattachment in 93%; severe uveitis in 0%; retinal fold in 18% (25% without polymer); subretinal fibrosis in 20% (32% without polymer). Collateral retinal vessels were identified near the retinotomy in 20% of eyes with polymer (18% without).

CONCLUSIONS: While administration of bolus cells through a 31G cannula have higher cell viability compared to 41G, RPE changes were more frequently seen in eyes with blebs given with a 31G cannula. Lower speed of injection is recommended for bleb creation to limit RPE changes. High rate of surgical success was achieved when implanting biodegradable polymers into the subretinal space with good local tolerability of polymer up to 6 months after implantation.
Optimization of Implant Insertion Procedure for the Port Delivery System with Ranibizumab (PDS) in the Ladder Phase 2 Trial

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PURPOSE: The PDS is an investigational drug delivery system for the treatment of nAMD. It consists of a surgically inserted, refillable, indwelling, intraocular implant that provides diffusion-mediated continuous delivery of ranibizumab into the vitreous. Key learnings from the optimization and standardization of the PDS implant insertion procedure are reported herein.

METHODS: Ladder (NCT02510794) was a randomized phase 2 clinical trial in patients with nAMD comparing the PDS with 3 customized formulations of ranibizumab with monthly intravitreal ranibizumab 0.5 mg injections. At trial initiation, the original PDS implant insertion procedure involved a sclero-pars plana stab incision 4 mm posterior to the limbus in the superotemporal quadrant. The prefilled implant was then inserted in the scleral wound followed by conjunctival suturing. We report how the occurrence of postoperative vitreous hemorrhage (VH) early in the trial led to optimization of the insertion procedure to improve surgical outcomes.

RESULTS: At study start, postoperative VH occurred in 11 (50%) of the first 22 patients. The trial was paused and a surgical study in minipigs was conducted to identify the root cause and a mitigation strategy. The pars plana (uvea) at the incision site was identified as the source of postoperative VH. Among alternative surgical methods tested, scleral dissection at the insertion site followed by thorough 532-nm laser ablation of the full extent of the exposed pars plana using overlapping 1000-ms spots before PDS implant insertion was the most effective method to mitigate VH. Following the implementation of this optimized procedure in Ladder, postoperative VH occurred in 4.5% (7/157) of PDS-treated patients. Surgery video review showed that adherence to the specified surgical methodology was key to mitigating VH occurrence and other postsurgical events.

CONCLUSIONS: 532-nm laser ablation of the exposed pars plana before inserting the PDS implant was effective in mitigating VH in Ladder, but adherence to the specified surgical methodology was key to success. These learnings have been implemented in the phase 3 Archway trial (NCT03677934) in the form of a surgical training plan including virtual reality simulation and video analysis to aim for procedural consistency, patient safety, and to inform best practices for performing this investigational procedure.
Topical Therapy as Primary Therapy for Small Secondary Full-thickness Macular Holes

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PURPOSE: Although full thickness macular holes (FTMH) traditionally require surgery to achieve closure, there have been anecdotal reports of anatomic closure with topical therapy. This study presents features of FTMHs successfully treated with topical therapy.

METHODS: A retrospective chart review of patients with FTMHs evaluated over the course of three years was examined. Those FTMHs that were treated initially with topical drop therapy were selected for further analysis. Patient demographics, FTMH type (primary vs. secondary), ocular history, type of drops used, duration of therapy, and follow-up were analyzed as were anatomic features including the presence of vitreomacular traction (VMT), epiretinal membrane (ERM), and cystoid macular edema (CME).

RESULTS: A total of 66 FTMHs was seen during the study period: 54 primary holes and 12 secondary holes. Nine secondary macular holes (in 8 patients) and one primary hole (Gass Stage 3) were treated with topical therapy. Secondary FTMHs were associated with retinal detachment repair with pars plana vitrectomy (PPV) in two (n=7), PPV for epiretinal membrane (n=1), or trauma (n=1). Hole diameter at initial presentation ranged from 44 to 132µ in the secondary FTMH eyes and was 426µ in the primary FTMH. All had at least some ERM and CME. Topical steroids were given to all holes, 7 also had carbonic anhydrase inhibitor and 2 had non-steroidal anti-inflammatory drops. The primary macular hole did not close with topical therapy. CME resolution correlated with hole closure in 8 out of 9 secondary macular holes after an average of six weeks of therapy (range 2-19 weeks) and 50 weeks of follow up (range 5–153 weeks), including a patient with VMT. Holes remained closed in two patients following completion of drop taper (81 and 22 weeks follow-up). Six patients remained on drops at the time of final follow-up with continued hole closure (mean 67 weeks, range 8–153 weeks).

CONCLUSIONS: Some FTMHs may respond to topical therapy and may not vitrectomy. Smaller holes and holes with CME may be amenable to closure with topical therapy. Topical therapy could be tried in these patients, especially during the time between initial consultation and possible surgery.
Pneumatic Vitreolysis for Resolving Focal Vitreomacular Traction: An Update on Clinical Outcome

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PURPOSE: To update our expanding case series on pneumatic vitreolysis (PVL) for treating focal vitreomacular traction, and to search for baseline factors associated with favorable outcome.

METHODS: This retrospective study assesses PVL on eyes with focal vitreomacular traction (VMT) with or without stage-2 macular holes (MH) performed from 2010 to 2019. Treated patients were required to avoid supine position after receiving 0.3 mL C3F8 gas until gas resolution. Half-time face-down position for at least 4 days was required for patients with MH.

RESULTS: Of 80 consecutive eyes (78 patients) with VMT, there were 55 women and 23 men with a mean age of 70.8. VMT release was achieved in 68 eyes (85.0%) within a mean of 2.8 weeks. Mean follow-up time was 8.4 months. Subgroup analysis showed VMT release in 80.7% (46/57) of eyes with VMT-only (impending macular holes), but up to 95.7% (22/23) of eyes with MH. Closure of MH occurred in 65.2% (15/23) of eyes with MH. All failed MH were closed with vitrectomy. For entire series, median baseline and spectacle corrected VA was 0.3979 LogMar (20/50) and 0.1800 LogMar (20/30), respectively (p<0.00001). Small size of VMT adhesion, phakia, younger age were predictors of success. Sixty-seven % of closed MH had an inner retinal flap at baseline. Complications (7.5%) included retinal tears in 3 eyes, retinal detachment in 1 eye, and VMT progressing to MH in 2 eyes; all resolved with treatment.

CONCLUSIONS: PVL induced VMT release in 85% of treated eyes and closed 65% of MH with limited adverse events. Closed MH often had an inner retinal flap at baseline. This is one of the largest case series on PVL.
Subretinal Fluid Application to Close Persisting Full-thickness Macular Holes

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PURPOSE: To close large persisting macular holes (PMH) after unsuccessful vitrectomy with epiretinal membrane peeling by secondary subretinal (SR) fluid application.

METHODS: 12 experienced VR-surgeons applied in a consecutive case series for the first time SR-fluid transretinal by a 41 gauge needle and gas endotamponade in large PMH and evaluated the novel surgical approach and anatomical success rate.

RESULTS: 23 out of 26 large PMH (diameter 800–1700 um) closed after surgery. Intraoperative firm adhesions and unsuccessful retinal detachment were present in 3/26 cases. Visual acuity improved by 2 lines and the negative scotoma vanished in 1/26 cases 6 weeks postop. 1 PMH in a myopic staphyloma with Alport Syndrome did not close. No serious advents except 1 small SR bleeding were observed. There was a quick adaption in experienced VR-surgeons.

CONCLUSIONS: SR fluid can release retracted retina in large PMH. The maneuver is safe and familiar to experienced VR-surgeons.
Autologous Retinal Transplantation (ART) for Primary and Refractory Macular Holes: The ART Global Consortium

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PURPOSE: To report the anatomical and functional outcomes of autologous retinal transplantation (ART) for the surgical repair of primary and refractory macular holes.

METHODS: Multicenter, retrospective, interventional, consecutive case series of 102 eyes (102 patients) undergoing ART, between January 2017 and April 2019. All patients underwent pars plana vitrectomy and autologous neurosensory retinal graft transplantation, with surgeon modification for several variables. Preoperative and intraoperative data was collected, including macular hole diameter, axial length, neurosensory graft size, harvest site, tamponade agent, and complications; statistical analysis was performed with subgroup analysis for primary versus refractory macular holes and combined macular hole–rhegmatogenous retinal detachments (MH-RRD). Macular hole closure rate, best corrected visual acuity (BCVA), and external limiting membrane and ellipsoid zone integrity on optical coherence tomography were assessed, among other variables.

RESULTS: 102 ART surgeries were performed by 30 vitreoretinal surgeons, globally. Demographics included: mean age 62±7.2 years, 64% females, 63% white, 26% Asian, and 11% black. Preoperative LogMAR BCVA was 1.43±0.14 (about 20/537), which improved significantly to 1.11±0.11 (about 20/149; p<0.001) postoperatively (mean follow-up 9.3±0.94 months). ART was performed for primary macular hole repair in 31% of cases, compared to 69% for refractory macular holes after failed ILM peel or flap (mean number of previous surgeries 1.7±0.2). There were 18 cases of combined MH-RRD for which ART was performed. Mean maximum macular hole diameter was 1490±206 μm, mean minimum macular hole diameter was 816±114 μm, and mean axial length was 26±4.1 mm. There was a 77% macular hole closure rate. Patients experienced an average BCVA gain of 2 lines, while 41% of patients experience at least a 2-line gain and 18% gained at least 5 lines. There were 5 cases of ART graft dislocation (4.9%), 5 cases of post-operative retinal detachment (4.95), and 1 case of endophthalmitis (0.98%).

CONCLUSIONS: Patients undergoing autologous retinal transplantation for large primary and refractory macular holes, in this initial world experience, achieved a 77% rate of macular hole closure and a 41% rate of at least 2-line improvement in BCVA. The surgery was safe, and various surgical variables can be modified to help improve outcomes.
Macular Blood Flow Increases on Optical Coherence Tomography Angiography after Panretinal Photocoagulation-results and Mathematical Model

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**PURPOSE:** To evaluate the macular microvascular changes in eyes with proliferative diabetic retinopathy (PDR) following panretinal photocoagulation (PRP).

**METHODS:** Using OCT angiography, we prospectively studied 10 eyes of 10 subjects with high risk PDR immediately before, 1 month and 3–6 months following PRP, using 3x3mm OCTA scan at each visit. The following parameters were calculated for the superficial (SCP), middle (MCP), and deep capillary plexuses (DCP): parafoveal vessel density, adjusted flow index (AFI) and percent area of non-perfusion (PAN). Parafoveal SCP vessel length density (VLD) was also evaluated. We performed univariate and multivariable statistics, adjusting for age and signal strength. To model the hemodynamic effect of PRP, we also present a mathematical model based on electrical circuits.

**RESULTS:** We found no significant difference for the vascular density parameters following PRP, except for decreased density at the MCP at the latest timepoint in the adjusted multivariable model. PAN, a metric of non-perfusion adjusted for noise, as well as AFI, a surrogate metric of blood flow showed significant increase at all capillary levels in the adjusted model. Our mathematical model explained how PRP would increase macular blood flow.

**CONCLUSIONS:** Using OCTA, we found an overall increase in the flow metrics of all capillary layers in the macula following PRP, unrelated to macular edema or thickening, in line with the mathematical model. Our results suggest an overall redistribution of blood flow to the posterior pole following PRP, adding a new dimension to our understanding of the complex biologic effects of PRP in PDR.
Treatment of Capillary Nonperfusion Secondary to Retinal Vascular Disease

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PURPOSE: To determine the effect of the first FDA approved anti-Vegf compound, pegaptanib sodium, on retinal capillary nonperfusion in eyes with retinal ischemia secondary to diabetic retinopathy and central retinal vein occlusion (CRVO) in a small, prospective trial and to compare these results to recent results assessing changes in capillary non-perfusion in large multi-centered trials using other anti-VEGF compounds.

METHODS: Nine eyes of nine subjects (eight with diabetic retinopathy and one with CRVO) found to have retinal capillary nonperfusion by widefield fluorescein angiography were enrolled in this prospective study. Eyes received a series of three injections of pegaptanib sodium at six-week intervals, then injections were given as needed for the remainder of the study period. The primary endpoint was the change in total pixel area of capillary nonperfusion as assessed by widefield fluorescein angiography. Secondary endpoints included macular thickness and visual acuity.

RESULTS: The average age of our subjects was 58.5 ± 14.3 years. Follow-up length ranged from 38.1 to 73.0 weeks with a mean of 58.4 ± 10.2 weeks. The mean number of injections was 3.9 ± 0.6. When injections were scheduled, five eyes (55.6%) demonstrated reperfusion and four eyes (44.4%) had no change in ischemia. When injections were given as needed, five eyes (55.6%) had an increase in ischemia, two eyes (22.2%) had a decrease, and two eyes (22.2%) had no change. During a six-month period without injections in this study, seven eyes (77.8%) showed an increase in their total area of ischemia and two eyes (22.2%) had no change, and zero eyes showed a decrease in ischemia. Our results are comparable to those of the ANDROID study by Heier et al and a similar study by Levin et al. Up regulation of intercellular adhesion molecules (ICAMs) by anti-VEGFs may be the common mechanism for promoting capillary reperfusion.

CONCLUSIONS: Intravitreal injection of pegaptanib sodium halted and sometimes reversed capillary nonperfusion in eyes with diabetic retinopathy and CRVO. Regular injections at fixed six-week intervals were required to sustain the benefit that was initially observed. While reversal of ischemia is clinically desirable in principle, we have not yet characterized objective direct benefits of such reversal, such as changes in cellular layers studied by adaptive optics or by OCT-A.
Clinical Outcomes of Eyes Lost to Follow-up with Proliferative Diabetic Retinopathy that Received Panretinal Photocoagulation versus Intravitreal Anti-Vascular Endothelial Growth Factor Injections: A Real World Analysis

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PURPOSE: The purpose of this study is to evaluate the incidence of poor clinical outcomes in eyes with proliferative diabetic retinopathy (PDR) after being lost to follow-up (LTFU) for at least six months following treatment with PRP or intravitreal anti-VEGF injections in a large national administrative database.

METHODS: The Vestrum Health database was electronically queried for all patients with a diagnosis of PDR in at least one eye between January 1, 2013 and January 31, 2017. Patients who received at least one injection or PRP session during this period and then had a lapse in follow-up ≥ 6 months prior to returning were analyzed. In the PRP cohort, eyes were included if no anti-VEGF injection had been performed in the 3 months prior to PRP. In the anti-VEGF cohort, eyes were included if there was no prior history of PRP. Visual acuity changes, as well as the incidence of poor clinical outcomes, defined as vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma, were evaluated.

RESULTS: Overall, 2,939 eyes of 2,730 patients met the inclusion criteria. Mean age was 58.7 years (SD: 12.2 years) and 45% were female. Prior to being LTFU, 1,051 eyes had received anti-VEGF treatment and 1,888 eyes had received PRP. A mean of 2.9 injections were given in the anti-VEGF cohort and 1.5 laser sessions in the PRP cohort prior to being LTFU. The average LTFU period was 13.0 months in the anti-VEGF cohort and 13.7 months in the PRP cohort. Prior to LTFU, the proportion of eyes with vitreous hemorrhage (29.6% for anti-VEGF vs. 33.1% for PRP, p=0.054), tractional retinal detachment (3.9% for anti-VEGF vs. 5.0% for PRP, p=0.18), and neovascular glaucoma (1.7% for anti-VEGF vs. 1.3% for PRP, p=0.33) was not significantly different between the groups. On return, the proportion of eyes with vitreous hemorrhage (37.0% for anti-VEGF vs. 39.9% for PRP, p=0.12), tractional retinal detachment (6.6% for anti-VEGF vs. 8.5% for PRP, p=0.06), and neovascular glaucoma (1.7% for anti-VEGF vs. 1.3% for PRP, p=0.33) had increased but was not significantly different between the groups.

CONCLUSIONS: In PDR eyes receiving either PRP or anti-VEGF, no significant difference in the proportion of eyes with poor clinical outcomes was found after a period of LTFU. Variations in methodology and patient selection, as well as the limitations of a large administrative dataset, could account for some of the differences seen between this study and prior studies.
Proliferative Diabetic Retinopathy: Outcomes of Combination Therapy in Clinical Practice

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PURPOSE: Recent Proliferative Diabetic Retinopathy (PDR) clinical trials have focused on comparing traditional panretinal photocoagulation (PRP) with anti-VEGF monotherapy. In our practice, a common management approach is utilizing a combination of anti-VEGF with modified, less aggressive PRP in an effort to reduce visual side effects. The goal of this study was to review the clinical course and real-world outcomes of patients with PDR managed with combination therapy.

METHODS: A retrospective review was conducted of consecutive patients with PDR between 2012-2017, treated with at least one intravitreal anti-VEGF injection and panretinal photocoagulation (PRP), and followed for minimum 1 year. Prior PRP or steroid injections were exclusions.

RESULTS: 200 patients were identified with a mean age of 57 years old. 20.4% of eyes involved Type 1 diabetes and the average known HgbA1c was 8.4. The average follow-up time was 629 days. Mean presenting VA was 20/39 and final VA was 20/42. 45.5% of eyes presented with a vitreous hemorrhage and 84.1% of eyes presented with DME. On average, each eye received 8.0 injections as well as 882 spots at 254 mW. 54.5% of eyes were lost to follow up for at least 2 months greater than prescribed. 22.7% of eyes underwent pars plana vitrectomy. 38.6% of eyes demonstrated worsening of disease as defined by increased neovascularization or another complication of PDR. 34.1% of eyes developed a new vitreous hemorrhage. 2.2% developed a new tractional retinal detachment. 2.2% of eyes developed neovascular glaucoma. 9.1% of eyes required vitrectomy due to worsening of disease. Of the small minority of patients with final vision 20/400 or worse, most initially presented with end-stage PDR. Overall, compliant patients had better outcomes.

CONCLUSIONS: Patients with PDR are known to have high rates of noncompliance. In addition to anti-VEGF therapy, patients in this study received modified PRP to decrease the risk of late vision loss. While most patients were successfully stabilized with this strategy, some patients still developed worsening of disease requiring additional interventions when failing to followup. However, final visual outcomes remained excellent with the exception of patients who initially presented with end-stage disease.
Visual Field Loss Over 5 Years in Patients Treated with Panretinal Photocoagulation or Ranibizumab for Proliferative Diabetic Retinopathy

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DRCR Retina Network

PURPOSE: To evaluate changes in Humphrey visual field results over 5 years in eyes treated with panretinal photocoagulation (PRP) compared with intravitreous injections of ranibizumab for proliferative diabetic retinopathy (PDR).

METHODS: A randomized clinical trial (Protocol S) was conducted by the DRCR Retina Network to compare intravitreous ranibizumab versus PRP for PDR. In an ancillary study, visual field testing data were collected from the Humphrey Field Analyzer (HFA) at baseline and annual visits among a subset of clinical sites.

RESULTS: Among the 167 eyes (81 ranibizumab group; 86 PRP group) that completed both test patterns at baseline meeting the quality criteria, mean ± SD combined total point score was 3365 ± 759 dB in the ranibizumab group and 3487 ± 659 dB in the PRP group at baseline. At 5 years, total point score was available for 79 (47%) eyes (41 ranibizumab group; 38 PRP group), and mean ± SD change in cumulative total point score from baseline was -330 ± 645 dB in the ranibizumab group and -527 ± 635 dB in the PRP group. The mean difference in cumulative total point score between the ranibizumab and PRP groups was 208 dB (95% CI, 9-408 dB; P = 0.04). After censoring VF data for eyes in the ranibizumab group post-PRP treatments, 5-year mean change in cumulative total point score from baseline was -201 ± 442 dB. From year 2 through year 5, the ranibizumab group had an average decrease in cumulative point score of 273 ± 539 dB while the PRP group had a decrease of 97 ± 481 dB.

CONCLUSIONS: Based on the limited data from this ancillary study, PRP eyes enrolled in Protocol S had more substantial VF loss from baseline compared with ranibizumab eyes and both groups continued decreases in VF sensitivity over 5 years. Even eyes in the ranibizumab group that did not receive PRP demonstrated increasing loss of visual field sensitivity over 5 years. This suggests that there exist factors other than PRP that are associated with VF loss in eyes with PDR. Future clinical research is warranted to further clarify the situation.
Association Between 4-Step or Greater Improvement in Diabetic Retinopathy Severity and Patient-Reported Visual Function in DRCR.net Protocol S

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PURPOSE: Previous studies of ranibizumab for diabetic retinopathy (DR) identified a subset of “ultra-responsive” patients who achieved >4-step improvement on the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (ETDRS-DRSS). This analysis examined the relationship between DR improvement and patient-reported visual function among ranibizumab-treated patients in DRCR.net Protocol S (NCT01489189).

METHODS: In Protocol S, eyes with proliferative DR were randomized to prompt panretinal photocoagulation or intravitreal ranibizumab 0.5 mg over 24 months (N=394 eyes in 305 patients). At baseline and annually, DR severity was measured by ETDRS-DRSS and participants with 1 study eye completed the National Eye Institute Visual Function Questionnaire-25 (VFQ-25). Change in VFQ-25 at years 1 and 2 was assessed in ranibizumab-treated patients with a valid VFQ-25 score at baseline. Patient-level data were analyzed based on ETDRS-DRSS change at years 1 and 2; missing data were imputed using last observation carried forward methodology. While the source of the data is DRCR.net, the analyses, content and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by DRCR.net.

RESULTS: Of 101 ranibizumab-treated patients, 28% and 27% achieved >4-step DR improvement from baseline at years 1 and 2, respectively. At year 1, mean change in VFQ-25 was +3.2 (95% CI, −1.9, +8.2) among ultra-responsive patients and +3.7 (95% CI, +0.9, +6.6) in patients with 0–3 steps of DR improvement; median change was +2.0 and +1.3 for ultra-responders and 0- to 3-step responders, respectively. At year 2, VFQ-25 improvement was greater in ultra-responsive patients (mean, +5.3; 95% CI, 0.0, +10.5) than patients with 0- to 3-step DR improvement (mean, +2.9; 95% CI, −0.9, +6.7); median change was +3.7 and +1.3 for ultra-responders and 0- to 3-step responders, respectively. Mean change in best-corrected visual acuity from baseline among ultra-responders and 0- to 3-step responders was 6.4 versus 7.7 letters at year 1, and 7.3 versus 3.4 letters at year 2, respectively.

CONCLUSIONS: Data from this post hoc analysis suggest a trend for greater improvements in patient-reported visual function among ranibizumab-treated patients with >4-step DR improvement at year 2 of Protocol S.
The PRO Study — Procedure Preferences and Outcomes for the Primary Repair of Rhegmatogenous Retinal Detachments Based on Training Era

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**PURPOSE:** Evidence suggests that retinal detachment repair using a scleral buckle is decreasing, while the use of vitrectomy is increasing with younger surgeons. If there is such a trend, what is the impact on patient outcomes? We hypothesized that training era affects a surgeon’s procedure preference and that this may impact anatomic and visual outcomes.

**METHODS:** The PRO Study is a retrospective multi-center review of 2620 patients who underwent primary repair by scleral buckling (SB), primary vitrectomy (PPV), or vitrectomy combined with scleral buckling (PPV/SB) for rhegmatogenous retinal detachment (RRD) in 2015. The 61 surgeons were grouped into 10-year cohorts based on years since graduation from fellowship.

**RESULTS:** In the subset analysis of phakic, medium-complexity primary RRDs, single surgery anatomic success (SSAS) was noted in 155/169 (91.7%) SB cases, 207/249 (83.1%) PPV cases, and 271/297 (91.2%) SB/PPV cases. Controlling for cataract and macular status revealed final visual acuities of 20/30 (SB), 20/41 (PPV), 20/35 (PPV/SB). Earlier training era was correlated with an increased preference for SB, less preference for PPV/SB, and worse SSAS in the PPV and PPV/SB categories. All procedure final visual acuities as well as SSAS for SB were similar across surgeon cohorts. In the pseudophakic subset, SSAS was seen in 529/628 (84.2%) of PPV cases, 170/184 (92.4%) SB/PPV cases. Controlling for macula-off RRDs revealed final visual acuities of 20/44 (PPV) and 20/29 (PPV/SB). There was no trend among preferences for PPV or PPV/SB. Final visual acuity in PPV cases, as well as SSAS among PPV and PPV/SB cases, was markedly worse in surgeons who graduated pre-1996. Other cohorts yielded similar outcomes.

**CONCLUSIONS:** In phakic patients, younger surgeons did fewer SB cases and more PPV/SB cases, with SSAS rates comparable among all surgeons. PPV/SB and PPV showed worse SSAS in older surgeons. Final visual acuity outcomes were similar across surgeon cohorts, but the use of a scleral buckle was correlated with better final vision. In pseudophakic patients, PPV/SB resulted in better final vision than PPV. There was not a significant trend in procedure preference, but SSAS and PPV vision outcomes were worse in surgeons who graduated pre-1996.
Retinal Redetachment after 23-Gauge Pars Plana Vitrectomy Alone for the Management of Primary Rhegmatogenous Pseudophakic Retinal Detachment

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PURPOSE: To report the incidence and describe the reasons for redetachment after 23-Gauge pars plana vitrectomy (PPV) alone for the management of primary pseudophakic retinal detachment (RRD).

METHODS: Retrospective interventional cohort study of all primary pseudophakic RRDs from January 2015 to December 2018 at the Vall d’Hebron Hospital with a minimum of 3-month follow-up. Attached posterior hyaloid, PVR grade C, retinal dyalisis, retinoschisis, giant tears and chronic retinal detachment were excluded. The surgical technique was 23-gauge PPV alone. Drainage of subretinal fluid for inferior breaks was performed with perfluorocarbon liquid. Air, SF6 or C3F8 were used as tamponade agents. Postoperative visits were performed at day 1, 7, 14 and 1, 3 and 6 months. Main variables recorded were intravitreal volume of gas, development of the chorioretinal scar and retinal reattachment. Single surgery anatomic success (SSAS) was defined as retinal attachment with no other RRD surgery within 90 days.

RESULTS: During a 48 month period, 296 consecutive primary pseudophakic RRDs were considered. Of these, 267 cases were included in the study. SSAS was achieved in 241 cases (90.2%). There were 26 cases that redetached during the first 3 months postoperatively (9.7%). Mean age was 57 years (38-81). High or extreme myopia was present in 8 cases (30.7%). Mean number of quadrants was 2.3 (1-4). Reasons for redetachment were: missed break in 3 cases (11.5%), inadequate gas filled from the first postoperative day in 7 cases (26.9%) and incomplete development of the chorioretinal scar around lasered breaks in 16 cases (61.5%). PVR grade B or C developed postoperatively in 6 cases (2.3%). Redetachment was diagnosed between the first and the second postoperative week in 15 cases (57.7%), at the first month postoperatively in 9 cases (34.6%) and between 1 and 3 months postoperatively in 2 cases (7.7%). Silicone Oil was used as tamponade agent in 10 cases (38.5%) and C3F8 in 16 cases (61.5%). One reoperation was performed in 18 cases (69.2%) and 2 or more procedures were performed in 8 cases (30.8%). Final reattachment was achieved in 24 cases (92.3%).

CONCLUSIONS: In primary pseudophakic RRD repaired with 23-Gauge PPV alone the main reason for redetachment was a failed development of the chorioretinal scar around the lasered retinal breaks.
Supplemental Scleral Buckle in the Era of Small Incision Vitrectomy and Wide-angle Viewing Systems—Decreasing Trends, Steady Outcomes

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**PURPOSE:** To evaluate trends and outcomes of scleral buckling (SB) as adjunct to pars plana vitrectomy (PPV) for the management of rhegmatogenous retinal detachment (RD) in the era of small gauge vitrectomy and wide-angle viewing systems.

**METHODS:** Retrospective, consecutive single-surgeon case series. Inclusion criteria: 300 consecutive cases of RD that underwent PPV. Exclusion criteria: follow-up <3 months, age <18 years, and open globe injury. The series was divided into 3 groups: group A (first 100 cases), group B (second 100 cases), and group C (third 100 cases). Outcome measures: retinal re-attachment and BCVA.

**RESULTS:** 300 eyes of 289 patients, mean age 61.0 years. The mean follow-up was 31.3 months (range 3-88 months) for group A, 28.5 months (range 3-69 months) for group B, and 12.0 months (range 3-28 months) for group C (P<0.001). RD involved the macula in 201 (67%) eyes. 120 (40%) eyes were pseudophakic, 72 (24%) eyes were highly myopic, and 13 (4.3%) eyes GRT. PVR ranged from none to funnel RD. The baseline mean LogMAR equivalent was 1.58 for group A, 1.31 for group B, and 1.33 for group C (P=0.15).

Adjunct SB was performed in 53 (53%) eyes in group A, 35 (35%) eyes in group B, and in 18 (18%) eyes in group C (P<0.001). Single surgery re-attachment rate was 93% for group A, 95% for group B, 97% for group C, and 95% for the entire cohort (P=0.48). The final mean LogMAR equivalent was 0.74 for group A, 0.50 for group B, and 0.62 for group C. The mean change in LogMAR equivalent was -0.84 for group A, -0.81 for group B, and -0.71 for group C (P=0.49). Single surgery re-attachment rate was 95.2% for the eyes with PPV+SB, and 94.7% for the eyes with PPV only (P=0.49).

**CONCLUSIONS:** The study demonstrates a decreasing trend in the use of adjunct scleral buckle procedure in the era of small gauge vitrectomy and wide-angle viewing systems. The anatomic and visual outcomes remain stable with no significant difference between the eyes with supplemental scleral buckle and those without.
Factors Associated with the Use of 360-degree Laser Retinopexy During Primary Pars Plana Vitrectomy with or without Scleral Buckle for Rhegmatogenous Retinal Detachment and Impact on Surgical Outcomes

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PURPOSE: To determine the factors associated with use of intraoperative 360-degree laser retinopexy during primary pars plana vitrectomy (PPV) with or without scleral buckle (SB) for rhegmatogenous retinal detachment (RRD) and to evaluate impact on surgical outcomes.

METHODS: This was a multicenter, retrospective, interventional study. Patients undergoing PPV or PPV+SB for non-complex primary RRD in 2015 were evaluated. Detailed demographic, clinical, and surgical variables including whether 360-degree laser retinopexy was performed were collected at the time of presentation, surgery, and each follow up visit. The primary outcomes were single surgery and final anatomical success. Secondary outcomes included final logMAR visual acuity, epiretinal membrane (ERM) formation, development of cystoid macular edema (CME), and number of subsequent retina surgeries. Multivariate logistic and linear regressions were performed for statistical analysis using Stata (StataCorp). P-values less than 0.05 were considered statistically significant.

RESULTS: A total of 2,248 surgeries (1,347 PPV and 901 PPV+SB) performed by 61 different surgeons were included. Of these, 516 underwent 360-degree laser retinopexy (315 PPV and 201 PPV+SB), and 1,732 did not (1,032 PPV and 700 PPV+SB). On multivariate analysis, younger patient age (p = 0.01), higher number of retinal breaks (p = 0.01), greater extent of retinal detachment (p < 0.001), and surgeon ID (p < 0.001) were significantly associated with the use of 360-degree laser retinopexy. Univariate analysis revealed no significant association between the use of 360-degree laser retinopexy and single surgery anatomical success (p = 0.44), ERM formation (p = 0.14), CME development (p = 0.28), or number of subsequent retina surgeries (p = 0.41). On multivariate analysis controlling for case complexity, there was a statistically significant association of 360-degree laser retinopexy with lower final anatomical success (p < 0.001) and worse final logMAR visual acuity (p < 0.001).

CONCLUSIONS: Surgeon preference played a large role in determining whether 360-degree laser retinopexy was performed during primary vitrectomy with or without scleral buckle for rhegmatogenous retinal detachment. The application of intraoperative 360-degree laser retinopexy was not associated with improved anatomic or visual outcomes.
Macular Edema after Successful Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment: Factors Affecting Edema Development and Considerations for Treatment

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PURPOSE: To investigate the incidence of macular edema after pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment (RRD) repair, the factors affecting its development and the efficacy of intravitreal dexamethasone implant for its treatment.

METHODS: Participants in this study 86 patients with RRD. All patients were examined postoperatively and incidence of macular edema was recorded, along with the factors affecting its development. Patients with macular edema were treated with intravitreal dexamethasone implant. They were followed-up with spectral domain-optical coherence tomography (SD-OCT) and best corrected visual acuity (BCVA) measurement until month 12 post treatment.

RESULTS: 14 out of 86 patients (16.3%) presented macular edema post PPV for RRD repair. Patients with pre-operative macula off RRD (p=0.027), duration of RRD >1 week (p=0.012), proliferative vitreoretinopathy (PVR) (p=0.042), and those with pseudophakic lens status (p=0.039) were more prone to develop macular edema. There was a statistically significant improvement in BCVA and central retinal thickness at month 12 post intravitreal dexamethasone implant compared to baseline. Total resolution of macular edema was observed in 10 out of 14 patients (71.4%) at month 12 with only one injection.

CONCLUSIONS: The incidence of macular edema post PPV for RRD repair was found to be 16.3%. Factors mainly influencing the appearance of macular edema after successful RRD repair were also discussed. Intravitreal dexamethasone implant seemed to be safe and effective in cases with post PPV macular edema after RRD repair, even with limited number of injections.
Retinal Displacement Detected with Fundus Autofluorescence Imaging Following Pneumatic Retinopexy vs Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment (INTEGRITY STUDY)

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PURPOSE: To compare retinal displacement following rhegmatogenous retinal detachment (RRD) repair with pars plana vitrectomy (PPV) vs. pneumatic retinopexy (PnR) and to determine if retinal displacement is associated with post-operative metamorphopsia and outer retinal abnormalities on optical coherence tomography (OCT).

METHODS: A multicenter study was carried out at three academic vitreoretinal units. Consecutive eyes with 3-month post-operative fundus autofluorescence (FAF) images were reviewed retrospectively. The primary outcome was the proportion of patients with retinal displacement detected by assessment of retinal vessel printings (RVP) on FAF in PPV vs. PnR.

RESULTS: 238 eyes were included in the study. 124 eyes had PPV and 114 eyes had PnR as the final procedure to achieve anatomical retinal re-attachment. There were no significant differences in baseline features (age, sex, lens status, macular status, quadrants of detachment) between groups. The proportion of eyes with RVP on FAF imaging was 44.4% for PPV (55/124) and 7.0% for PnR (8/114) (p<0.0001). Among eyes that had retinal displacement, mean displacement in the PnR group was 0.137mm (SD=0.086) vs. 0.293mm (SD=0.286) in the PPV group (p=0.008) and the direction of displacement was superior in 75.0% (6/8) of PnR cases and inferior in 92.3% (48/52) of PPV cases. There was no significant difference in retinal displacement between PPV patients who had drainage though the break compared to posterior retinotomy (p=0.123). 96.5% (55/57) and 83.3% (25/30) with displacement had OCT interdigitation zone (IDZ) abnormalities and vertical metamorphopsia vs 83.2% (134/161) and 55.6% (65/117) in those without displacement (p=0.011, p=0.005). Mean logMAR visual acuity was 0.57 (SD=0.46) vs 0.35 (SD=0.34) among patients who had retinal displacement vs those that did not (p=0.002).

CONCLUSIONS: Retinal displacement occurs more frequently and is more severe with PPV vs. PnR and is associated with vertical metamorphopsia. This study demonstrates for the first time a difference in the anatomical integrity of retinal re-attachment with different surgical procedures by comparing retinal displacement assessed by retinal vessel printings on FAF. Recognition of the importance of retinal displacement and integrity of retinal re-attachment will lead to further refinements in vitreoretinal surgery techniques for primary RRD repair with improved functional outcomes.
Relaxing Retinectomy for Proliferative Vitreoretinopathy in Rhegmatogenous Retinal Detachment

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PURPOSE: Relaxing retinectomy is an option for the treatment of proliferative vitreoretinopathy (PVR) complicating rhegmatogenous retinal detachment (RRD). It is our practice to exclusively use this method in all patients with PVR unresponsive to simple vitrectomy and tamponade.

METHODS: All patients from single surgeon’s service who received retinectomy over a 17-year period were reviewed on an electronic medical record (VITREOR). Prognostic factors for anatomical and visual outcome were analysed. Primary success rate was defined as a flat retina with one operation without tamponade, secondary success was a flat retina with more than one operation with or without tamponade and failure the presence of any retinal detachment at last follow up.

RESULTS: 134 eyes from 134 patients were examined with a median follow up of 1.4 years. 87 were male, mean age was 67 years, with 75 right eyes. Mean retinectomy size was 166 degrees. Primary anatomical success was 13%, secondary 72% and failure was seen in 13%. Those patients operated upon by small gauge surgery had higher success rates (p=0.01). 88 had a procedure for removal of silicone oil. 16% of these patients had oil in at the end of follow up. 9% were classified as failure in this group. Overall, 47% achieved 20/200 vision or better, 10.4% 20/40 or better. Those patients with no oil in situ at follow up had better vision of 63% 20/200 or better, 15% 20/40 or better.

CONCLUSIONS: Relaxing retinectomy can achieve good results in the management of RRD complicated by PVR. Success rates improved over time perhaps related to the adoption of small gauge surgery. Those patients who achieve silicone oil removal have better visual outcomes.
**Only Close Surgical Dissection of the Vitreo Retinal Interface Can Prevent/Treat Proliferative Vitreo Retinopathy (PVR) in the Entire Eye In Vivo**

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**PURPOSE:** PVR is an Epithelial-to-Mesenchyme Transition process with conversion to a contractile Extra Cellular Matrix (ECM). The retinal ECM can be ablated by high magnification surgical dissection. Pharmacotherapy, promising in retinal pigment epithelium (RPE) cultures, revealed unsuccessful in clinical practice. Rhegmatogenous Retinal Detachment (RRD) is a central nervous system (CNS) injury of primarily mechanical nature. Epithelial Growth Factor Receptor (EGFR) is pivotal for CNS cell death, survival, repair and wound healing (WH). This study investigates its role in the natural course of RRD.

**METHODS:** EGFR expression has been studied in ten entire human globes with RD and/or primarily metabolic (ischemia, infection) diseases, and two entire porcine eyes with experimental RRD (ERRD) (core vitrectomy and retinal browsing).

**RESULTS:** In cases of primarily metabolic disease, EGFR is either not expressed, or weakly expressed when RD complicates the evolution. EGFR is over-expressed in cases of RD and ERRD. Over-expression is diffuse (neuronal, glial, RPE and endothelial cells), and dramatic, « glioma-like ». Necrosis and cells injury are observed in the subretinal fluid (SRF). At Day14 of ERRD, EGFR-positive RPE and fusiform cells are present at the vitreo-retinal interface. WH, CNS trauma, and EGFR literature unravel the pathways leading to « tumor-like » EGFR over-expression 1) plasma membrane (PM) injury drives either PM re-sealing or passive cell necrosis 2) endogenous Damage Associated Molecular Patterns (DAMPs) are released 3) DAMPs induce PM ectodomain shedding of physical trauma-specific EGFR ligands that trigger (within seconds) and amplify EGFR activation 4) the physiological endocytic control of EGFR signaling is overwhelmed, and transcription is considerably expanded 5) delayed necroptosis which further releases DAMPs, and chronic mechanotransduction and flow-shear stresses induce resilient EGFR re-activation via sustained ligand shedding.

**CONCLUSIONS:** During RRD in the entire eye in vivo, the primary mechanical nature of injuries triggers instant, unavoidable, irreversible and re-activated EGFR over-activation, via previously underscored PM injury and passive necrosis. Pharmacotherapies for PVR, promising in vitro, target in vivo downstream EGFR proliferation pathways which carry escape routes provided by multiple cross-talks, as in cancer. Early high magnification surgical disruption and ablation of the modified retinal ECM (video) results in a non pharmaceutical upstream manipulation of EGFR.
PURPOSE: To compare the severity of macular thickness and vasculature changes in children with sickle cell disease (SCD) versus age- and race-matched controls.

METHODS: In this prospective observational study, children (<18 years old) with HbSS and HbS variant (HbSC and HbS thalassemia) genotypes, and their age- and race-matched controls were recruited between January 2017 and December 2018. All subjects underwent visual acuity testing, dilated ophthalmoscopy and optical coherence tomography angiography (OCTA) scans centered on the fovea and temporal macula. Using generalized linear mixed models adjusting for age and gender with patients as random effect, retinal thickness, superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density (VD), and foveal avascular zone (FAZ) size were measured and compared between HbSS and HbS variant versus controls.

RESULTS: 34 HbSS, 34 HbS variant and 24 control eyes (total 48 children, ages 5-17 years) with logMAR visual acuity (mean ± standard deviation) of 0.052 ± 0.117, 0.075 ± 0.122, 0.011 ± 0.033 respectively (p>0.05) were included. The proportion of eyes with no retinopathy, non-proliferative retinopathy and stage 3 proliferative retinopathy was 53%, 44% and 3% respectively in the HbSS group, and 26%, 71% and 3% respectively in the HbS variant group (p=0.06). A higher proportion of HbSS (n=18, 55%) than HbS variant eyes (n=9, 26%) had pathologic areas of retinal thinning associated with SCP and DCP flow loss (p=0.03). Total VD (6mm ETDRS circle) was lower in HbS variant eyes than controls for both the SCP (47.1% versus 49.3%, p=0.01) and DCP (48.3% versus 52.5%, p=0.01). In HbSS eyes, VD was lower in the DCP (47.2%, p=0.04) but not in the SCP (49.7%, p=0.6) compared to controls. However, retinal thickness measurements and FAZ size did not differ between either HbSS or HbS variant group versus controls.

CONCLUSIONS: OCTA demonstrates microvascular changes in children with SCD, including those with good visual acuity and no significant proliferative sickle cell retinopathy changes on dilated fundus exam. Children with SCD have similar retinal thickness measurements but less dense vasculature on OCTA compared to age and race-matched controls, suggesting that microvascular insult may precede structural thinning.
In honor of J. Donald M. Gass, M.D. and his unending curiosity with ocular tumors, we will explore four topics relative to uveal melanoma including tumor imaging, The Cancer Genome Atlas (TCGA) classification, nanoparticle therapy for small melanoma, and novel observations with immunotherapy for metastatic melanoma.

Regarding imaging, new risk factors have been identified based on multimodal imaging, predictive of choroidal nevus transformation into melanoma. These can be remembered by the mnemonic “To Find Small Ocular Melanoma Doing IMaging” (TFSOM-DIM) representing Thickness >2 mm (by ultrasonography), Fluid subretinal (by OCT), Symptoms vision loss (by Snellen VA), Orange pigment (by autofluorescence), Melanoma hollow (by ultrasonography), and DIaMeter >5mm (by photography). The 5-year rate of growth was 1% for those with 0 risk factor, 11% with 1 factor, 22% with 2 factors, 34% with 3 factors, and >50% with 4, 5, or 6 factors.

A new classification for melanoma, TCGA, based on genetic markers, was recently published. A second analysis applied this classification to a cohort of 658 patients with uveal melanoma and found robust prognostication with more advanced TCGA class demonstrating increased 5-year risk for metastasis (4% vs. 20% vs. 33% vs. 63%, p<0.001). A third analysis compared TCGA to the American Joint Committee on Cancer (AJCC) classification for melanoma and TCGA was superior in prediction.

A novel infrared dye-conjugated virus-like nanoparticle (AU-011) is currently under investigation for treatment of small choroidal melanoma, with a goal to induce tumor regression and minimize collateral vision loss. AU-011 diffuses through tissue to reach the melanoma, and laser stimulation leads to local activation of the drug causing tumor necrosis. Randomized phase 3 trials are upcoming in late 2019 to confirm the efficacy of AU-011 for small choroidal melanoma.

Immunotherapy for uveal melanoma metastasis is slowly evolving. Checkpoint inhibitors are not quite effective, likely due to low mutational burden of uveal melanoma. However, ImmTACs (immune modulated T cells against cancer) have been remarkable at metastatic control with 74% overall survival at 1 year, a big improvement over prior therapies.
An Important Marker for Anti-VEGF Resistance — Subretinal Aneurysmal Neovascularization Diagnostic of the Polypoidal Choroidal Vasculopathy Subtype of Exudative Age-related Macular Degeneration

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PURPOSE: To evaluate polypoidal choroidal vasculopathy (PCV) or subretinal aneurysmal neovascularization as a marker for anti-VEGF resistance, to assess any possible PCV lesion characteristics that may be associated with anti-VEGF resistance, and to document the prevalence of PCV diagnosed by indocyanine green angiography (ICGA) in different ethnic populations.

METHODS: Baseline data was collected on all eyes diagnosed with exudative AMD, which included ethnic data and potential predictive factors for PCV. PCV was diagnosed utilizing indocyanine green (ICG) angiography with the scanning laser ophthalmoscope. Exudative AMD eyes were separated into two groups — anti-VEGF resistant eyes with persistent subretinal fluid, subretinal hemorrhage or macular edema after four anti-VEGF injections, and anti-VEGF sensitive eyes defined as eyes without residual disease activity. The prevalence of PCV was determined in each group based on ICG angiography.

RESULTS: Exudative AMD was diagnosed in 253 eyes of 221 patients. PCV was noted to have a prevalence of 45.1% (114/253 eyes) in the overall population. PCV was noted in 51.6% (81/157) of eyes with wet AMD in Asians, 31.9% (23/72 eyes) of eyes with wet AMD in Caucasians, and 28.6% (4/14 eyes) in a small group of Pacific Islanders. PCV was diagnosed in 50% (60/120 eyes) of eyes in the anti-VEGF resistant group, which is more prevalent than the 30.2% (29/96 eyes) in the anti-VEGF sensitive group (p

CONCLUSIONS: PCV is more prevalent in anti-VEGF resistant eyes in both Caucasian and Asian patients, and the diagnosis of PCV could help to predict therapeutic response and to guide alternative therapy. PCV is more prevalent in exudative AMD in Asian patients, but is more prevalent than generally recognized in Caucasian patients.
Evaluation of Polyp Morphology during Course of Active Treatment of Polypoidal Choroidal Vasculopathy

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**PURPOSE:** Polypoidal choroidal vasculopathy (PCV) is a retinal disease characterized by polypoidal lesions and a branching vascular network. While studies typically evaluate the frequency of complete polyp regression among different treatment arms, few studies have characterized the course of polyp development and regression. We aimed to evaluate polyp status among patients with symptomatic macular PCV, and to differentiate between polyps originally present at baseline and new polyps.

**METHODS:** EVEREST II was a 24-month, phase IV, double-masked, multicenter study which included 322 eyes from Asian patients with symptomatic macular polypoidal choroidal vasculopathy (PCV) who were randomized 1:1 to receive ranibizumab and verteporfin photodynamic therapy (n = 168) or ranibizumab monotherapy (n = 154). Graders from the Central Reading Center reviewed indocyanine green angiograms (ICGA) of 30 patients randomly selected from EVEREST II. ICGA was performed at baseline, 3, 6, 12 and 24 months. Polyps present at follow-up visits were classified into polyps present at baseline and new polyps that developed subsequently.

**RESULTS:** The individual polyps exhibited a variable course throughout the study period. At 24 months, 15 of 30 patients (50%) had complete resolution of all polyps. Of the 15 patients with active polyps, 4 had both persistent polyps from baseline and new polyps, 8 had only new polyps with complete resolution of baseline polyps, and 3 had only persistent polyps which were originally present at baseline. The mean area of all polyps present at month 24 was 0.12 mm², with mean area of original polyps accounting for 0.05 mm² (36.3% of total area) and mean area of new polyps accounting for 0.08 mm² (63.7% of total area). New polyps developed in 65% of patients and were only detected after the 12 month visit.

**CONCLUSIONS:** The individual polyps in PCV vary during the course of treatment, with some polyps originally present at baseline persisting, while in some eyes new polyps develop. Most new polyps developed from 12 months.
What Does Optical Coherence Tomography Angiography Reveal About the Choroidal Neovascularization Response to the Port Delivery System with Ranibizumab Compared with Monthly Ranibizumab Injections?

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PURPOSE: Ladder evaluated the Port Delivery System with ranibizumab (PDS) for nAMD. To understand the choroidal neovascularization (CNV) response to PDS versus intravitreal ranibizumab injections, optical coherence tomography angiography (OCTA) data were collected to image CNV lesions over time.

METHODS: The randomized phase 2 Ladder trial (NCT02510794) for nAMD compared the PDS with 3 customized ranibizumab formulations with monthly intravitreal ranibizumab 0.5 mg. Monthly OCTA imaging was performed at sites that had the OCTA system available; images were evaluated for CNV type, area, and vessel density by certified masked graders at the Boston Image Reading Center. Overall, 26 patients with both baseline and month 9 assessments were analyzed, with 7, 9, and 5 patients in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively, and 5 patients in the monthly intravitreal ranibizumab 0.5 mg arm.

RESULTS: Mean baseline CNV area was 1.89 (min, max, 0, 5.93) mm², 1.97 (0, 10.78) mm², and 1.05 (0, 1.98) mm² in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively, and 2.21 (0, 6.18) mm² for the monthly intravitreal ranibizumab 0.5 mg arm. Mean change in CNV area from baseline to month 9 was +0.56 (0.05, 2.24) mm², +0.44 (-0.23, 2.03) mm², and +0.23 (-0.35, 1.19) mm² in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively, and +0.20 (-0.23, 0.62) mm² for the monthly intravitreal ranibizumab 0.5 mg arm. Mean change in CNV vessel density (%) from baseline to month 9 was -6.01 (-17.78, 3.38; n=5) for PDS 10 mg/mL, -9.15 (-20.76, 3.13; n=8) for PDS 40 mg/mL, +3.60 (-6.24, 19.18; n=3) for PDS 100 mg/mL, and +11.27 (8.13, 14.81; n=3) for monthly intravitreal ranibizumab 0.5 mg (P=0.0675).

CONCLUSIONS: In this pilot OCTA study of a small number of Ladder patients, the CNV morphologic response appeared to be similar between the PDS 100 mg/mL and monthly intravitreal ranibizumab arms. At month 9, the change in CNV area from baseline trended towards being comparable between the 2 arms and CNV vessel density seemed to increase. Larger studies are required to confirm these findings.
Quantitative Fundus Autofluorescence (qAF) Characterizes Two Pathways and Two Phenotypes of Geographic Atrophy (GA) secondary to Age-related Macular Degeneration (AMD)

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PURPOSE: Quantitative autofluorescence (qAF) offers scaled, reproducible AF measurements between patients and over time. We studied qAF in lobules of geographic atrophy (GA) to correlate with two main pathways from intermediate age-related macular degeneration (iAMD) to two phenotypes of GA.

METHODS: We studied 25 pseudophakic eyes of 18 patients with GA with color fundus photography, near-infrared reflectance (NIR) imaging, spectral-domain optical coherence tomography (SD-OCT) and qAF imaging. We examined prior serial tracked OCT scans of 52 Regions-of-interest (ROIs) that included all individual or coalescent atrophic lobules for each eye over a mean follow-up of 5.5 years (range, 1.2-10 years) to divide them into 3 pathways by the dominant predecessor intermediate AMD lesion type: soft drusen/pigment epithelial detachment (PED), main pathway 1, subretinal drusenoid deposits (SDD), main pathway 2, and mixed, pathway 3. Mean qAF values of GA ROIs were measured and compared between the 3 pathways.

RESULTS: The mean qAF levels of the ROIs were significantly different between the 2 main pathways to GA. Main pathway 1 (19/52) was the soft drusen/PED pathway to GA, and GA lesions were isolated and “black” on AF, with lower qAF (37.0±11.9 qAF units), displaying complete loss of RPE, the complete atrophy of the RPE and outer retina (cRORA) phenotype of GA. Main pathway 2 (15/52) was the SDD pathway to GA, and GA lesions were multilobular and “gray” on AF, with higher qAF (72.4±12.3 qAF units, P<0.001, t-test), usually displaying the incomplete atrophy of the RPE and outer retina (iRORA) phenotype of GA. The mean qAF of ROIs from mixed pathway (18/52) was 57.6±12.5 qAF units, significantly different from those of either main pathway (P<0.001, t-test), cases of post-operative retinal detachment (4.9%), and 1 case of endophthalmitis (0.98%).

CONCLUSIONS: GA lesions can in most cases be simply divided by qAF levels (lower/higher) into 2 non-exclusive groups that correlate both with the precursor pathways of intermediate AMD lesion (drusen/PED or SDD, resp.) and their final OCT atrophy classification (cRORA or iRORA), with remaining lesions arising from both forms of iAMD and displaying intermediate qAF levels. Thus, qAF of GA lobules reflects both their pathogenesis and structure, and would be an easily implemented and useful metric for clinical GA research.
Analysis of In Vivo Stimulation of Retinal Pigment Epithelial Regeneration in the Axin2lacZ Knock-in Mouse

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PURPOSE: The retinal pigment epithelium (RPE) maintains tissue homeostasis through long-term survival, with little evidence of de novo cell production. Due to continued growth with aging, cell density decreases and RPE cells undergo hypertrophy. This process is accelerated in atrophic AMD. Several lines of evidence suggest that a subpopulation of RPE may contain distinct properties contributing to regeneration: the peripheral RPE displays enhanced proliferative capacity and regenerative animal models, including mouse, can regenerate RPE after chemically induced injury. We hypothesize that genetic modulation of signaling pathways that promote RPE development can stimulate regenerative proliferation and activate RPE differentiation.

METHODS: Using funds from the Retina Society (Award of Merit in Retina Research), we induced oxidative injury in the adult mouse RPE using intraperitoneal injection of sodium iodate (35 mg/kg bodyweight). We used the Axin2lacZ knock-in mouse allele to disrupt function of the Wnt pathway inhibitor Axin2, that has been shown to result in ectopic upregulation of the canonical Wnt pathway, which is critical for differentiation of developing mouse RPE. Production of newly produced cells in the RPE layer was monitored by 2 injections of the thymidine analogue EdU (30 mg/kg) at 5-8 days post-injury. Nine days following sodium iodate treatment, the eyes were harvested, cryosectioned and processed for EdU labeling. The number of EdU-labeled cells was counted separately in the peripheral, intermediate and central RPE on 7-16 cryostat sections.

RESULTS: Our preliminary data shows that hemizygous disruption of Axin2 induces a 3-fold increase in the number of EdU-labeled cells in the damaged RPE layer, particularly in the central and adjacent intermediate RPE regions. Currently, we are characterizing the temporal and spatial dynamic of induced proliferation and differentiation using co-labeling with RPE-specific markers (e.g. Otx2, RPE65).

CONCLUSIONS: Our results suggest that canonical Wnt signaling stimulates proliferation of cells in the RPE layer after chemical injury, suggesting the potential for regeneration in areas of atrophy. This observation has stimulated further efforts to determine the molecular and cellular mechanisms of regenerative proliferation and differentiation and apply this knowledge to achieve regeneration of damaged RPE.
Human Plasma Metabolomics in Age-related Macular Degeneration—Meta-analysis of Two Cohorts

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PURPOSE: To assess and validate plasma metabolomic profiles in patients with age-related macular degeneration (AMD).

METHODS: A prospective, cross-sectional study was performed in two cohorts (Boston, United States and Coimbra, Portugal) including subjects with AMD (any stage of disease) and controls. Color fundus photographs were graded on all participants using the AREDS classification scheme. Fasting blood samples were processed and analyzed using ultrahigh-performance liquid chromatography and high-resolution mass spectrometry. Plasma metabolites of patients with AMD versus controls from the two distinct cohorts were assessed using logistic regression analysis accounting for potential confounders (age, sex, body mass index, and smoking status) and false discovery rate (FDR). The two cohorts (Boston and Coimbra) were analyzed separately, as well as combined through meta-analysis based on the Liptak-Stouffer weighted Z-method. Significant levels were also calculated using FDR similar to that in the individual cohort analysis. Pathway analysis was performed on significant metabolites using Metaboanalyst 4.0 to interpret biological relevance.

RESULTS: A total of 491 subjects—149 patients with AMD and 47 controls from Boston and 242 patients with AMD and 53 controls from Coimbra—were included in the study. After excluding 61 exogenous metabolites, analyses were performed on 544 metabolites. Meta-analysis identified 69 significantly different metabolites (p<0.04), sphingolipid (p=0.0010), glycerophospholipid (p=0.0037), and nitrogen metabolites (p=0.0404).

CONCLUSIONS: Patients with AMD have a distinct plasma metabolomic profile compared to controls. Metabolomics may provide a useful AMD biomarker, that can be combined with other defining features—including imaging biomarkers, genomic profile, and functional testing—to identify subtypes of early and intermediate AMD. This precision medicine approach may lead to successful therapies for early and intermediate AMD.
Metabolomic Genomic association in Age-related Macular Degeneration

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PURPOSE: Age-related macular degeneration (AMD) is a multifactorial disease involving genetic and environmental risk factors. However, the interaction among these factors and how they promote AMD remains largely unknown. Molecular traits on a quantitative scale may be more associated with causal genes than GWAS studies and better contribute to the understanding of AMD pathogenesis. The aim of this study was to analyze associations between metabolites and single nucleotide polymorphisms (SNPs) in a multicenter cohort of AMD patients and controls.

METHODS: Prospective, cross-sectional, multicenter study (Boston, United States and Coimbra, Portugal). We included 388 subjects with AMD (any stage of disease) and 98 controls without any vitreoretinal disease (age > 50 years). Color fundus photographs were used for AMD grading (AREDS classification scheme). Fasting blood samples were processed and analyzed using ultrahigh-performance liquid chromatography and high-resolution mass spectrometry. SNPs were genotyped using an Illumina Omni express platform. Associations between metabolites and AMD were tested using logistic regression and meta-analysis to account for the inclusion of two populations. Analyses of metabolomic quantitative trait loci (mQTL) were conducted using linear regression models, adjusted for age, gender and 10 first principal components (PC) of both metabolites and SNPs. Benjamini–Hochberg procedures were used to account for false discovery rate (FDR) in all performed analysis.

RESULTS: We first compared plasma metabolomic profiles of AMD patients with controls and observed that 28 metabolites differed significantly between them (FDR<0.05). Among these metabolites, half (n=14) were significantly associated with at least one SNP in patients with AMD and not in controls (p < 2.6 e-7). These metabolites corresponded to 916 mQTL (metabolite SNP pairs).

CONCLUSIONS: To our knowledge, this is the first study on metabolomic-genomic associations in AMD. In our cohort we identified mQTL associated with significant metabolites for AMD, thus providing a basis for further exploration. This approach has the potential to increase our understanding of the pathogenesis of this blinding condition.
Plasma Vinculin is Elevated in Advanced Age-related Macular Degeneration

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PURPOSE: Plasma proteomics allows analysis of differences in plasma proteins that are relevant to disease states and are a reflection of systemic alterations in cellular function. We screened plasma for high-interest proteins using an aptamer-based analysis, identified elevated vinculin in the plasma of patients with advanced age-related macular degeneration (AMD) and then confirmed this elevation using mass spectrometry.

METHODS: The Colorado Age-Related Macular Degeneration Registry is a bio-bank of over 1000 patients and controls. Plasma from 10 age-matched patients with bilateral geographic atrophy AMD (GA), neovascular AMD (NV) and 10 controls without retinal disease was analyzed for 4001 proteins using an aptamer-based analysis. Relative protein levels were log2transformed and compared by linear regression. After identifying vinculin as one of several high-interest proteins, nano-particle enriched tandem mass spectrometry with label-free quantification was utilized to evaluate plasma vinculin levels in the same patients.

RESULTS: Using the aptamer platform, the log2 vinculin levels in controls were lower and measured 10±0.2 relative-fluorescent-units compared with 10.4±0.6 units for GA (p<0.13) and 11±0.7 units for NV (p<0.01). Vinculin levels were elevated in NV compared with GA (p<0.02). Using mass spectrometry, vinculin was 1.66-fold elevated in GA (p<0.01) and 1.84-fold elevated in NV (p<0.006) compared with controls.

CONCLUSIONS: Using two independent analytic techniques, we have found that plasma vinculin is elevated in advanced AMD compared with controls. This confirm the previous findings of Kim et al. (IOVS,55:7166–7176,2014) of elevated levels of vinculin in the plasma of AMD patients relative to controls. Both the aptamer-based and mass spectrometry analysis can quantify low protein levels. Vinculin is a cytoskeletal protein involved in cell adhesion and mobility and is found in low concentrations in plasma. The presence of elevated vinculin in the plasma suggests that there is a systemic abnormality in cellular adhesion, cell-cell junctions or cell-matrix binding in advanced AMD, which may be present as well in retinal pigment epithelial cells. The presence of elevated vinculin could also be a marker of increased cellular damage. The use of plasma proteomics, and specifically the study of vinculin, may enhance predictive analysis in the evolution and treatment of AMD.
The Frequency of the Age-related Macular Degeneration Risk Alleles, Y402H and A69S, in a Direct-to-Consumer Genetic Database

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PURPOSE: The CFH Y402H (rs1061170) and ARMS2 A69S (rs10490924) genetic variants are the most common variants associated with an increased risk of developing AMD. Y402H and A69S variants are likely responsible for approximately 43% and 36% of AMD in older adults, respectively. Understanding the frequency of these alleles in the general US population can better inform population health approaches.

METHODS: Here, we assessed the frequency of Y402H and A69S in an unselected group of genotyped individuals who used direct-to-consumer (DTC) genetic testing (23andMe, Inc. Mountain View, CA). This was a national cross-sectional study. Study participants were genotyped between 2013 and 2017 on custom Illumina genotyping arrays. Eligible subjects were 23andMe customers who consented to participate in research. IRB approval was obtained from Ethical & Independent Review Services.

RESULTS: More than 80% of genotyped individuals consented to participate in online research. Of the 1,285,669 participants tested for Y402H, we found an allele frequency of 35.2%. Of the 1,287,821 participants tested for A69S, we found an allele frequency of 22.9%. The most common genotypes (Table 1) were Y402H heterozygotes (27.6%), homozygous non-risk genotype (24.5%), Y402H and A69S compound heterozygotes (15.7%), A69S heterozygote (14.9%) and Y402H homozygotes (7.5%). Overall, about 75% of genotyped individuals in our cohort carry one or more AMD Y402H and A69S variant(s).

CONCLUSIONS: This is the first description of an unselected cohort with Y402H and A69S alleles identified through DTC genetic testing. DTC genetic testing can identify individuals with high-risk genotypes and may aid in personalized medicine approaches. A large DTC genetic database can also provide further insights into the genetic epidemiology of AMD. Analysis to stratify the allele frequencies are ongoing.
Association of Age-related Macular Degeneration with Mortality in Patients with AIDS: Role of Systemic Inflammation

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PURPOSE: To evaluate the relationships among age-related macular degeneration (AMD), mortality, and biomarkers of systemic inflammation in patients with the acquired immunodeficiency syndrome (AIDS).

METHODS: A case control study was performed on participants in the Longitudinal Study of the Ocular Complications of AIDS cohort. 189 participants with intermediate-stage AMD at enrollment were matched 2:1 with controls (n=385) for age and gender. Cryopreserved baseline plasma specimens were assayed for biomarkers of inflammation: high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, interferon-γ inducible protein (IP)-10, soluble CD14 (sCD14), soluble CD163 (sCD163), kynurenine/tryptophan (KT) ratio, and intestinal fatty acid binding protein (I-FABP). Plasma levels were normalized and expressed as quartiles of the standard deviation. The primary outcome was mortality.

RESULTS: In the unadjusted analysis, AMD was associated with mortality (hazard ratio [HR] 1.48; 95% confidence interval [CI] 1.02, 2.15; P=0.04). In an analysis adjusted for blood CD4+ T cells and plasma human immunodeficiency virus (HIV) viral load, plasma CRP (HR 1.46; 95% CI 1.23, 1.74; P<0.001), IL-6 (HR 1.45; 95% CI 1.23, 1.71; P<0.001), IP-10 (HR 1.33; 95% CI 1.11, 1.59, P<0.001), and sCD14 (HR 1.20; 95% CI 1.02, 1.40; P=0.02) all were associated with increased mortality. In the Cox regression analysis adjusted for CD4+ T cells, plasma HIV load, and plasma biomarker levels, CRP, IL-6, and IP-10 all remained associated with mortality, whereas the association of AMD with mortality was attenuated (HR 1.08; 95% CI 0.73, 1.59; P=0.70). Step-wise variable selection demonstrated that the attenuation of the association of AMD with mortality primarily was due to the addition of the plasma biomarker levels.

CONCLUSIONS: These data suggest that the increased mortality observed in patients with AIDS with AMD is, at least in part, a result of systemic inflammation. Because AMD is associated with increased mortality in HIV-uninfected persons, and because antiretroviral-treated, immunorestored, HIV-infected persons have immunologic features of immunosenescence, immune activation, and systemic inflammation similar to those in HIV-uninfected elderly, these results may have relevance for AMD in HIV-uninfected persons.
Extended Dual Release of Dexamethasone and Aflibercept from a Single Drug Delivery System

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PURPOSE: Monthly/bimonthly intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) became the standard of care for wet age-related macular degeneration and other retinal vascular diseases. Even though anti-VEGF therapy is successful for a majority of patients, there is a subset of non-responders to repeated anti-VEGF monotherapy. Recent studies demonstrated positive outcomes with a combination treatment of an intravitreal dexamethasone implant with repeated anti-VEGF injections. The purpose of this study was to demonstrate an extended and controlled dual release of dexamethasone (DEX) and aflibercept (AFL) from a single drug delivery system (DDS).

METHODS: DEX was encapsulated into poly(lactic-co-glycolic acid) (PLGA) nanoparticles using a single emulsion technique and AFL was encapsulated into PLGA microspheres using a modified double emulsion technique. DEX-loaded nanoparticles (20 mg) and AFL-loaded microspheres (20 mg) were suspended within a single degradable thermoresponsive hydrogel DDS. The combination releases of DEX and AFL were compared to the individual drug release profiles. Size distribution and mean diameter were analyzed using Nanoparticle Tracking Analysis. The initial burst (IB) was calculated by quantifying total drug release in the first 24 hours.

RESULTS: Average nanoparticle diameter for DEX was 138.9±6.2 nm with drug encapsulation efficiency of 53.62±9.67%. Average microparticle diameter for AFL was 7.0±0.4mm with drug encapsulation efficiency of 77.64±1.66%. On average of ~80% AFL microspheres and ~15% DEX nanoparticles were encapsulated within the hydrogel. AFL release profiles from combination DDS were slightly faster compared to the individual AFL-DDS release. The average IB was lower (21%) and average release time was ~150 days. The presence of DEX nanoparticles did not significantly affect the AFL release. DEX release profiles from the combination DDS were also similar to the individual DEX-DDS release where average IB of 12% and average release time of ~196 days were achieved. The presence of AFL microspheres did not affect the DEX release.

CONCLUSIONS: Neither DEX nor ALF release kinetic was significantly affected by the mixture of nanoparticles and microspheres in our combination DDS. This study suggests that an extended and controlled simultaneous release of both DEX and AFL from a single DDS can be achieved.
Intravitreal Aflibercept Injection for Nonproliferative Diabetic Retinopathy: 52-week Results from the Phase 3 PANORAMA Study

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PURPOSE: Vascular endothelial growth factor inhibitors can slow disease progression in eyes with diabetic retinopathy in patients with diabetic macular edema (DME). In the phase 3 VISTA and VIVID studies, more eyes treated with intravitreal aflibercept injection (IAI) had a >=2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score versus laser photocoagulation in patients with both diabetic retinopathy and DME. PANORAMA (NCT02718326) is the first large, prospective trial of eyes with moderately severe to severe (high-risk) nonproliferative diabetic retinopathy (NPDR) in patients without DME since the Early Treatment Diabetic Retinopathy Study. PANORAMA compared the efficacy and safety of IAI versus sham.

METHODS: Eligible patients were aged >=18 years with type 1 or 2 diabetes mellitus and had moderately severe to severe NPDR (DRSS score 47 or 53), absence of centre-involved DME, and a baseline best-corrected visual acuity (BCVA) score of >=69 letters (approximately >=20/40) in the study eye. In total, 402 eyes were randomised to IAI 2 mg q16 weeks after 3 monthly doses and one q8 interval (2q16, n=135), IAI 2 mg q8 weeks after 5 monthly doses (2q8, n=134), or sham (n=133). The primary endpoint was the proportion of eyes with a >=2-step improvement in DRSS score at week 52.

RESULTS: Overall, 44.0% of patients were women, with a mean (SD) age of 55.7 (10.5) years and a mean (SD) baseline BCVA score of 82.4 (6.0) letters. Eyes randomised to 2q16 and 2q8 received a mean of 5.5 and 8.6 injections through week 52, respectively. In total, 65% and 80% of 2q16 and 2q8 eyes, respectively, versus 15% of sham eyes had a >=2-step improvement in DRSS score (P<0.0001 for both). In addition, 4% of 2q16 eyes and 3% of 2q8 eyes versus 20% of sham eyes (P<0.001 for both) developed vision-threatening complications (proliferative diabetic retinopathy or anterior segment neovascularisation). The incidence of centre-involved DME was lower with 2q16 (7%) and 2q8 (8%) versus sham (26%, P<0.001 for both). No new safety signals were identified with IAI.

CONCLUSIONS: IAI improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME.
Vision-threatening Proliferative Diabetic Retinopathy (PDR) Events in Diabetic Retinopathy (DR) Patients with Diabetic Macular Edema (DME): A Post Hoc Analysis of the VISTA and VIVID Trials

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PURPOSE: The phase 3 VISTA and VIVID trials showed that patients with DME treated with intravitreal aflibercept injection (IAI) achieved significantly greater improvements in visual and anatomic outcomes compared with those treated with laser photocoagulation (laser control). This post hoc analysis assessed vision-threatening PDR events (proliferative DR, panretinal photocoagulation, or vitrectomy) in DR patients with DME in VISTA and VIVID.

METHODS: VISTA (NCT01363440) and VIVID (NCT01331681) were two similarly designed phase 3 studies that randomized patients with center-involving DME to laser control, IAI 2 mg every 4 weeks (2q4), or IAI 2 mg every 8 weeks after 5 monthly doses (2q8). This post hoc analysis of the integrated VISTA and VIVID datasets included 235 patients treated with laser and 475 patients treated with IAI (combined) who had a gradable Diabetic Retinopathy Severity Scale (DRSS) score and no PDR at baseline.

RESULTS: Through week 100, 11.1% of laser-treated and 4.4% of IAI-treated patients developed a vision-threatening PDR event, with an adjusted difference of –6.7% (97.5% confidence interval: –11.7, –1.6; P=0.0008). Vision-threatening PDR events occurred relatively earlier with laser versus IAI (log-rank PP=0.0001).

CONCLUSIONS: In patients with DME, IAI reduced the incidence of vision-threatening PDR events and increased the proportion of patients who achieved a DRSS score 35 at week 100 compared with laser.
Diabetic Retinopathy Improvements with Intravitreal Faricimab in the BOULEVARD Trial

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PURPOSE: Faricimab, the first bispecific antibody designed for intraocular use, binds and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). Ang-2 promotes vascular destabilization, leakage, and inflammation, and drives pericyte apoptosis under hyperglycemic conditions. This exploratory analysis of the phase 2 BOULEVARD clinical trial of faricimab evaluated improvements in diabetic retinopathy (DR) in treatment-naïve patients with diabetic macular edema (DME).

METHODS: BOULEVARD (NCT02699450) was a phase 2, prospective, multicenter clinical trial that evaluated the efficacy and safety of faricimab in patients with center-involving DME. Anti-VEGF treatment-naïve patients were randomized 1:1:1 to intravitreal 1.5 mg faricimab, 6.0 mg faricimab, or 0.3 mg ranibizumab, dosed every 4 weeks for 20 weeks. The primary efficacy outcome measure was mean best-corrected visual acuity change from baseline at week 24 in treatment-naïve patients. This exploratory analysis evaluated the proportion of patients with DR improvement on the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (DRSS) from baseline at week 24 in anti-VEGF treatment-naïve (n = 168) patients.

RESULTS: At baseline, DR severity was well distributed across treatment arms, with the majority of BOULEVARD patients having nonproliferative DR (DRSS 43/47/53). At week 24, 27.7% and 38.6% of treatment-naïve patients receiving 1.5 mg and 6.0 mg faricimab, respectively, had a greater than or equal to 2-step DRSS improvement versus 12.2% with 0.3 mg ranibizumab.

CONCLUSIONS: Among treatment-naïve patients, a higher proportion of faricimab-treated patients achieved a greater than or equal to 2-step DR severity improvement at week 24 compared with ranibizumab-treated patients. This finding highlights a potential role of simultaneous Ang-2 and VEGF-A blockade in DME and DR, where the anti-inflammatory, anti-leakage, and vascular pericyte stabilization properties provided by faricimab may result in better outcomes for this group of patients.
TIME-2b Study of AKB-9778 on DRSS in Patients with Moderate to Severe Non Proliferative Diabetic Retinopathy

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PURPOSE: Assess the effect of 48-weeks of treatment with AKB-9778, a small molecule Tie2 activator, on DRSS in eyes with moderate to severe NPDR (the TIME-2b Study).

METHODS: Patients with DRSS grades of 43, 47, or 53 and no center-involved DME in at least one eye were randomized to receive either 15 mg AKB-9778 subcutaneously (sc) administered QD, 15 mg sc AKB-9778 BID, or sc placebo BID. DRSS was measured at 12-week intervals. The primary outcome was the percentage of patients who had a 2-step improvement in DRSS at week 48. Secondary endpoints included the percentage of patients who developed DME or PDR in the study eye over the course of the trial, effects on kidney function (measured by UACR) and effects on IOP.

RESULTS: There were 167 patients randomized in the study at 44 sites in the US. At week 48, 0% of eyes in the AKB-9778 QD group, 9.6% of eyes in the AKB-9778 BID group, and 3.8% of eyes in the placebo group improved their DRSS by 2-steps (BID vs. placebo p=0.270) and 23.1%, 19.2%, and 18.9% of eyes progressed to DME or PDR over the study period in the 3 treatment groups respectively (BID vs. Placebo p=0.886). Urine albumin was reduced by approximately 20% compared to baseline and IOP was reduced by 1.3 mmHg compared to placebo.

CONCLUSIONS: Although AKB-9778 15 mg BID demonstrated a positive effect on DRSS, the effect was smaller than anticipated and did not reach statistical significance. It is possible that a different dose form of AKB-9778, or use in combination with a VEGF-inhibitor, would increase the effect of Tie2 activation on diabetic retinopathy. Positive effects on kidney function and IOP were observed, replicating effects found in a previous 3-month study.
Determining the Long-term Progression of Untreated Atrophic Lesions in Age-related Macular Degeneration (AMD) and Stargardt Disease (STGD)

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PURPOSE: Clinical trials are limited by relatively short duration and loss to follow-up, making it virtually impossible for a single trial to determine the natural history of atrophic lesion enlargement over several decades. Thus, different studies have reported widely varying growth rates of atrophic lesions in untreated eyes with AMD or STGD. Herein we apply a novel mathematical approach to infer the decades-long natural history of atrophic lesion expansion.

METHODS: We searched 6 major literature databases and included 32 studies, from which we extracted study-level data regarding the atrophic lesion progression in untreated AMD (25 studies; 2942 eyes) and STGD (7 studies; 564 eyes) for > 6 months. Among them, we also extracted individual-level data of 228 unique eyes with STGD. We analyzed the lesion progression in both diseases using 3 models: (1) area linear model (ALM; lesion area enlarges linearly with time), (2) radius linear model (RLM; lesion radius expands linearly with time), and (3) area exponential model (AEM; lesion area changes exponentially with time). A horizontal translation factor was added to shift each dataset to correct for differences in subjects’ entry time into each study.

RESULTS: After correction for different entry times, the study-level data shows the effective radius of atrophy in AMD and STGD enlarges linearly over a course of 10 and 15 years, respectively but the growth rate is higher in AMD (0.16 mm/year (R2=0.99)) than STGD (0.10 mm/year (R2=0.99)). Individual-level data of STGD shows similar results with the effective radius of atrophic lesion enlcosenlinearly over 40 years at 0.09 mm/year (R2=0.93). The estimated age of onset of GA and STGD is 67.4±5.2 and 22.7±5.0 years, respectively.

CONCLUSIONS: Study- and individual-level data demonstrate that the effective radius of atrophic lesions in AMD and STGD enlarges linearly over the course of decades. Thus, the effective radius growth rate is a reliable outcome measure to monitor lesion progression in both diseases. The lesion progression rate in AMD is much faster than in STGD.
Progression of Stargardt Disease as Measured by Spectral-domain Optical Coherence Tomography (SD-OCT) in the ProgStar Study

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PURPOSE: To evaluate progression of loss in various retinal layers on SD-OCT in eyes of participants with Stargardt disease type 1 (STGD1) over 24 months follow-up in the prospective multicenter Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study.

METHODS: 259 patients with molecularly confirmed STGD1 (ABCA4 gene mutations) were enrolled from nine sites in the United States and Europe. SD-OCT scans were obtained at baseline from a 20° x 20° scan area centered on the fovea and repeated at months 6, 12 and 24 using the built-in follow-up mode. Retinal layers were manually segmented (with some limited automated assistance) to quantify outer segments (OS), inner segments (IS), outer nuclear layer (ONL), inner retina, and total retinal thickness. The mean thickness (MT) of individual layers and the intact area relative to the scanned area within the central subfield (CS; 0.5mm radius) and inner ring (IR; 0.5-1.5mm) were calculated by a custom software.

RESULTS: Based on these criteria, a subset of images from 355 eyes was included in this analysis. Eighty-six percent of the eyes, had a MT=0 for IS and OS layers in the CS, and the CS was excluded from further analysis as there could be no further progression in 86% of eyes with respect to these two layers. The estimated decline of total retinal thickness over 24 months was -3.1 (± 0.3) µm/year. There was a statistically significant change (p2/year for the ONL, -0.34 (±0.02) mm²/year for the IS and -0.27 (±0.01) mm²/year for the OS).

CONCLUSIONS: Significant loss could be detected in multiple outer retinal layers by SD-OCT over a 24 month period in patients with STGD1. Loss of thickness and/or intact area of IS, OS and ONL, may serve as potential endpoints for clinical trials that aim to slow disease progression.
Month 24 Results from the Scotopic Microperimetric Assessment of Rod Function in Stargardt Disease (SMART) Study

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PURPOSE: Sensitive, reproducible surrogate outcome measures are needed for clinical trials investigating the efficacy of emerging treatments for Stargardt disease with mutations in ABCA4 (STGD1).

METHODS: In STGD1 patients, photopic and scotopic macular sensitivity was tested over 24 months (6-monthly intervals) as the primary endpoint of a multicenter, prospective, observational study (NCT01977846).

RESULTS: A total of 118 eyes (118 patients) were enrolled, mean age of 34.5 (SD±15) years. Baseline mean sensitivity was 11.5 dB (±5.1) for photopic (pMP) and 11.3 dB (±5.3) for scotopic testing (sMP). The yearly change was -0.63 dB/yr (p <0.001) for pMP and -1.42 dB/yr (p< 0.001) for sMP. The count of normal test points decreased in both groups (pMP, -4.3 %; sMP, -10.9 %).

CONCLUSIONS: In STGD1, scotopic macular function declines significantly faster than photopic loss. Measuring rod function may be the earliest functional change in STGD1 and a useful outcome measure for clinical trials.
Rapid Symmetrical Progression of Retinal Degeneration in Patients with CLN2-associated Batten Disease

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PURPOSE: The lysosomal storage diseases neuronal ceroid lipofuscinosis (NCL) represent the most common progressive neurodegenerative disorders of childhood. Mutations in CLN2 gene lead to late infantile NCL (LINCL, Batten disease). Recently approved central nervous system (CNS) enzyme replacement therapy slows neurologic progression; however, the retinal degeneration continues unabated usually with total vision loss by age 7 years. In anticipation of CNS and retina-specific CLN2-gene therapy, our purposes were to: (1) Characterize the evolution of LINCL-associated retinopathy using the Weill Cornell Batten Scale (WCBS); (2) Determine the rate of retinal degeneration utilizing central macular thickness (CMT) measurements; (3) Correlate WCBS scores between fundus photography (photos) and OCT to identify optimal imaging modality for monitoring progression; (4) Determine correlation of progression rates between both eyes.

METHODS: Retrospective review of fundus photos, OCTs and records of pretreatment Batten patients enrolled in a prospective Phase 2a CNS gene-therapy trial at Weill Cornell. Images for both eyes were reviewed by three masked graders and categorized based on our previously validated WCBS criteria. OCT CMT and peripapillary retinal nerve fiber layer thickness were measured.

RESULTS: 84 eyes from 42 patients, 13 serially evaluated, were included. A progressive retinal degeneration, worsening with advancing age, was identified and readily categorized using WCBS. WCBS in left and right eyes were well correlated (OCT and Photo Pearson’s: 0.96 and 0.82, respectively). CMT correlated with left and right WCBS OCT scores (Pearson’s -0.83 and -0.92) and photo scores (-0.80 and -0.83). OCT thickness was negatively associated with advancing age and was symmetrical between the two eyes (Figure 1). On average, patients lost -31 um in CMT per year, with the greatest loss coming between months 48-72.

CONCLUSIONS: LINCL manifests as a symmetrical, progressive retinal degeneration, accelerating during a critical period at age 48-72 months. WCBS is valuable to stage the extent of retinal degeneration with OCT or fundus photos. These findings suggest that: (1) LINCL retinal degeneration could be targeted by ocular CLN2-gene therapy administered prior to the critical period; and (2) the effect of retina-specific CLN2-gene therapy can be monitored using the fellow eye as a control employing OCT and photo-based WCBS.
Suprachoroidal Injection of AAV8 Using Microneedles for Ocular Gene Delivery in the Nonhuman Primate

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PURPOSE: Retinal gene therapy using adeno-associated virus (AAV) is constrained by the mode of viral delivery. Intravitreal injections are limited by the internal limiting membrane (ILM) barrier, while subretinal injections are invasive, require vitreoretinal surgery, and have risks of retinal detachment. In this study, we evaluate suprachoroidal injection of AAV vectors as a novel mode of ocular gene delivery in rhesus macaques.

METHODS: Rhesus macaques between age 4-10 years were pre-screened for absence of pre-existing neutralizing antibodies (Nabs) against AAV8, which has known tropism for both photoreceptors and retinal pigment epithelium (RPE) when given subretinally. Five animals were given 7 x 1011-12 vg / 100mL AAV8 expressing enhanced green fluorescent protein (EGFP) under a cytomegalovirus (CMV) promoter to both eyes administered by transscleral microneedle injection to the subretinal or suprachoroidal space, or standard 30g needle for intravitreal delivery. EGFP expression was evaluated using in vivo scanning laser ophthalmoscopy (SLO) at 1 week, 1 month, 2 months, and 3 months, followed by ex vivo histological analysis at necropsy. Retinal anatomy was assessed by optical coherence tomography (OCT) and histology.

RESULTS: Suprachoroidal delivery of 7 x 1012 vg AAV8 resulted in EGFP expression that was diffuse, punctate, and confined to the periphery. By contrast, subretinal AAV8 produced focal expression near the injection site, while intravitreal AAV8 showed only limited peripapillary expression. EGFP expression after suprachoroidal delivery was detectable at 1 week, increased to maximal expression at 1 month, but decreased by 3 months after injection. Histological analysis showed that suprachoroidal AAV8 transduced RPE, but triggered inflammatory cellular infiltration likely due to the absence of immune privilege. Subretinal AAV8 provided robust EGFP expression in the outer nuclear layer and RPE, as well as some retinal ganglion neurons and axons.

CONCLUSIONS: Suprachoroidal delivery of AAV8 using microneedles may be a feasible mode of ocular gene delivery. The pattern of expression, transduced cell-types, and presence of choroidal inflammation may pose different advantages and hurdles compared to conventional subretinal AAV delivery for ocular gene therapy.
Surgical Technique with Intraoperative Optical Coherence Tomography for Subretinal Gene Therapy in Patients with Inherited Retinal Degenerations

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PURPOSE: To describe main hurdles and possible solutions for steps of gene therapy delivery to the subretinal space of patients with Inherited Retinal Degenerations.

METHODS: Based on surgical experience delivering viral vectors to the subretinal space in patients with choroideremia, achromatopsia, and retinitis pigmentosa as part of clinical trials and FDA-approved therapy, possible solutions to the challenging steps were developed by our team. Microscope-integrated Intraoperative Optical Coherence Tomography (MI-OCT) is utilized to confirm the correct tissue plane and minimize adverse events of subretinal therapy delivery.

RESULTS: Hyaloid removal, penetration of the retina with balanced salt solution (BSS) to open the potential subretinal space, and delivery of the viral vector to the target zone will be described. For machine injection, the syringes are connected to the viscous fluid injection port. For manual injection, extension tubing connects the vector-filled syringe to the needle. MI-OCT allows visualization of the BSS bleb and viral injection and detection of excessive foveal stretching.

CONCLUSIONS: Treatment of the target zones is achievable in most cases. Intraoperative complications include macular hole formation and peripheral retinal breaks. Utilization of this technique would likely be helpful to the retina surgeons involved in FDA-approved gene therapy administration and future clinical trials.
In Vitro Mutagenesis of RPE65 Protein for Verification of Mutational Pathogenicity Prior to Gene Therapy Surgery

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PURPOSE: To describe an in vitro mutagenesis assay to assess the pathogenicity of variants in RPE65. With the advent of gene therapy for patients with biallelic RPE65 mutations, clear-cut cases of RPE65 retinal dystrophy can now be treated. However, advances in next-generation sequencing have also resulted in more frequent detection of variants of uncertain significance (VUS), some of which would not benefit from gene therapy.

METHODS: This was a retrospective case series of four patients with Leber congenital amaurosis at two tertiary referral centers. Retinal dystrophy panels uncovered two VUS in these four patients. Site-directed mutagenesis was performed to incorporate these two variants into RPE65, and an in vitro assay of RPE65 function (all-trans retinol to 11-cis retinol) in HEK293-F cells was utilized.

RESULTS: Four patients with Leber congenital amaurosis had VUS in RPE65. Cases 1 and 2 were siblings with homozygous RPE65 VUS c.311G>T (p.G104V). Case 3 was a compound heterozygote with one known pathogenic variant c.1202_1203insCTGG and the VUS c.311G>T (p.G104V). Case 4 was also a compound heterozygote with one known pathogenic allele c.11+5G>A and the VUS c.1399C>T (p.P467S). In vitro mutagenesis of RPE65 revealed that the G104V and P467S RPE65 proteins were catalytically inactive (0% isomerase activity). Cases 1 and 2 were excluded from participation in a Phase 1 trial due to high adeno-associated virus capsid-neutralizing antibodies. Cases 3 (p.G104V) and 4 (p.P467S) underwent successful gene therapy surgery with voretigene neparvovec-rzyl, and their response to lower white light intensity and visual field increased less than 30 days after bilateral gene therapy surgery.

CONCLUSIONS: In patients with missense mutations in RPE65, functional assays of protein function can be performed to demonstrate the pathogenicity of variants in both compound heterozygous and homozygous cases. Given the potential risks of gene therapy surgery, in vitro RPE65 activity testing should be considered to avoid the possibility of treating a false genotype.
Four-year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation-associated Inherited Retinal Disease

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PURPOSE: To determine whether ambulatory navigation, light sensitivity, and visual field (VF) improvements 1 year after voretigene neparvovec-rzyl (VN) administration in subjects with biallelic RPE65 mutation-associated inherited retinal disease (IRD) are maintained at 4 years, and to review safety outcomes over the entire period.

METHODS: Subjects were randomized to either original intervention (OI:bilateral subretinal VN at baseline; n=20) or delayed intervention (DI:VN after 1 year; n=9). The primary endpoint was bilateral performance on the Multi-Luminance Mobility Test (MLMT) at 7 standard light levels as measured by a change score. Additional endpoints were full-field light sensitivity threshold (FST) testing, visual acuity (VA), and Goldmann kinetic VF (GVF). Safety outcomes included adverse event reporting, laboratory testing, and changes in physical and ophthalmic examinations.

RESULTS: For OI patients at Year 4 (n=20) and DI patients at Year 3 (n=8), the MLMT mean (SD) bilateral light level change score was 1.7 levels (1.1) and 2.4 levels (1.5), respectively. Subsequent to the 1-year outcome, a change of 1 light level occurred in 5 patients; but none were below the pre-treatment performance, and all maintained functional MLMT scores. Mean change in white light FST in log10 (cd.s/m2) averaged over both eyes was >1.90 (1.33) log10 at Year 4 for OI patients (n=19) and >2.91 (1.05) log10 at Year 3 for DI patients (n=8). Mean change in VA (Holladay Scale) averaged over both eyes (logMAR) was -0.00 (0.75) at Year 4 for OI subjects and -0.06 (0.24) at Year 3 for DI subjects (n=8). Mean change in GVF III4e sum total degrees averaged over both eyes was 197.7 (282.7) at Year 4 for OI subjects (n=18) and 157.9 (325.3) at Year 3 for DI subjects (n=8). The safety profile was consistent with vitrectomy and the subretinal injection procedure. One OI subject had a retinal detachment 4 years after treatment. There were no deleterious immune responses.

CONCLUSIONS: Improvements in ambulatory navigation, light sensitivity and VF are maintained for at least 4 years after VN administration in OI subjects. Improvements in DI subjects were consistent with those observed in OI subjects. The safety profile of VN is consistent with the administration procedure.
Gene Therapy for X-linked Retinitis Pigmentosa Caused by Mutations in RPGR

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PURPOSE: Retinitis pigmentosa (RP) leads to severe sight loss in young people. X-linked RP is caused by mutations in the RPGR gene which has a highly mutagenic purine rich distal region that undergoes alternative splicing. We developed a codon-optimised version of RPGR in order to stabilise it so that it could be delivered successfully by gene therapy in affected patients.

METHODS: The codon optimised RPGR transgene was driven by a rhodopsin kinase promoter using a bovine polyA signal. The construct was packaged into an AAV serotype 8 vector and administered in 18 patients in a Phase I/II dose escalation clinical trial, involving two centers in the UK and one in the US. The trial was sponsored by Nightstar Therapeutics (Clinicaltrials.gov: NCT03116113). All patients received a subretinal injection of up to 0.1 ml vector suspension targeting the fovea.

RESULTS: Part I enrolment has been completed and 1-month assessments are available on 18 male subjects (mean age 32.3±9.4 years). AAV8-RPGR was shown to be safe, with no occurrence of serious AEs or DLTs. In this ongoing study, 45 treatment-emergent events (TEAEs) have occurred in 15 subjects: 11 non-ocular and 34 ocular, 30 of which occurred in the study eye. No subjects have been withdrawn due to a TEAE. Despite undergoing macular detachment, mean visual acuity recovered from 57.2±4.3 letters at baseline to 57.3±3.8 by month 1. Retinal sensitivity however improved (defined by gain of at least 7 dB in at least 5 loci) in 6 of the 18 treated eyes versus 1 untreated eye at Month 1. The largest gain was seen in a cohort 4 patient who went from 0.5 dB in his treated eye at baseline (untreated eye 0.7 dB) to 3.4 dB at month 1 (untreated eye 0.5 dB) and 6.6 dB at month 3 (untreated eye 0.5 dB). The patients with microperimetry gains also reported subjective visual field improvements in their treated eyes.

CONCLUSIONS: With a single dose of AAV8-RPGR, improvements in retinal sensitivity have been observed in XLRP patients. This unexpected finding may relate to improved cone function by rescuing ‘dormant’ photoreceptors with regeneration of outer retinal structures following successful delivery of the full length RPGR protein.
Safety and Efficacy of rAAVtYF-CB-hRS1 Intravitreal Gene Therapy for X-linked Retinoschisis — One Year Results

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PURPOSE: X-linked retinoschisis (XLRS) is caused by mutations in the RS1 gene and leads to a vitreoretinopathy characterized by macular and peripheral schisis, synaptic defects, and a propensity for retinal detachments. rAAVtYF-CB-hRS1 is a vector optimized for intravitreal injection and to mediate gene augmentation therapy.

METHODS: 27 subjects with genetically confirmed XLRS were enrolled in a Phase I/II clinical trial at 7 sites enrolled at least one patient. Patients were divided into cohorts and received ascending doses of rAAVtYF-CB-hRS1 ranging from 1 x 10^{11}vg/eye to 6 x 10^{11}vg/eye. Safety and efficacy were monitored with ETDRS visual acuity, static and kinetic visual fields, electroretinograms, and optical coherence tomography (OCT).

RESULTS: Subjects tolerated the procedure well. Subjects demonstrated mild to moderate intraocular inflammation that typically resolved on its own or with topical or oral steroids. Three subjects required treatment with methotrexate due to long-term need for steroids or recurrence of inflammation. Measurements of cyst volume by OCT and retinal sensitivity by visual fields were variable and did not detect convincing evidence of efficacy. ERG results demonstrated safety but did not show improvement in the B:A-wave ratio.

CONCLUSIONS: Treatment with rAAVtYF-CB-hRS1 overall was safe and well tolerated but did not demonstrate convincing evidence of efficacy at one year. Patients will be followed for continued evidence of safety and efficacy.
Patient-reported Outcomes in Retinal Degenerations

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PURPOSE: The lack of inherited retinal degeneration (IRD) validated patient-reported outcome (PRO) measures for assessing efficacy of therapeutic trials have led to reporting of anecdotal reports of effectiveness by investigators. The Michigan Retinal Degeneration Questionnaire follows the FDA guidelines in development of a PRO for this purpose.

METHODS: Adult patients with a confirmed diagnosis of either autoimmune retinopathy, cone dystrophy, cone-rod degeneration, macular dystrophy, or rod-cone dystrophy were enrolled in this study at the University of Michigan. Through a process of in-depth interviews, and coding of subject responses in Atlas.ti software led to revelation of scenarios, adaptations and behavior modifications by subjects suffering different aspects of visual dysfunction. Items were generated and after cognitive interviewing and pilot testing, the items for psychometric analysis were created.

RESULTS: A total of 61 patients were interviewed, ages ranging from 22–72 years old. Coded items were analyzed for frequency of occurrence and related themes, then organized into common domains. Within each domain, PRO questions were drafted to address target functional limitations or adaptations experienced by patients.

CONCLUSIONS: An IRD specific PRO (Michigan Retinal Degeneration Questionnaire) has been created and tested in the target retinal degeneration population. The items have demonstrated content validity and will undergo psychometric analysis.
Computer Assisted Immersive Visual Rehabilitation in Retinal Prosthesis Recipients

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PURPOSE: The field of retinal and visual cortex prostheses is expanding. However, the best approach to training and assessing functional benefit of post-operative vision has not been established. A single-center prospective interventional case series was completed to evaluate the feasibility and effectiveness of using the virtual reality Computer Assisted Rehabilitation ENvironment (CAREN) system as a visual rehabilitation tool in Argus II patients.

METHODS: Four Argus II retinal prosthesis recipients (3 male and 1 female) participated in eight visual rehabilitation sessions utilizing the CAREN system (2x/week for 4 weeks). Baseline and post-intervention assessments consisted of visual function, mobility, and balance tests.

RESULTS: All patients successfully completed training on the CAREN system. Walking speed, while the Argus II device was active, increased from baseline to post-intervention on flat and undulating surfaces and while localizing objects by 20, 10, and 18 percent, respectively. A 26 percent improvement in time to complete the Timed Up and Go Test was observed.

CONCLUSIONS: Novel methods of visual rehabilitation for retinal prostheses recipients, such the CAREN system, are feasible and may result in improved ability to use the Argus II while performing functional tasks. Immersive technology may provide a solution for the standardization of effective rehabilitation approaches to augment retinal prosthesis performance.
PDE 5/6 Treatment of Choroidal Ischemia in Macular Degeneration and Dystrophy

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PURPOSE: We have shown that dry age-related macular degeneration (AMD) is significantly related to choroidal ischemia. Additionally, we have shown that sildenafil increases choroidal perfusion and a small off-label series of patients on long-term sildenafil showed positive visual effects and no long-term adverse effects. This study is now 4 to 5 years of systemic sildenafil to treat dry age-related macular degeneration and macular dystrophies. This series demonstrates the preservation of photoreceptor function can be enhanced by PDE5/6 inhibition with sildenafil.

METHODS: In an IRB (Institutional Review Board) approved study, patients with dry AMD and macular degenerations/dystrophies are treated with systemic sildenafil, 20-40 mg twice daily. Vision and OCT mapping of the macula was performed every 2 months.

RESULTS: 15 patients treated for up to 5 years with sildenafil maintained photoreceptor function as long as Bruch’s membrane did not thicken and reduce the effect of increased oxygenation. Treatment of central serous retinopathy showed early and positive treatment effects. Macular dystrophy of age-related and Best’s disease dystrophy have maintained better vision than typical of these diseases. Early results with PED (pigment epithelial detachment) elevations show evidence of sub PED-absorption on OCT, and maintenance of vision.

CONCLUSIONS: Systemic PDE-5/6 inhibitors such as sildenafil has a positive benefit in treating dry age-related macular degeneration as well as other macular degeneration and dystrophies.
Multimodal Imaging in Transthyretine Amyloidosis

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PURPOSE: Vitreous findings in patients with transthyretin (TTR) amyloidosis are well-described. We wished to examine the retinal and choroidal findings in this disease.

METHODS: Six unrelated patients (12 eyes) with known transthyretin amyloidosis-5 with familial and one with wild type underwent multimodal imaging using fundus photography, OCT, fluorescein and ICG.

RESULTS: The median age was 55 years (range 41–67 years). There were 2 males and 5 females. All but the WT had vitreous involvement and 4 had undergone vitrectomies. All had ICG hyperfluorescence with 3 (6 eyes) having extremely marked involvement. Three had inner retinal strands extending into the vitreous cavity from the internal limiting membrane and one patient (two eyes) showed that the strands accumulated over time.

CONCLUSIONS: Besides the vitreous findings, retinal involvement by OCT and choroidal involvement by ICG is very common in TTR amyloidosis. It also appears to increase over time. Multimodal imaging can be biomarkers for treatment of TTR amyloidosis.
Use of a Conjoint Analysis Survey to Understand Patient Preferences in Potential Ocular Stem Cell Therapies

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**PURPOSE:** There has been significant interest in the potential of stem-cell-based transplants to restore vision, but there is little understanding of patient perspectives. This survey aimed to assess patient preferences given one potential unique risk associated with cell-based therapies: that immature cells introduced into the eye could form cancer.

**METHODS:** A convenience sample of patients at an academic medical center were approached to complete a survey, which was read aloud, consisting of a discrete choice experiment and the National Eye Institute Visual Function Questionnaire-9 (VFQ-9). The discrete choice experiment consisted of 10 hypothetical scenario questions asking patients to choose between 2 options. Each option had a level of visual acuity (20/20, 20/40, 20/70, 20/100, 20/200) with a description of functional vision at that level, and a level of eye cancer risk (1%, 5%, 20%). Demographics and clinical characteristics were abstracted from medical records. A conditional logit model was used to determine part-worth utility estimates.

**RESULTS:** 164/222 patients approached elected to participate (74% response rate). 43% were recruited from retina clinic, 15% from retinal dystrophy clinic, 16% from glaucoma clinic, and 26% from comprehensive clinic. Mean BCVA was logMAR 0.3 (±0.6 SD; Snellen equivalent 20/40). 35% had at least 1 eye with BCVA worse than 20/40, and 15% had at least 1 eye with BCVA worse than 20/200. 53% had previous eye surgery, 20% had previous intravitreal injection, and 27% had previous laser procedure. 10% had history of cancer. The average VFQ-9 score was 72.4 (±19.7 SD). The part-worth estimates (SE) of utility for visual acuity were 0 for 20/200, 0.33 (0.12) for 20/100, 1.58 (0.15) for 20/70, 2.26 (0.18) for 20/40, and 2.33 (0.22) for 20/20. The part-worth estimates of utility for risk of cancer were 0 for 20%, 0.89 (0.11) for 5%, and 0.70 (0.15) for 1%. The relative importance of visual acuity was 71%, and the relative importance of risk of cancer was 29%.

**CONCLUSIONS:** In this survey using conjoint analysis, patients presented with hypothetical scenarios placed significant value on vision when asked to weigh potential benefit of vision against potential risk of cancer.
**PURPOSE:** Sub-cellular changes in the vitreous are not well understood. Vitreous microparticles are small, 0.5-2µm-sized vesicles surrounded by a lipid bilayer thought to play a role in disease pathogenesis in diverse vitreoretinal disorders. We evaluated the differences in these microparticles in diabetic eyes compared to non-diabetic eyes undergoing vitrectomy.

**METHODS:** This is an un-masked cross-sectional series of 34 eyes that have undergone vitrectomy for various diseases. Inclusion criteria included patients that did not undergo a prior vitrectomy. Vitreous specimens were collected at the beginning of each case and frozen in a -80°C freezer. The specimens were later processed to evaluate expression of surface markers on vitreous microparticles. Markers for membrane integrity (DAPI), apoptosis (Annexin-V), endothelial-cell origin (V-Cadherin / CD144), and hematopoetic lineage (CD45) were included. A BD LSR II flow cytometer was used for analysis and standardized sub-micron-sized beads were used for size comparison. Mann-Whitney-U Test was used to compare groups.

**RESULTS:** Thirty-four specimens underwent flow cytometric evaluation. Greater levels of Annexin-V were found in specimens in which blood had entered the vitreous (n=11) compared to those without blood (n=23), (45.4% ± 32.6 S.D. vs. 21.4% ± 24.6, p=0.023). The endothelial cell marker V-cadherin (CD144) was expressed at a greater level in blood-containing vitreous (n=6) compared to vitreous without blood (n=13) (21.0% ± 23.1 vs. 0.8% ± 1.68, p=0.009). When evaluating vitreous hemorrhage in non-diabetic patients, however, the level of Annexin-V expression was no longer different compared to other disease processes (46.5% ± 37.2, n=5 vs. 18.3% ± 24.6, n=14, p=0.070).

**CONCLUSIONS:** An increased percentage of apoptotic-markers were detected on vitreous microparticles in patients undergoing vitrectomy for vitreous hemorrhage. When evaluating vitreous hemorrhage in non-diabetic patients, the apoptotic signal is not significant. Increased apoptotic signals within the vitreous may contribute to a diseased-vitreous state which in turn may contribute to the progression of diabetic retinopathy and the pathogenesis of tractional detachment. Vitrectomy in diabetics, and improvement in visual outcomes, may be related to the removal of a diseased, pro-apoptotic vitreous, although further investigation is warranted in order to identify the molecular characteristics of microparticles that regulate disease.
Optical coherence tomography (OCT) is an example of a biomedical technology that has been translated from bench to bedside. OCT originated in ultrafast optics, interferometry and optical communications. It can generate micron resolution, cross-sectional and three-dimensional images of subsurface structure in biological tissues or materials by measuring the magnitude and time delay of backscattered light. OCT enables “optical biopsy,” visualizing pathology in situ and in real time without excision or histological processing. The translation of OCT from fundamental research to clinical practice would not have been possible without a complex ecosystem with interaction among physics, engineering, and clinical medicine; government funding of fundamental and clinical research; collaborative and competitive research in the academic sector; entrepreneurship and industry; addressing clinical needs; harnessing the innovation that occurs at the boundaries of disciplines; and economic and societal impact.

OCT has had its largest impact in ophthalmology where there are an estimated 20-30 million imaging procedures every year. The recent development of OCT angiography (OCTA) enables depth resolved visualization of microvasculature using motion contrast from flowing blood. Swept source OCT (SS-OCT) can achieve faster imaging speeds than spectral domain OCT (SD-OCT) as well as image at longer 1050nm wavelengths which have reduced attenuation. Increased imaging speed is especially important for OCTA because it requires repeated scanning of the same retinal position to detect blood flow. High speeds enable wider fields of view as well as advanced OCTA protocols which use large numbers of repeated scans and assess blood cell motion using different interscan times. High speed also enables volumetric Doppler techniques which can measure total retinal blood flow by sampling the cardiac cycle.

This presentation reviews the history of OCT, its translation from fundamental research to clinical practice, as well as applications in retinal imaging research.
Optical Coherence Tomography Angiography (OCTA) Quality in DRCR Retina Network Multicenter Clinical Studies

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DRCR Retina Network

PURPOSE: Good quality optical coherence tomography angiography (OCTA) data are critical to quantify potentially meaningful vascular biomarkers in diabetic retinopathy. This study assessed the quality of OCTA data taken by certified technicians in the DRCR Retina Network.

METHODS: OCTA images obtained from two DRCR Retina Network studies (Protocol AA [N = 4067 scans] and Protocol W [N = 1632 scans]) were analyzed by trained graders at the OHSU Casey Reading Center. OCTA systems were used to capture macula (3x3 mm and 6x6 mm), and optic nerve scans. Determination of good versus poor image quality was performed using an empiric signal strength index (SSI) threshold of 55 for one and 7 for another, and whether artifacts (excess motion, media opacities, beam defocus, incorrect axial position, other artifacts) were present.

RESULTS: A total of 5699 images from 729 eyes were included. 3464 (61%) images were of good quality. Good quality was demonstrated in 62% (N = 1059 of 1717) of 3x3mm scans, 62% (N = 1272 of 2061) of 6x6mm scans, and 59% (N = 1133 of 1921) of optic nerve scans. Among the 4845 images captured on the Optovue, (61%) passed quality control. Reasons for poor quality included low SSI (66%), followed by excess motion (24%). Of the 854 images captured using Zeiss, 62% were of good quality. Excess motion accounted for 48% of scan failures, while media opacity and low SSI accounted for 22% and 17%, respectively. Study participants with good quality scans were likely to be younger (60±13 vs. 65±13 years, p<0.001) and have better visual acuity (ETDRS letter score 86.6±6.4 vs. 81.9±10.1, p<0.001).

CONCLUSIONS: Obtaining OCTA images of sufficient quality for precise quantification of non-perfused areas and vascular density has been a challenge within DRCR Retina Network multicenter studies, despite the certification and training of Network imagers, and ongoing feedback to sites. Image acquisition factors that may contribute to scan quality, including device hardware and software, imager training, subject compliance, and real-time operator feedback should be explored to help improve pass rates in future multicenter clinical trials.
Microaneurysm Imaging in Diabetic Retinopathy using Multiple En Face Optical Coherence Tomography Angiography Image Averaging

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PURPOSE: In diabetic retinopathy (DR), optical coherence tomography angiography (OCTA) could not image some fluorescein angiography (FA)-detected microaneurysms. We investigated if multiple image averaging could enhance its microaneurysm detection capability in DR.

METHODS: This prospective- and cross-sectional observational study included 62 eyes from 31 patients with DR who underwent FA, and 3 x 3 mm fovea-centered OCTA images were obtained using two devices (RTVue XR Avanti: Optovue Inc. and OCT HS-100: Canon Inc.). OCTA imaging (HS-100) was performed ten consecutive times. Microaneurysm detection capability was compared among five OCTA images (single image, 3x, 5x, and 10x averaged images, and single scan image with RTVue XR Avanti). The correlation between microaneurysm clinical characteristics or morphology, and extent of image averaging required for OCTA detection was examined.

RESULTS: A total of 415 microaneurysms could be analyzed in 31 eyes from 25 cases. Microaneurysms detected on single image, 3x, 5x, 10x averaged OCTA images numbered 144 (34.7%), 227 (54.7%), 285 (68.7%), 306 (73.7%), respectively. Microaneurysms detection capabilities significantly increased with increased image averaging. Microaneurysm detection on OCTA was not correlated with retinal thickness, FA leakiness and IA detection, nor the number of averaged images, whereas there was significant correlation between microaneurysm morphology and microaneurysm visibility by image averaging process for four morphologies, particular the focal bulge types (P < 0.01).

CONCLUSIONS: In DR, multiple image averaging is useful for increasing OCTA microaneurysm detection capability, especially for focal bulge type.
Nonperfusion and Reperfusion Following Anti-VEGF Treatment Using Reference-based Optical Coherence Tomography Angiography Perfusion Density Mapping

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PURPOSE: Assessing non-perfusion and re-perfusion following anti-VEGF treatment can be challenging given normal interscan variability in OCT angiography. Using a novel reference-based perfusion density mapping algorithm, acute and chronic changes in a variety of retinopathies were studied.

METHODS: 38 patients with retinopathy (20 diabetic (DR), 9 vein occlusion (RVO), 5 macular degeneration (AMD), 2 sickle cell (SCR), 2 radiation (RR), and 20 controls were imaged using a SD OCT-A (Avanti RTVue-XR; Optovue). Acute perfusion changes were assessed in 19 patients before and immediately after intravitreal injections, intermediate changes were evaluated in 10 patients at 2 weeks and 4 weeks following anti-VEGF injection, and chronic perfusion changes were assessed in 9 patients for follow up intervals ranging from 6 months to 4 years. Image registration was performed for each pair of OCT-As using ImageJ and a novel MATLAB protocol measured and mapped perfusion density change. Non-perfusion and re-perfusion areas in patients were defined as difference in perfusion density between scans with lower than 0.1% or higher than 99.9% of the normal distribution, based on the within-subject variability in controls, respectively. Capillary segments with intermittent flow and changes in microaneurysms were also recorded at each visit.

RESULTS: In patients with acute post-injection perfusion changes, highest acute non-perfusion and re-perfusion area changes were noted in patients with RR and RVO, followed by DR and AMD. In eyes followed over 1 month, average perfusion densities were similar between pre-injection, 2 weeks and 4 weeks after injection, but re-perfusion area gradually increased over 4 weeks while non-perfusion increased then partially resolved over the same interval. Corresponding capillary segments were seen fill, disappear or fluctuate in sequential scans, while microaneurysms typically regressed following injection. In patients followed for chronic perfusion changes, eyes with RVO showed the greatest progression of non-perfusion, while eyes with DR demonstrated an interesting mix of re-perfusion with non-perfusion.

CONCLUSIONS: Reference-based OCTA perfusion density mapping facilitates identification of non-perfusion and re-perfusion and enables quantitative analysis of treatment effects and disease progression. Larger studies with longer followup will be needed to confirm the value of this approach studying novel therapies.
Measurable Aspects of the Retinal Neurovascular Unit in Diabetes, Glaucoma and Controls

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PURPOSE: To study structural and angiographic optical coherence tomography (OCT) data of the macula from controls, diabetics, and those with glaucoma to evaluate neurovascular and structural relationships.

METHODS: This is a retrospective study of 89 eyes from 49 patients in a community-based retinal referral practice with diabetes, glaucoma, and normal controls. The patients were evaluated with OCT to include retinal nerve fiber layer (RNFL) thickness measurement and ganglion cell layer (GCL) volume determination. The vascular density of the radial peripapillary capillary network and the vascular plexuses in the macula were evaluated with OCT angiography. The main outcome measures were the data obtained per disease state and the interrelationships the data displayed.

RESULTS: The mean GCL volumes were significantly lower than the Control Group (1.06 mm³) in both the Diabetic (0.97 mm³, P=.016) and Glaucoma groups (0.87 mm³, P<.001). The difference between the Diabetic and Glaucoma groups was not significant (P=.052). The mean superficial plexus vascular density was greater in the Control group (6.56% coverage ratio) than the Diabetic group (5.83%, P=.002,) and the Glaucoma group (5.17%, P<.001). The deep capillary plexus had a greater coverage ratio in the Controls as compared with both the Diabetic (P=.001) and Glaucoma (P<.001) groups. The RNFL was not significantly different in the Diabetic group (91.9 µm) as compared with the Control group (98.8 µm, P=.11), but both were greater than the Glaucoma group (mean 76.2 µm, P=.021 and P<.001, respectively). Both the Diabetic (P = .018) and Glaucoma groups (P<.001) had lower radial peripapillary network density values as compared with the Control group.

CONCLUSIONS: While there are important differences in disease pathogenesis differ between diabetes and glaucoma, they share certain similarities in the structural and angiographic abnormalities eventually produced. This suggests that in addition to canonical pathways of disease, a component of both could represent neurodegenerative disease, offering the possibility for the development of new treatments that may be applicable to both.
Advanced Technical Development in Diagnostic B-Scan Ultrasound

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**Purpose:** Describe and demonstrate new, multi-element, annular array ultrasound device permitting “live”, moveable focus to improve image quality and diagnostic interpretation in localized areas of interest within the globe and orbit.

**Methods:** Multiple element, annular array, probes (12, 18 MHz) replace fixed single element transducers permitting “live” moveable, beam focus for vitreous, vitreoretinal and orbital areas during real-time diagnostic B-Scan ultrasound.

**Results:** Image quality is markedly improved especially at localized sites of diagnostic interest by “live” beam focus movement during Real Time scanning. These improvements aid in ultrasonic interpretations.

**Conclusions:** New annular array device with moveable beam focus markedly improves image quality during diagnostic B-Scan especially in localized areas of interest. Examples will be presented.
Longitudinal Ellipsoid Zone Mapping on Spectral Domain Optical Coherence Tomography in Eyes with Hydroxychloroquine Use to Evaluate for Subclinical Outer Retinal Alterations

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PURPOSE: Loss of ellipsoid zone (EZ) integrity on optical coherence tomography (OCT) is a hallmark feature of hydroxychloroquine (HCQ) toxicity but early alterations can be subtle. The purpose of this study is to evaluate longitudinal changes on OCT that may precede clinical HCQ toxicity using a semi-automated EZ mapping platform.

METHODS: Retrospective image analysis of patients on HCQ who had OCTs at two time points. Patients with concurrent macular disease were excluded. The two macular cube scans were exported and analyzed in the EZ mapping platform. Seven outer retinal parameters were utilized to evaluate for subtle alterations over time: central subfield EZ-RPE thickness/volume, mean parafoveal (central 2-mm) EZ-RPE thickness/volume, EZ-RPE volume, en face percentage of EZ total attenuation (EZ thickness = 0µm), en face EZ attenuation (EZ thickness < 20µm).

RESULTS: Four hundred one eyes of 401 subjects were included. Mean age was 57.6±0.2 years, mean daily HCQ dose was 367.1±72.6 mg, mean HCQ dose based on actual body weight was 4.9±1.8 mg/kg, and mean HCQ dose based on ideal body weight was 6.6±1.6 mg/kg. At time of the first OCT, mean duration of HCQ use was 5.8±3.9 years and cumulative HCQ dose was 0.77±0.56 kg. Mean time between the two OCT time points was 3.1±0.9 years. There was a significant increase in en face EZ attenuation from the first OCT (4.6±18.2%) to the second OCT (5.8±19.1%; p=0.02). The increase in EZ loss significantly correlated with age (p=0.008), daily dose (p=0.01), and dose based on actual body weight (p=0.04) and on ideal body weight (p=0.004), but not drug duration, cumulative dose, or time between OCTs (all p>0.14). There was no significant longitudinal change in en face EZ total attenuation, central subfield EZ-RPE thickness/volume, parafoveal (central 2-mm) EZ-RPE thickness/volumes or EZ-RPE volume (all p>0.09).

CONCLUSIONS: Longitudinal OCT assessment revealed a significant increase in EZ attenuation which correlated with age, daily dose, and dose based on actual as well as ideal body weight. Additional research is needed to further validate these subclinical progressive changes and their impact on identification of HCQ toxicity.
Comparing Optical Coherence Tomography Angiography Density Measurements of Eyes With and Without Radiation Retinopathy after I-125 Plaque Brachytherapy and Non-irradiated Fellow Eyes

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PURPOSE: To determine if commercial OCTA measurements can provide quantitative markers for detection of radiation retinopathy (RR) s/p I-125 plaque brachytherapy for choroidal melanoma.

METHODS: Retrospective review of 6x6mm OCTA images of nonirradiated fellow eyes (group 1, 28 eyes), eyes without RR s/p I-125 plaque brachytherapy (group 2, 22 eyes), eyes with RR s/p I-125 plaque brachytherapy (group 3, 13 eyes). We used automated OCTA software determinations of FAZ size, perimeter size, and 27 capillary density measurements (nine ETDRS grid regions of each segmentation: full-thickness inner retina, superficial plexus, deep plexus).

RESULTS: Average years since irradiation was 1.9 in group 2, 3.7 in group 3. FAZ size was 1.2mm in group 3 compared with 0.2mm in group 1 and 0.3mm in group 2 (both p<0.001). Perimeter size was also significantly different between groups 1 and 3 (p<0.001), and groups 2 and 3 (p=0.047). Capillary density was statistically significantly reduced in group 3 compared with group 1 in all 27 regions. Group 2 had decreased superficial plexus capillary density compared with group 1 of the entire and most parafoveal ETDRS regions. The deep plexus and full thickness density measurements were not a significantly different between groups 1 and 2. Finally, group 3 had statistically significantly reduced capillary density compared with group 2 in 17/27 (63%) ETDRS grid regions.

CONCLUSIONS: Quantitative OCTA may aid in early detection of RR particularly using FAZ and perimeter sizes and superficial capillary plexus density measurements.
Artificial Intelligence Screening for Diabetic Retinopathy: Analysis from a Pivotal Multi-center Prospective Clinical Trial

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PURPOSE: To evaluate the sensitivity and specificity of an artificial intelligence (AI) system for diabetic retinopathy (DR) screening.

METHODS: In this prospective study (NCT03112005) at 15 centers, diabetic patients were consecutively enrolled initially and then preferentially based on enrichment criteria. Study subjects underwent undilated 2-field, 45 degrees, fundus photography (macula centered and disk centered images) using the EyeArt AI eye screening system and then dilated 4-wide field stereoscopic fundus photography. The EyeArt system provided automatic eye level results regarding referable DR (rDR), defined as 1. moderate non-proliferative DR (NPDR) or higher using the International Clinical DR severity scale or 2. clinically significant diabetic macular edema (CSDME). If the EyeArt system could not grade the initial images, the 2-field photos were repeated after dilation. The dilated wide field photographs were used as the reference standard and were graded by Wisconsin Fundus Photograph Reading Center graders, who used the Early Treatment Diabetic Retinopathy Study (ETDRS) Severity Scale. The rDR detection rates of the automated EyeArt system were compared with the reference standard (with variance adjustment to account for the correlation between eyes of the same patient).

RESULTS: Of 1822 enrolled eyes (911 subjects), 1718 had gradable 4-wide field standard images and 1674 had both gradable 2-field and 4-field images. Of these 1674 eyes, 310 eyes were positive for rDR (281 moderate NPDR, 4 severe NPDR, 24 proliferative DR, 1 questionable DR; 83 CSDME) and 1364 eyes were negative for rDR (1108 no apparent DR and 256 mild NPDR). The sensitivity of the EyeArt system using only undilated images was 95.5% [95% CI: 92.4% - 98.5%], specificity was 86.0% [95% CI: 83.7% - 88.4%] and the gradability rate was 87.5% [95% CI: 85.4% - 89.7%]. Dilated 2-field photos were required for 214 eyes; 170 eyes were gradable and 44 (2.6% of 1718) remained ungradable per the EyeArt system. With this dilate-if-needed photography protocol, the gradability rate of the EyeArt system improved to 97.4% [95% CI: 96.4% - 98.5%]; sensitivity was 95.5% [95% CI: 92.6% - 98.4%], and specificity was 86.5% [95% CI: 84.3% - 88.7%]. Of the 14 false negative rDR eyes, all had ETDRS levels below 43 moderate NPDR and none had DME. Of the 184 false positive for rDR, 119 had mild DR and 20 had non-DR conditions (AMD, vein occlusion, ERM, vitreous opacities, optic disc edema, atrophy, scar and nevus).

CONCLUSIONS: This AI system compared favorably with the clinical reference standard and has high enough sensitivity and specificity for the detection of referable DR in diabetics.
Deep Learning Systems for Detecting Age-related Macular Degeneration: Comparison of Technical Architectures, Image Quality and Patients’ Characteristics with Implications on Clinical Deployment

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PURPOSE: Most deep learning systems (DLSs) are built and validated from an ethnically homogenous patient population. To simulate physicians examining across different races and ethnicities, we aimed to compare the diagnostic performance of two DLSs that were developed independently for detection of referable age-related macular degeneration (AMD).

METHODS: A total of 167,790 de-identified, macula-centered retinal images acquired from Age-related Eye Disease Study (AREDS, 66,943 images, predominantly white) and Singapore Eye Research Institute (SERI, 72,610 images, predominantly Asian) were used to build DLS-A and DLS-B, respectively, with reference to expert human graders from reading centers. A total of 2400 images (1800 discordant and 600 concordant images) were further selected for quantitative and qualitative analysis by 2 retinal specialists, using the modified National Health and Nutrition Examination Survey (NHNES) grading forms.

RESULTS: For DLS-A, the AUCs (95% CI) for AREDS and SERI were 0.947 (0.945-0.949) and 0.891 (0.883-0.898), whereas for DLS-B, they were 0.879 (0.876-0.882) and 0.956 (0.952-0.959), respectively. The presence of dust, haze, and poor focus (both datasets), presence of an artefactual arc (AREDS) from flash at iris-pupil border, and suboptimal field definition (SERI) were primary causes affecting both DLSs performances. When both DLS A&B had disagreement with the expert graders, both retinal specialists also showed high disagreement rates with the expert graders (>74%). The disagreement rates were the lowest when both DLSs agreed upon on the diagnosis in AREDS and SERI. In the multi-variate analysis, DLS-A performance was affected by the presence of dust for false negatives and positives in AREDS dataset, and the presence of dust, haze, field definition and illumination in SERI dataset. DLS B was affected similarly by presence dust in AREDS dataset, and presence of arc, haze and field definition in SERI dataset.

CONCLUSIONS: DLSs with different pre-processing algorithms are susceptible to different image qualities and retinal lesions, depending on the area of interest. Suboptimal image quality secondary to dust, haze and poor focus could potentially affect the DLSs performances, irrespective of the pre-processing methods. It is, therefore, critical to consider all these factors in developing and clinically translating DLSs for AMD detection within the clinical settings.
Machine Learning Analysis of SD-OCT Features Predicting Short-term Progression of Intermediate Age-related Macular Degeneration (AMD) to Geographic Atrophy (GA)

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**PURPOSE:** The objective of this study was to identify OCT features that can be used in machine/deep learning analyses and can provide guidance to patient selection for trials targeting the treatment of dry AMD and prevention of atrophy. We propose a classification of intermediate AMD (iAMD) based on specific Spectral-Domain optical coherence tomography (SDOCT) features and their risk for short-term (1-4 years) progression to geographic atrophy (GA).

**METHODS:** Qualitative and quantitative multimodal variables from the Age-Related Eye Disease Study 2 (AREDS2) Ancillary SDOCT study database were derived at each visit over 5 years. We analyzed imaging data from patients with intermediate age-related macular degeneration (iAMD) (n = 316) with adequate SDOCT imaging for repeated measures. Based on statistical techniques developed for the Framingham Heart Study, a pooled database was generated using an algorithm that selected only person-years without GA on color fundus photography or SDOCT at baseline. The analysis employed machine learning to generate classification trees.

**RESULTS:** Eyes were stratified based on retinal and subretinal OCT features (hyperreflective foci axial distance score, photoreceptor loss, neurosensory retina volume, RPE drusen complex volume and abnormal thinning volume, drusen volume, choroidal thickness, presence of subretinal drusenoid deposits and high reflective drusen), and age by the risk of GA development as rare, low, low-intermediate, intermediate, and high risk in 1, 2, 3, and 4 years.

**CONCLUSIONS:** We propose a risk-stratified subgrouping of iAMD based on OCT-derived drusen characteristics, retinal pathology and age, for progression to OCT-determined GA. The composite early endpoints may be used as exclusion or inclusion criteria for future clinical studies focused on prevention of GA progression.
Quantitative Analysis of Vascular Severity in Patients Diagnosed with Plus Disease in the Imaging and Informatics in Retinopathy of Prematurity Study

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PURPOSE: To analyze differences in ROP severity in patients diagnosed with plus disease and requiring treatment by examiner.

METHODS: Fundus photographs of all babies undergoing ROP screening were obtained as part of the Imaging and Informatics in ROP (i-ROP) cohort study. An ROP severity score (1-9) was generated for each image using methods previously published. Images were analyzed for this study for babies who were diagnosed with plus disease and treatment initiated by an examining i-ROP physician based on the ophthalmoscopic exam. We analyzed differences in ROP vascular severity by treating physician, adjusting for birthweight and gestational age.

RESULTS: 168 eyes diagnosed with plus disease from 8 participating i-ROP centers met inclusion criteria for this study. The mean vascular severity score for patients diagnosed with plus disease was 7.4 (standard deviation of 1.9). A multi-level linear regression analysis was conducted to determine whether there were differences between examiners in the level of severity diagnosed as plus disease. One examiner (I) had a lower mean ROP severity score than the others (P<0.01). The mean (±SD, examiner) for each examiner was 8.0 (±1.3, examiner A), 7.7 (±1.7, examiner B), 8.7 (±0.2, examiner C), 8.6 (±1.0, examiner D), 7.2 (±2.5, examiner E), 7.3 (±1.6, examiner F), 7.4 (±1.8, examiner G), 7.8 (±1.6, examiner H), 3.6 (±1.8, examiner I), 8.9 (±0.1, examiner J), and 8.9 (±0.2, examiner K).

CONCLUSIONS: There are several key findings to this study: 1) A quantitative ROP vascular severity score can be used to evaluate differences in vascular severity at time of making the diagnosis of plus disease among examiners. 2) There was a wide variance around the severity score at time of diagnosis of plus disease for each examiner, suggesting that factors other than the level of vascular severity may play a role in treatment decisions. 3) We found that experts treated at different levels of vascular severity in the diagnosis of plus disease in the i-ROP cohort study. Future work may illuminate the factors relevant for the diagnosis of plus disease and how the level of vascular severity should factor into treatment decisions based on avoidance of unfavorable anatomic outcomes, and optimization of visual outcomes.
Regression Patterns after Ranibizumab Treatment of ROP: An Anti-VEGF Class Effect

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PURPOSE: To test the hypothesis that regression patterns on fluorescein angiography (FA) after intravitreal injection of ranibizumab (IVR) in ROP correlated with previously-described patterns with intravitreal bevacizumab (IVB).

METHODS: This is an observational retrospective single center case series including all infants treated with 0.2mg/0.2ml IVR for Type 1 ROP or APROP. Follow-up FAs using 10% fluorescein at a dose of 0.1 ml/kg were performed at 40, 52 and 62 weeks PMA. Digital mosaics of angiograms were made using i2KRetina and manually aligned using Pixelmator. Using the optic disc diameter as reference, the peripheral avascular area and the distance between the vascular-avascular junction and the ora serrata were measured. Eyes were classified as follows: vascular maturity (vessels <2DD from ora serrata, vascular arrest alone (VAA), vascular arrest with tortuosity (VAT), and reactivation (dye leakage). The distances were measured manually using ImageJ in pixels and then converted into mm using the conversion constants provided by the manufacturer (0.0306 mm/pixel for Retcam 2 and 0.016 mm/pixel for Retcam 3).

RESULTS: Twenty-three eyes from 13 patients receiving IVR bilaterally for type 1 ROP or AP-ROP were available at a mean PMA of 54 weeks. Among them, 3 patients underwent unilateral FA due to clinical instability during examination done without general anesthesia. None of the 23 eyes reached vascular maturity; 9 (39%) eyes had VAA, 6 (26%) had VAT and ROP reactivated in 8 (35%) eyes. No statistically significant demographic differences, including GA, BW, and gender, have been found among this cohort of infants except for multiple gestations. 4 of the 8 reactivated eyes were of multiplets. In this cohort only 1 eye with AP-ROP was present and it reactivated at 51 PMA weeks.

CONCLUSIONS: Anti-VEGF drugs have a class-effect pattern of regression in ROP: maturation, VAA, VAT, and reactivation. Area of peripheral ischemia might be proportional to the risk of reactivation of ROP. Vascular maturation up to 54 weeks is unusual following anti-VEGF therapy, indicating continuing risk for reactivation. Fluorescein angiography should be considered prior to discontinuing active screening of ROP in patients treated with anti-VEGF.
Reactivation of Previously Stable Retinopathy of Prematurity (ROP) in Adults and Adolescents

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PURPOSE: To review the prevalence, clinical features, and treatment outcomes of adolescent and adult patients with previously regressed ROP who develop late onset exudation and fibrovascular proliferation.

METHODS: After Emory University Institutional Review Board approval, a retrospective review of all patients older than 10 years with a diagnosis of ROP evaluated at the Emory Eye Center, Atlanta, GA from (2000 to 2018) was performed. Patients with new subretinal yellow exudates or worsening fibrovascular proliferation were included.

RESULTS: Of 138 patients greater than the age of 10 with ROP, 5 (3.6%) developed late-onset exudative and/or fibrovascular proliferation in the posterior segment. Three patients were female. Three patients had ROP treatment as a neonate. Neonatal treatments included peripheral laser ablation in 3, scleral buckle in 2, and pars plana vitrectomy in 2. Management strategies for reactivation included 1 with observation, 3 with serial anti-VEGF injections, 2 with vitrectomy and 1 with cryotherapy. With mean follow-up of 4.8 years (range of 1 month to 7 years), outcomes were 2 with resolution of exudation/proliferation without recovery to baseline vision, and 3 with progressive tractional changes and severe loss of vision, including 1 with phthisis.

CONCLUSIONS: Late onset exudation and fibrovascular proliferation in adults with ROP can occur with previously regressed ROP. Three of 5 cases in our series were severe and refractory to all forms of treatment including serial anti-VEGF, vitrectomy, and cryotherapy. One case had exudation and proliferation in the form of a retinal reactive astrocytic tumor. Our findings highlight the need for continued monitoring with regular fundus examination in adolescents and adults with regressed ROP.
Ocular and Neurodevelopmental Outcomes Among Infants Treated for Retinopathy of Prematurity (ROP)

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PURPOSE: To evaluate neurodevelopmental outcomes among infants treated for retinopathy of prematurity (ROP) at (1) our institution and (2) in the whole of the United States.

METHODS: Part 1: Before-and-after retrospective chart review identified 40 infants treated with laser and 46 treated with primary intravitreal bevacizumab (IVB). Primary outcomes were death, hearing loss, bilateral visual impairment (BVI), and cerebral palsy (CP); odds ratios were calculated to determine factors associated with CP. Secondary outcomes were mean Bayley-III scores. Part 2: Using Marketscan, a national claims database, neurodevelopmental and ocular outcomes among infants treated from 2011–2014 with at least 2 years follow-up were evaluated.

RESULTS: Part 1: Overall, there were no significant differences in primary outcome measures. However, adjusted odds of BVI were significantly higher with laser compared to IVB (OR 13.1, p = 0.038). Although IVB was not associated with CP, both hydrocephalus and BVI were strongly correlated with CP. Mean Bayley-III scores were similar comparing 9 laser-treated infants to 13 IVB-treated infants. Part 2: Of 18,384 infants identified with ROP, 224 received laser and 59 received injections. Four patients in the laser group and no patient in the IVB group expired. There was a trend towards less retinal detachment with injections than laser (5% and 11%, p=0.19). Comparing injection to laser, rates of any developmental delay were 93% and 91%; other delays were motor (19% and 22%, p=0.541), cognitive (37% and 34%, p=0.676) and language (63% and 49%, p=0.063). Rates of CP were 37% with injections and 17% with laser, p=0.001, although infants receiving injections were more also likely to have severe intraventricular hemorrhage (29% and 17%, p=0.05). The difference in CP by treatment group was not statistically significant after propensity score matching (OR = 1.96, p=0.06).

CONCLUSIONS: Visual outcomes are an important aspect of neurodevelopment. BVI and retinal detachment were more frequent after laser. IVB was not associated with severe developmental disabilities at our institution. Across the US, although developmental outcomes seem to favor laser treatment, severe intraventricular hemorrhage likely represents a confounding factor. There appears to be a propensity to treat sicker infants with injections.
Protective Effects of Erythropoietin in Oxygen-induced Retinopathy

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PURPOSE: Erythropoietin (EPO) is being tested for neuroprotection in prematurity. However, little is understood about proposed non-hematopoietic effects of EPO because of difficulty studying EPO receptor (EPOR) signaling. We used a humanized mouse model with reduced EPOR signaling and addressed the hypothesis that independent of hematocrit, increased EPOR signaling protects the retina from oxygen-induced retinopathy (OIR).

METHODS: Humanized knockin EPOR mice were developed in which the murine EpoR gene was removed and substituted for the human EPOR gene. These humanized mice (hLoEPOR) had hypoactive EPOR signaling compared to littermate murine wild type EpoR mice (mWTEpoR). Postnatal day (p)7 mice of each genotype were exposed to 75% oxygen until p12 and then placed into room air (RA) until p17 in the OIR model and compared to RA-raised pups. At time points in OIR or RA (p8, p12, or p17), pups were sacrificed and analyzed for hematocrit, avascular retinal area (AVA), or intravitreal neovascular area (IVNV). Eight-week old hLoEPOR and mWTEpoR mice that had been in OIR or RA underwent electroretinography (ERG). Data were analyzed using a multilevel regression model to account for litter variability; p<0.05 was considered statistically significant.

RESULTS: Compared to mWTEpoR at p12 and p17 OIR, hLoEPOR had reduced hematocrits (p12: mWtEpoR: 27.79±0.82 vs. hLoEPOR: 24.2±0.55 p<0.001; p17: mWtEpoR: 26.74±0.56 vs. hLoEPOR: 23.16±0.79; p<0.001) associated with increased avascular retina (p<0.001). However, p8 hLoEPOR had increased AVA (p<0.001) but no difference in hematocrit compared to mWTEpoR. Heterozygous p17 pups had reduced hematocrits (mWtEpoR: 26.74±0.56 vs. heterozygous: 25.57±0.54; p<0.021) without significant differences in AVA. Despite increased AVA at p12 and p17 OIR, there was no difference in IVNV between hLoEPOR and mWTEpoR at p17 OIR. After OIR, hLoEPOR mice had reduced a- and b-wave amplitudes compared to mWTEpoR.

CONCLUSIONS: Increased EPOR signaling was associated with reduced oxygen-induced vascular loss and ERG dysfunction, but was not always associated with hematocrit. These findings suggest non-hematopoietic protective effects from EPOR signaling on the retina. Future studies are needed to determine whether EPOR signaling directly protects the neural retina or indirectly affects neural retinal function through vascular or other protection.
Early Gut Microbiome Profile in High-risk Preterm Infants with and without Retinopathy of Prematurity

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PURPOSE: Recent data have shown that gut microbiome may play a role in ocular diseases such as uveitis and age-related macular degeneration, but its role in retinopathy of prematurity (ROP) has not been explored. It is incompletely understood why some high-risk infants develop severe ROP and other high-risk infants do not. We sought to determine if there is an association between early microbiome composition and ROP development by comparing the gut microbiome in high-risk preterm infants with type 1 ROP and high-risk preterm neonates without any ROP.

METHODS: Fecal samples were collected weekly from birth through 34 weeks postmenstrual age (PMA) from high-risk preterm neonates 27 weeks gestational age (GA) or birth weight (BW) 750g that underwent ROP screening at a single level III neonatal intensive care unit. Subjects were stratified into two groups: 1) high-risk preterm infants with type 1 ROP (n=9) and 2) high-risk preterm infants that did not develop any ROP (n=5). Bacterial DNA was extracted from fecal samples followed by amplification of the 16S rRNA V4 region using Illumina MiSeq sequencing. For 16S rRNA analysis, 16 million paired-end reads were joined and de-multiplexed with QIIME 1.9.1, and exact sequence variants (ESV) were selected using the DeBlur pipeline. Alpha and beta diversity were analyzed using QIIME 1.9.1 and Phyloseq. Pathway abundance analysis was also performed. Significance was determined using PERMANOVA for alpha-diversity, t-tests for beta-diversity, and ANCOM for ESV differences.

RESULTS: Neonatal fecal samples showed divergence in microbiome composition, in which infants with type 1 ROP showed significant enrichment of Enterobacteriaceae 28 weeks PMA (p<0.05) and enrichment of Lactobacillus, Bacteroides and Acinetobacter 29 weeks PMA (p<0.05 for all comparisons). Pathway abundance analysis suggested possible protective roles of several metabolic pathways enriched in infants without ROP.

CONCLUSIONS: To our knowledge, this is the first report showing a difference in early gut microbiome composition in high-risk premature infants that developed type 1 ROP compared to similarly high-risk neonates that did not develop any ROP. These data suggest that the early gut microbiome profile and abundance of specific strains may play a significant role in ROP pathogenesis.
Retinal Vascular Abnormalities are More Common Than Previously Reported in Incontinentia Pigmenti

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PURPOSE: Most references report that Incontinentia Pigmenti (IP) is associated with retinal disease in approximately 35% of patients, based on older literature prior to the availability of wide angle fluorescein angiography (FA). We sought to determine the prevalence and spectrum of retinal vascular abnormalities in IP using FA.

METHODS: We queried an email group of pediatric retina specialists to identify patients with IP who underwent examinations under anesthesia (EUAs) with fluorescein angiography (FA). The primary analysis evaluated the prevalence of FA abnormalities among patients seen at institutions where the standard practice was to perform EUAs and FAs on all patients with IP. In order to reduce selection bias, we excluded referral practices restricted to IP patients referred for obvious retinovascular pathology on clinical examinations.

RESULTS: We identified 39 patients screened for retinal findings related to IP by EUA and FA from 3 institutions in the last 10 years. 37/39 (95%) were female. 18 / 39 (46%) were noted to have ophthalmoscopic abnormalities prior to EUA. 29 / 39 (74%) had abnormal vascular findings on FA. 19/29 (66% of those with findings) received laser treatment at the time of first EUA with laser more commonly applied in patients with evident neovascularization on FA.

CONCLUSIONS: The prevalence of angiographic disease in IP was higher in this sample than that reported in the literature. Part of this finding may be due to improved ability to detect nonperfusion and occult neovascularization on FA. These data further suggest that the presence of retinal disease cannot be excluded without EUA and FA. There are no clinical trial data to guide treatment decisions in IP, but anecdotal reports of retinal detachments in older children with IP suggest close observation with serial FA is warranted if laser is not performed to avascular retina.
Ocular Histopathologic Findings of Congenital Zika Syndrome

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PURPOSE: Congenital Zika syndrome (CZS) is known to be associated with severe malformations in newborns. Although microcephaly is the hallmark of the disease, the ocular findings are important given the severe visual impairment that has been observed in these patients. The ocular findings of chorioretinal atrophy, optic atrophy and retinal vascular changes have been described. The purpose of this study is to evaluate the presence of Zika Virus antigens and describe the associated ocular histopathologic features of 7 cases of CZS.

METHODS: Ocular tissue samples from 7 deceased fetuses with a diagnosis of Congenital Zika Syndrome from the National Institute of Health in Colombia, gestational ages 21 to 29 weeks, were sent to the Florida Lions Ocular Pathology Laboratory were obtained and evaluated for histopathologic changes and immunostaining was performed using a ZIKV NS2B protein antibody.

RESULTS: The seven eyes manifested with pupillary membranes, immature anterior chamber angles, loss of pigment and thinning of the retinal pigment epithelium, choroidal thinning, undifferentiated nuclear layers of the retina, an inflammatory infiltrate within the iris and a perivascular inflammatory infiltrate in the choroid. Expression of ZIKV antigen was present in the iris, neural retina, choroid, ciliary body and optic nerve.

CONCLUSIONS: The findings of pupillary membranes, immature anterior chamber angles and lack of migration of the neural retinal layers is likely secondary to gestational age. The presence of inflammation within the iris and choroid, attenuation of the retinal pigment epithelium, thinning of the choroid and optic atrophy with associated Zika Virus localization in these tissues may be secondary to Zika Virus Infection.
**Serous Macular Detachment Due to Congenital Optic Disk Abnormalities: A Comparative Study**

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**PURPOSE:** To compare the outcomes between minimally invasive procedures (MIP) and pars plana vitrectomy (PPV) for the treatment of serous macular detachment (SMD) due to congenital optic disk abnormalities (CODA).

**METHODS:** Retrospective, comparative case series study. Patients with SMD due to CODA (Optic disk Pit, Morning Glory and Optic Disk Coloboma) were included. Patients were divided into 2 groups: Group Minimally invasive procedures (MIP): office-based laser photocoagulation monotherapy, gas tamponade with office-based laser; Group Invasive procedures (IP): pars plana vitrectomy with or without of one or more of the following procedures: gas tamponade; posterior hyaloid removal; internal limiting membrane removal; endophotocoagulation.

**RESULTS:** Forty-two eyes of 41 patients were included. Mean age at diagnosis was 29.2 years-old (range, 7 to 70 years); 20 right eyes; 36 caucasian; 6 Black; 39 eyes had SMD due to Optic disk pit; 2 eyes due to morning glory and 1 due to Optic disk coloboma. Thirteen eyes were treated with MIP (7: laser monotherapy; 6: laser plus gas tamponade); Twenty-nine eyes were treated with IP (6: PPV without gas endotamponade; 10: PPV with gas endotamponade, 12 eyes with PPV and ILM peeling. One eye had spontaneous resolution. Among eyes treated with MIP, 76.9% (CI 46.2% - 95%, p = 0.0769, Kruskal-Wallis H) has anatomical regression of the SMD; Among eyes treated with IP, 52.3% (CI 38.8% - 77.6%, p = 0.0769, Kruskal-Wallis H) obtained SMD regression.

**CONCLUSIONS:** There is no gold standard to treat SMD due to CODA due to its rarity. Most of the treatments rely on the physicians’ personal choice. CODA is a more prevalent in young subjects, such in our series. Our study showed that the least invasive type of treatment, was associated to a higher success rate than surgical procedures involving PPV (76.9% vs. 52.3%). Therefore, less invasive approach may be taken into account in the treatment of SMD secondary to CODA, avoiding a possible complications of PPV, such as retinal detachment and early onset of cataract.
Optical Coherence Tomography Angiography of Pediatric Choroidal Neovascular Membranes

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PURPOSE: Compared to fluorescein angiography (FA), the gold standard for diagnosing CNV activity, optical coherence tomography angiography (OCTA) is non-invasive without risks associated with fluorescein dye use, and may be especially advantageous in the diagnosis and monitoring of children with CNV.

METHODS: Eight eyes from eight patients aged 12 months to 18 years were imaged with the investigational OCTA and the RTVue. Two patients were imaged during examination under anesthesia while six patients were imaged in the clinic. Demographic information, ocular characteristics, treatment history and imaging studies (color photos, fluorescein angiography, OCT) were collected and reviewed.

RESULTS: Three eyes had active CNV while five had quiescent CNV at the time of imaging. CNVs were idiopathic or secondary to trauma, retinal vascular dysgenesis versus retinopathy of prematurity, pigmentary retinopathy, Best vitelliform macular dystrophy, panuveitis, Morning glory disc anomaly and optic disc drusen. OCTA of two active CNVs demonstrated presence of a main trunk with multiple fine capillaries, vessel loops and anastomoses. OCTA was repeated after treatment for two CNVs and demonstrated a decrease in size with loss of fine capillaries, vessel loops and anastomoses. For the third active CNV, OCTA verified flow in the CNV complex despite the uncertainty of FA hyperfluorescence in the setting of grossly abnormal retinal vasculature. The five quiescent CNVs all lacked fine capillaries, vessel loops and anastomoses on OCTA.

CONCLUSIONS: OCTA demonstrates morphological differences between active and quiescent pediatric CNVs.
PURPOSE: In the age of ultra-wide-angle scanning laser ophthalmoscopes (SLOs) and declining ophthalmoscopy skills amongst graduates it is worthwhile reflecting on the technological hurdles and historical figures responsible for what is arguably one modern medicine’s major advances.

METHODS: Personal collection of over 400 instruments, historical monographs, instrument instruction literature and catalogues, Der Augenspiegel by Alfred Schett.

RESULTS: Herman von Helmholtz first recognized and incorporated the 3 major principles of ophthalmoscopy into a working instrument in 1851 which still remain relevant. Illumination source and a means of directing it into the patient’s eye. Alignment of reflected light from the patient’s fundus with the observer’s eye. Optical means of correcting defocused images of the fundus. Illumination has progressed from candles, oil and gas lamps to electric bulbs in the instrument of Dennet in 1885 and finally LEDs. Helmholtz reflected light into the eye using semi-reflective glass plates. This was followed in 1852 by more efficient plane (Epkens) and concave mirrors (Ruete) with central apertures. Ruete also developed indirect ophthalmoscopy. Improvement in mirror design continued up until the development of reliable electric bulbs. Initial ophthalmoscopes used separate lenses to correct defocused images. Rekoss added rotatable discs of lenses in 1852 and later instruments used more complicated combinations which enabled practitioners to estimate refractive errors during ophthalmoscopy. The chain of lenses was invented by Couper in 1883 and remains current. The binocular indirect ophthalmoscope was invented in France by Giraud-Teulon in 1861 however did not become practical until the head mounted unit was developed by Schepens in 1947. During the 20th century advances in bulb, battery, prism, lighting, electronics and filters made the ophthalmoscope into a portable and practical instrument. Ophthalmoscopy today has become less reliant on individual instruments with the development of SLOs. The concept was originally developed in 1979 by Robert H Webb and has now progressed into the ultra-wide-angle Optos units.

CONCLUSIONS: The ophthalmoscope has evolved significantly over the last 150 years. Skills are required to utilize it correctly and whilst technological advances such as SLOs have improved our ability to detect retinal disorders, dynamic ophthalmoscopy remains an indispensable tool.
Release of Silicone Oil and the Off-label Use of Syringes in Vitreoretinal Diseases: Understanding this Public Health Problem

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PURPOSE: To assess silicone oil (SO) release by different brands of syringes used for intravitreal injection under different handling conditions.

METHODS: Eight types of syringes were analysed: from the USA, Terumo 0.5 mL, Becton-Dickinson (BD) Tuberculin 1 mL, BD Luer-lok 1 mL, BD Ultra-Fine 0.3 mL and Exel Insulin 0.3 mL; from Germany, Braun Omnifix-F 1 mL and Braun Injekt-F 1 mL and from Spain, BD Plastipak 1 mL. The impact of air, priming the plunger, agitation by flicking and fluid temperature on SO release were assessed by light microscopy. Fourier transform infrared spectroscopy (FTIR) was performed to identify the molecular compound in each syringe.

RESULTS: Five hundred and sixty syringes were analysed. Terumo 0.5 mL and BD Ultra-Fine 0.3 mL released more SO than all others. BD Luer-lok 1 mL, BD Plastipak and Braun Omnifix-F 1 mL released little SO; BD Tuberculin 1 mL, Exel 0.3 mL and Braun Injekt-F 1 mL released the least SO. Priming the syringe and different temperatures did not significantly affect SO release. Agitation by flicking caused a significantly higher proportion of samples to have SO droplets and an increased number of oil droplets. Air had an additive effect on the release of oil in the agitation groups. FTIR identified polysiloxane in all syringes but Injekt-F.

CONCLUSIONS: Syringes commonly used for intravitreal injections frequently release SO droplets, especially when agitated by flicking. To avoid unnecessary ocular risks, syringes should not be agitated before intravitreal injection. It is desirable that syringes be manufactured specifically for ophthalmic use.
Variable Risk of Silicone Oil Microdroplets Following Multiple Bevacizumab, Ranibizumab and Aflibercept Intravitreal Injections

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PURPOSE: To compare the incidence of vitreous silicone oil microdroplets detected by slit lamp biomicroscopy in eyes with 6 or more intravitreal injections of the same anti-VEGF drug.

METHODS: A prospective cross-sectional study of 260 consecutive eyes receiving exclusively one of three anti-VEGF drugs for choroidal neovascularization, diabetic macular edema or macular edema from venous occlusive disease. The control group was 147 fellow eyes with no prior intravitreal injections. The anterior and mid-vitreous were carefully examined using 12x to 16x magnification through dilated pupils with ocular saccades. Silicone oil microdroplets were graded on a scale from 0 to 4+ based on the number and size of droplets.

RESULTS: Each of the 3 anti-VEGF drugs were delivered using 3 different syringes. Bevacizumab was delivered with 0.3 ml BD polypropylene insulin syringes, ranibizumab with 1.0 ml BD polypropylene tuberculin syringes (or prefilled syringes-PFS, once available) and aflibercept with 1.0 ml BD polycarbonate syringes. Silicone oil is used in small quantities to lubricate the barrel of each of the three BD syringes. The number of treatments were similar in each group. Silicone microdroplets were detected in 53/68 eyes (77.9%) receiving bevacizumab, 18/125 eyes (14.4%) receiving ranibizumab and 33/67 eyes (49.3%) receiving aflibercept. No silicone oil microdroplets were found in any of the 147 control eyes or the subset of 14 eyes treated only with ranibizumab PFS. The difference in incidence of silicone microdroplets was significant when comparing bevacizumab to ranibizumab, aflibercept and controls (P<.001). The difference in incidence of silicone microdroplets was also significant comparing ranibizumab to aflibercept (P<.001) and controls (P<.001) as well as aflibercept to controls (P<.001). The silicone microdroplet severity was 2+ or greater in 35/68 eyes (51.5%) receiving bevacizumab, 0/125 eyes with ranibizumab, 2/67 eyes (2.99%) with aflibercept and 0/147 controls. Patients with 2+ to 4+ silicone oil microdroplets were frequently symptomatic.

CONCLUSIONS: Silicone microdroplets are very common in eyes receiving multiple bevacizumab injections via 0.3 ml BD polypropylene insulin syringes. All intravitreal injections should be given using silicone free syringes and the use of BD 0.3 ml insulin syringes for intravitreal injections should be abandoned.
Mishandling of Syringes and the Risks to the Eye

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**PURPOSE:** Twenty-five million intravitreal injections (IVI) are performed annually worldwide. The objective of this study was to investigate whether syringe mishandling might increase the release of silicone oil droplets into the vitreous, and thereby increase the risk of noninfectious inflammation (NII).

**METHODS:** Six models of syringes (Descarpack 1mL, Solidor 1mL, Injex Stilly Line 0.5mL, BD Ultra Fine II 0.5mL, SR 1mL and BD Plastipak 1mL) were analyzed by light microscopy for the release of silicone oil under agitation (n=10 for each model) and compared with no agitation (n=10). Fourier-Transform Infrared Spectroscopy (FTIR) was performed to identify the molecular compounds inside the syringes. Additionally, a cross-sectional study was carried out in subjects undergoing routine IVI and controls to detect silicone oil in the vitreous by biomicroscopy and ultrasonography. The third arm of the study analyzed which syringe, and its handling technique, was associated with a case series of NII after aflibercept IVI.

**RESULTS:** One hundred and twenty syringes were analyzed. Agitation by flicking caused a significant increase in the number of positive samples for silicone oil as well as in the number of oil droplets in comparison to no agitation. FTIR identified the presence of polysiloxane (silicone oil) in all models. The clinical study included 30 control and 37 previously treated eyes. Biomicroscopy and ultrasonography, respectively, found silicone oil droplets in 68% and 76% of treated and 0% and 3% of controls. In the series of 6 cases with NII, a statistically significant association was found with the SR 1 mL syringe. Additionally, its flicking was a common procedure by the retina specialist.

**CONCLUSIONS:** Silicone oil droplets are common in the vitreous after intravitreal injection, and agitation of syringes prior to injection tends to release more silicone oil. The case series reported herein was associated with a single syringe model that releases silicone oil and had been flicked prior to injection. Although it is common among retina specialists, such agitation of the syringe might increase the complications of IVI, namely silicone oil droplets and inflammation.
Ranibizumab and Aflibercept Levels and Their Impact on Vascular Endothelial Growth Factor in Human Breast Milk Following Intravitreal Injection

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**PURPOSE:** To measure the levels of VEGF-A and ranibizumab or aflibercept in the breast milk of lactating women after receiving intravitreal anti-VEGF therapy.

**METHODS:** This is a prospective, multi-center study performed at St. Michael’s Hospital and Calgary Retina Consultants, Canada. Three lactating women were started on treatment with intravitreal anti-VEGF agents: patients 1 and 2 received treatment with ranibizumab for myopic choroidal neovascularization and patient 3 received aflibercept for diabetic macular edema. Breast milk samples from patients 1 and 2 were collected 1 hour before the first injection and at days 1-7, 14, 21, and 28 after the injection. Samples from patient 3 could only be collected until day 4 due to the lack of production of additional breast milk. Patients 1 and 3 were treatment-naïve and did not breastfeed or pump breast milk outside of study visits. Patient 2 had received one ranibizumab injection 4 weeks prior to baseline and continued to breastfeed regularly throughout the study. Ranibizumab and aflibercept levels were measured using ELISA, and VEGF-A concentrations were determined using an immunoassay.

**RESULTS:** In patient 1, ranibizumab was detected in the breast milk on day 3 (34.7ng/ml), with generally increasing levels over time until day 28, while VEGF-A levels were reduced from 22.8ng/ml at baseline to 12.3ng/ml on day 1 and with generally decreasing levels over time until day 28. In patient 2, ranibizumab levels remained below the lower limit of quantitation (LLOQ) of the assay (1.6ng/ml) at all time points and VEGF-A remained largely unchanged with trough level of 7.3ng/ml on day 7 compared with 11.5ng/ml at baseline. Patient 3 had aflibercept detected in the breast milk on day 4 (10.4ng/ml) with VEGF-A levels being reduced from 10.6ng/ml at baseline to 4.9ng/ml on day 1.

**CONCLUSIONS:** Ranibizumab and aflibercept are excreted into the breast milk of lactating mothers following intravitreal injections, with corresponding reductions in breast milk VEGF-A levels. However, in actively nursing mothers, the levels of ranibizumab remained below the LLOQ of the ranibizumab assay. This data is important to consider when counseling nursing women who develop diseases requiring anti-VEGF injections.
Process Mapping and Activity-based Costing of the Intravitreal Injection Procedure

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PURPOSE: Intravitreal injections (IVI) represent the most common procedure performed by retina specialists today, yet the actual cost of performing IVIs is not fully understood when one takes into account the operational flow, resources, and personnel involved. An observational cost analysis study was performed to quantify the average cost of an IVI procedure, independent of the drug injected.

METHODS: The study design is an observation cost analysis based on activity-based costing, an accounting method which allocates a cost to each component on a process map. Cost pools were divided by their practical capacity, then multiplied by an activity rate. 14 patients were observed at an academic center retina clinic to develop the process map. Direct material, employee, and overhead costs were determined by a combination of internal records and national reported averages. The calculated cost was benchmarked against the reimbursement revenue drawn from the Centers for Medicare & Medicaid Services Fee Schedule for HCPCS 67028: Injection eye drug.

RESULTS: On average, 11.78 minutes (min) were spent on technician work-up, 5.30 min were spent on imaging, 27.97 min were spent on in-room waiting and injection preparation, 20.08 min were spent on the injection delivery and associated documentation, and 3.01 min were spent on check-out and scheduling. Interestingly, more retina specialist labor time was spent on EHR documentation (μ=6.68 min, SD=1.80 min) than patient greeting (μ=3.49 min, SD=1.97 min) or the injection itself (μ=2.34 min, SD=0.67 min). The average direct material, direct labor, and overhead costs per IVI procedure were $0.15, $80.04, and $53.01, respectively (Figure 2). 2018 Medicare reimbursement for an IVI procedure is $104.40, netting a gross margin of -$28.79 (-27.6%). The largest indirect costs were rent ($24.46), electronic health record (EHR) fees ($10.76), and billing/coding fees ($10.44). The largest direct cost was ophthalmologist labor ($62.35, 95% CI=19.02-105.67).

CONCLUSIONS: The negative gross cost margin found suggests that intravitreal injections may not be appropriately valued by payors. Further study is warranted to identify targets for cost reduction without compromising quality of care or patient safety. Advocacy efforts on behalf of our specialty are imperative to ensure that valuation of our procedures is accurate.
The Retina as a Window to Understanding Sub-types of Alzheimer’s Disease

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PURPOSE: Alzheimer’s disease (AD) is a heterogeneous disease with neuropathological and structural heterogeneity allowing us to distinguish between typical/atypical AD. Retinal pathological changes have been reported in AD, but it is unknown how heterogeneous their manifestations are in AD variants. The purpose of this cross-sectional study was to analyse our cohort of well-characterised cases with posterior cortical atrophy (PCA), typical AD (tAD) and healthy controls (HC), for potential retinal biomarkers on ultrawide field (UWF) retinal images using established and novel grading criteria. PCA, a variant of AD, is characterized by progressive degeneration of occipital and parietal lobe with associated cortical visual impairment.

METHODS: UWF colour and autofluorescence images were acquired of 33 PCA (Mini Mental State Examination (MMSE), MMSE28) using OPTOS P200Tx scanning laser ophthalmoscope (SLO). The images were analysed using the well-characterised Manchester and Moorfields image grading grids. Images were graded for absence/presence of pathological retinal abnormalities by two independent, certified, masked graders. Statistical analysis was carried out using SPSS statistical software. Patient groups fulfilled consensus criteria for PCA and the National Institute of Ageing-Alzheimer’s Association (NIA-AA) criteria for tAD. PCA patients with Lewy-bodies dementia, corticobasal degeneration or prion-disease were excluded. The study had Ethical Committee approval.

RESULTS: There was no significant age difference (p> .05) between PCA (66.1±6.9), tAD (64.7±7.1) and HC (66.2±7.6). UWF imaging detected a higher prevalence of sub-retinal deposits (pseudo-drusen) in tAD (35%) compared to PCA (17%) or HC (16%) \( \chi^2=7.792, \text{df}=2, p= .02 \). There was a lower prevalence of far-peripheral reticular degeneration (PRD) and far-peripheral hyper-fluorescence changes in tAD compared to PCA and HC respectively: tAD (9%) vs PCA (42%) vs HC (28%) \( \chi^2=6.471, \text{df}=2, p= .045 \), tAD (24%) vs PCA (44%) vs HC (43%) \( \chi^2=5.736, \text{df}=2, p=.05 \). Both in tAD and PCA, the peripapillary vascular caliber was increased significantly compared to HC (p=0.01).

CONCLUSIONS: In this cohort of well characterised cases in each group, UWF imaging highlighted an unequivocal retinal manifestation of AD showing the importance of detailed phenotyping to be included in dementia studies in which ocular biomarkers are sought. The vascular biomarkers require further investigation to understand their utility.
Analysis of Emergent Non-hospital Based Retina Consultation Requests in an Academic Non-hospital Associated Retina Practice

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PURPOSE: The purpose of this study is to evaluate the outcomes of after-hour encounters concerning patients referred by eye physicians to on-call retina services for emergent evaluation not seen in or referred by an emergency department.

METHODS: A chart review was conducted composing of all patients who presented emergently and after clinic hours to an academic non-hospital associated private practice retina-only institution over a four-year period.

RESULTS: 275 charts were reviewed. Of these encounters, 25% of after-hour encounters led to a procedure within 24 hours, of these encounters 12% led to emergent surgery within 24 hours. Overall, 18% of encounters resulted in surgery within 96 hours of the visit. When the call was made by a provider, there was a 20% intervention (9% procedure, 11% surgery) chance that the encounter led to an emergent intervention an versus 15% (5% procedure, 10% surgery) if it was a patient call. The most common presenting complaints were for flashes and/or floaters, decrease in visual acuity, decrease in visual field, eye pain, and eye pain after intra-vitreal injection or surgery. The most common in-office intervention was laser retinopexy for a retinal tear, and the most common emergent surgical intervention was a vitrectomy for mac-on retinal detachment.

CONCLUSIONS: Hospital-independent retina services are able to fill an important gap in the management of urgent retinal evaluations by providing easy access to care while avoiding the congestion and expense of emergency rooms. A quarter of all after hours appointments lead to emergent intervention which led to efficient patient care, and possibly avoided future medico-legal issues that may arise from a delay in transfer of patient care. These services have a moderate catchment area and their absence would require the patient to travel greater distances for care. This study reinforces the need for access to a retinal specialist for the evaluation of acute patient/provider consultations in the absence of a hospital-based system.
NAD+ Based Therapeutic Development

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**PURPOSE:** Aging is a significant risk factor for impaired tissue functions and chronic diseases. Neuroretinal degeneration is a major cause of visual impairment and is associated with inherited and acquired retinal diseases. A significant challenge in treating retinal degenerative diseases is their genetic and phenotypic heterogeneity. However, despite this diversity, many of these diseases share a common endpoint involving death of light-sensitive photoreceptors. Identifying common pathogenic mechanisms that contribute to photoreceptor death in these diverse diseases may lead to a unifying therapy for multiple retinal diseases that would be highly innovative and address a great clinical need. Because the retina and photoreceptors, in particular, have immense metabolic and energetic requirements, we hypothesized that metabolic dysfunction may be a common link unifying various retinal degenerative diseases. Here, we present data that identifies NAD(+) metabolism as therapeutically modifiable and relevant to both aging and retinal diseases.

**METHODS:** Data from studies conducted in animal models, cell culture and patient samples will be presented. All studies were approved by the Washington University Institutional Research Board (IRB) and Human Research Protections Office.

**RESULTS:** We found that rod or cone photoreceptor-specific deletion of nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme in the major NAD(+) biosynthetic pathway beginning with nicotinamide, caused retinal degeneration. In both cases, we could rescue vision with nicotinamide mononucleotide (NMN). Significantly, retinal NAD(+) deficiency was an early feature of multiple mouse models of retinal dysfunction, including light-induced degeneration, streptozotocin-induced diabetic retinopathy, and age-associated dysfunction. Mechanistically, NAD(+) deficiency caused metabolic dysfunction and consequent photoreceptor death. We further demonstrate that the NAD(+) dependent mitochondrial deacylases SIRT3 and SIRT5 play important roles in retinal homeostasis and that NAD(+) deficiency causes SIRT3 dysfunction. In addition, increasing circulating extracellular NAMPT (eNAMPT) levels in aged mice by adipose-tissue specific overexpression of NAMPT increases NAD(+) levels in multiple tissues including the retina, thereby enhancing function and extending healthspan in mice. Of note, eNAMPT is carried in extracellular vesicles (EVs) through systemic circulation in both mice and humans. EV-contained eNAMPT is internalized into cells and enhances NAD(+) biosynthesis.

**CONCLUSIONS:** These findings demonstrate that NAD(+) biosynthesis is essential for vision, provide a foundation for future work to further clarify the mechanisms involved, and identify a unifying therapeutic target for diverse blinding diseases. Clinical trials are currently ongoing to test the safety and feasibility of this approach. Our findings have also revealed a novel EV-mediated delivery mechanism for eNAMPT, which promotes systemic NAD(+) biosynthesis and counteracts aging, suggesting a potential avenue for anti-aging intervention in humans.
Prospective Evaluation of Genomic Prognostic Risk Factors in 921 Uveal Melanomas: Report from the Collaborative Ocular Oncology Group Study Number 2

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PURPOSE: The purpose of this prospective study is two-fold: (1) to compare the gene expression profile and PRAME status of small uveal melanomas (UM) to larger UM, and (2) to report on the clinical characteristics of small tumors by GEP class type.

METHODS: The Collaborative Ocular Oncology Group Study 2 (COOG2) is a 22 center, prospective observational study of UM patients undergoing clinical prognostic testing using the CLIA-certified DecisionDx-UM test (Castle Biosciences) between July 2017 and April 2019. De-identified data were entered into a REDCap database using an online portal. GEP and PRAME results were collected for a small tumor cohort (STC), defined as tumor thickness, and a large tumor cohort (LTC), defined as tumor thickness > 3 mm. Statistical significance of comparisons between groups was determined using MedCalc software (v19).

RESULTS: A total of 921 eyes of 921 patients were enrolled, of which 272 were STC patients (30%) and 649 were LTC patients (70%). GEP status differed significantly (p<0.001) between the STC vs LCT, respectively: class 1A (55% vs 38%), class 1B (28% vs 22%), and class 2 (17% vs 40%). PRAME was positive in 21% of STC tumors versus 37% of LTC tumors (P<.0001). Among the STC, PRAME was positive in 17% of class 1A, 21% of class 1B, and 40% of class 2 tumors (P=0.004). Among the LTC, PRAME was positive in 27% of class 1A, 31% of class 1B, and 50% of class 2 tumors (P<.0001). Overall, the STC was associated with class 1, spindle cytology, closer proximity to the optic disc, and PRAME negativity, whereas the LTC was associated with ciliary body involvement, epithelioid cytology, and PRAME positivity (all P<.001). Among the STC, orange pigment, subretinal fluid, low internal reflectivity, and drusen were not associated with one GEP class over another.

CONCLUSIONS: Most UM with thickness 3 mm are class 1 and PRAME negative, and thus have low metastatic potential. Most class 2 and PRAME positive UM have thickness > 3 mm. Clinical risk factors commonly used to predict nevus expansion did not improve the accuracy of identifying small tumors with high metastatic risk.
Intravitreal Bevacizumab to Prevent or Delay Radiation Maculopathy after Transfoveal Plaque Radiotherapy for Choroidal Melanoma: The PRELAY Study

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PURPOSE: Evaluate the safety and efficacy of intravitreal bevacizumab used to prevent or delay radiation maculopathy.

METHODS: Retrospective, nonrandomized interventional study of patients treated with palladium-103 plaque radiotherapy for choroidal melanoma. Patients were defined as high-risk to develop radiation maculopathy when their foveal dose was >50 Gray (typically subfoveal or juxtafoveal tumors). This group received periodic intravitreal bevacizumab (IVB) prior to onset of radiation maculopathy (RM) and periodically thereafter. In contrast, we selected a case-matched (location, dose to fovea) control group treated prior to the advent of IVB. Ophthalmic evaluations included visual acuity, ophthalmic examination, optical coherence tomography, fundus photography, and fluorescein angiography.

RESULTS: Fourteen eyes were evaluated in the treatment group. American Joint Committee on Cancer Staging T-size ranged from T1 (n=11) to T2 (n=3). The mean foveal dose was 108 Gray in the treatment group versus 108 Gray in the control group. For the IVB treated group, monthly anti-VEGF was initiated an average of 24 days after plaque radiation therapy. At the time of diagnosis, the mean visual acuity was 20/25 and 20/40 for the IVB and control groups respectively. Of these, there were 79% and 57% with 20/40 or better vision respectively. At 12 months, the visual acuities remain 20/40 or better in 86% and 29% respectively. Comparing Finger-Stages of Radiation Retinopathy when first diagnosed: there were Stage 0 (50% versus 14.3%), Stage 1 (0% vs 0%), Stage 2 (43% versus 7.1%), Stage 3 (7% versus 64.3%) and Stage 4 (0% vs 14.3%). The IVB treatment group experienced a mean decrease of 172 microns of central foveal thickness compared to their pre-treatment measurements. Macular anatomy evaluations were performed on both groups and suggest that minimizing structural changes to the macular architecture results in better functional outcomes. No complications were related to IVB therapy.

CONCLUSIONS: This pilot study suggests that early treatment with intravitreal bevacizumab appears to preserve vision and prevent or delay radiation maculopathy for high-risk choroidal melanoma patients following plaque radiation therapy.
Targeted Treatment of Uveal Melanoma: Increased Survival and Enhanced Visual Function

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PURPOSE: The purpose of this study was to evaluate shifting treatment trends at a major adult ocular oncology service focused on tumor control, anatomic and visual function, and mortality in uveal melanoma patients treated by a single oncology practice (MOOR) over a three-decade period. This study evaluated the shift in personalized ocular oncology care to deliver earlier treatment, to avoid enucleation, and to use secondary pharmacotherapy to improve outcomes for the most common primary adult ocular malignancy.

METHODS: An IRB approved, retrospective review of all patients undergoing treatment for primary posterior uveal melanoma over three decades. Patient demographics, tumor size, primary treatment, adjunctive treatment, secondary surgery, metastasis and mortality were recorded for all patients. From the third decade forward, all patients underwent molecular genomic profiling with GEP classification. Outcomes analysis utilized treatment intervals from: 1991–2001, 2002–2011, and 2012–2017 and stratified tumors by size from small (10 mm apical height OR >16mm base).

CONCLUSIONS: Personalized treatment of uveal melanoma incorporating earlier tumor treatment, avoidance of enucleation, and integration of molecular genomics and targeted anti-VEGF therapy has decreased tumor specific mortality, eliminated secondary enucleations, and improved anatomic and functional visual outcomes. Radiosparing treatment for small melanoma enables accurate molecular genomics, enhances anatomic outcomes, and eliminates radiation related complications of retinopathy, optic neuropathy, secondary glaucoma and cataract. This study cohort clearly defines the improvements in survival for a disease commonly reported to have a 50% mortality rate. In the absence of clinical trials data, ongoing review of treatment specific outcomes is critical to ensure best patient care.
Proton Irradiation of Uveal Melanomas involving the Iris and Ciliary Body without Surgical Localization (Light Field)

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PURPOSE: To assess treatment outcomes after proton irradiation of uveal melanomas involving the iris and ciliary body without surgical localization (light field).

METHODS: One hundred thirty-two patients evaluated at Mass Eye and Ear between 1975 and 2017 were selected for irradiation using transillumination instead of surgery to localize the tumor. The tumors were located as follows: iris (n=20, 15%), ciliary body (n=12, 9%), iris and ciliary body (n=56, 42%), ciliary body and choroid (n=29, 22%), and iris, ciliary body and choroid (n=15, 11%). Rates of complications, visual loss, eye loss, tumor recurrence and melanoma-related deaths were calculated.

RESULTS: Most patients had good vision at the time of tumor diagnosis (68% had baseline visual acuity (BLVA) of 20/40 or better) and only 12 patients (9%) had BLVA worse than 20/200. Median follow up in the cohort was 5 years. Median VA at last follow-up was 20/80. Recurrences occurred in 9% (n=12) of patients and eye loss in 15% (n=20). Most of the recurrences (n=9) occurred in patients with iridociliary (n=6) or iris only (n=3) tumors. All recurrences were treated by repeat PBI (n=5) or enucleation (n=7). Sixty percent of patients who underwent enucleation did so because complications occurred (e.g., NVG, blind, painful eye). NVG developed in 13% (n=18) of patients, and half of these were patients with tumors involving the iris. Only 1/20 patients with iris only tumors developed NVG. Of 81 patients who were diagnosed with cataracts after treatment, 54 (66.6%) were considered related to radiation. Over 50% of the cohort died. Metastatic uveal melanoma was the cause of death in 38% (n=26) of deceased patients (19.7% of cohort).

CONCLUSIONS: Patients treated with proton irradiation using a light field technique are able to avoid surgery and experience good outcomes after irradiation. Eye retention and good visual acuity are seen in the majority of cases, and the tumor recurrence rate is low.
Outcomes of Intravitreal Methotrexate to Salvage Eyes with Relapsed Primary Intraocular Lymphoma

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PURPOSE: To report the outcomes of intravitreal methotrexate (MTX) injections to rescue eyes with relapsed primary vitreoretinal intraocular lymphoma (PIOL).

METHODS: Retrospective case series of patients with ocular relapse of PIOL who had initially received systemic chemotherapy (all 5 cases) and external beam radiotherapy (EBRT) to the brain and orbits (2 cases). Injections of MTX (400 µg/0.1ml) were given through the pars plana into vitreous cavity once weekly for one month, then every other week for 4 months, followed by a maintenance phase of one injection monthly for 8 months (total of 20 injections in a year).

RESULTS: From April 2008 to February 2016, there were 9 eyes of 5 patients (3 males, 2 females; average age at first presentation 62 years, range 53–68 years) treated with our rescue protocol of intravitreal MTX injections. Ocular relapse occurred at a mean interval of 15 months (range 5–34 months) after the completion of initial systemic treatment. Tumour control was achieved in 8 out of 9 eyes (89%); 1 eye failed, with persistent retinal infiltrates despite of increasing the frequency of injections, resulting in severe keratopathy. The only other complication occurred in 1 eye, developing cystoid macular oedema from MTX injections that resolved with topical anti-inflammatory medications and reduced frequency MTX. At mean follow-up of 31 months (range 5–104 months), there was no cases of reduced vision or ocular relapse, but 2 patients died (1 of CNS lymphoma).

CONCLUSIONS: Intravitreal methotrexate was found to be a safe and effective treatment modality for relapsed PIOL after systemic chemotherapy and radiotherapy, achieving local tumour control in 89%. However, given the rare nature of PIOL, larger collaborative studies with longer follow up are needed to determine optimal treatment.
Choroidal Nevus Risk Factors for Transformation into Melanoma Using Multimodal Imaging in 3806 Cases

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PURPOSE: To use multimodal imaging for identification of risk factors for choroidal nevus growth into melanoma

METHODS: Retrospective chart review of 3806 consecutive choroidal nevi with imaging.

RESULTS: The median patient age was 62.5 years and Caucasian race in 3167 (95%). The choroidal nevus demonstrated median basal diameter of 4.0 mm and thickness of 1.4 mm. Imaging included optical coherence tomography (OCT) showing subretinal fluid (SRF) in 312 (9%), ultrasonography (US) with acoustic hollowness in 309 (9%), and hyper-autofluorescence (AF) in 100 (3%). Of those 2355 choroidal nevi with follow up, Kaplan-Meier estimates of nevus transformation into melanoma at 1, 5, and 10 years were 1.2%, 5.8%, and 13.9%, respectively. Multivariate analysis, using multimodal imaging for detection of factors predictive of nevus transformation into melanoma, included thickness >2 mm on US (hazard ratio (HR) 3.80, p<0.0001), fluid subretinal (OCT), symptoms vision loss (Snellen acuity), orange pigment (AF), melanoma hollowness (US), and diameter >5 mm (photography). The mean 5-year estimates of nevus growth into melanoma were 1% (HR 0.8) for those with 0 risk factor, 11% (HR 3.09) with 1 factor, 22% (HR 10.6) with 2 factors, 34% (HR 15.1) with 3 factors, 51% (HR 15.2) with 4 factors, 55% (HR 26.4) with 5 risk factors, and not-estimable with all 6 risk factors.

CONCLUSIONS: Multimodal imaging was capable of detecting risk factors for nevus transformation into melanoma, including thickness >2 mm (US), fluid subretinal (OCT), symptoms vision loss (Snellen acuity), orange pigment (AF), melanoma hollowness (US), and diameter >5 mm (photography). Increasing number of risk factors imparted greater risk for transformation.
Focal Aggregates of Normal Choroidal Melanocytes (Choroidal Melanocytic Clusters): A Distinct Clinical Entity

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PURPOSE: Most investigators who have published on the frequency of melanocytic choroidal nevi have reported values between 2% and 9% among Caucasian adults; however, one well known examiner (J.D.M. Gass) reported a frequency of over 30% among Caucasian persons >50 years of age. No one has ever challenged or explained the discrepancy between the Gass’ results and those of other investigators. The purpose of this study was to determine the frequency of melanocytic choroidal lesions \( \geq 0.25 \) mm in diameter in an independent group of Caucasian adults >50 years old.

METHODS: The authors evaluated 79 newly referred adult Caucasian individuals >50 years old prospectively. All of these individuals were referred for evaluation of an anterior segment or epibulbar lesion and not a fundus lesion. The authors performed a detailed fundus examination of every patient and identified and mapped all discrete melanotic choroidal lesions \( \geq 0.25 \) mm in diameter in each eye.

RESULTS: At least one discrete melanotic choroidal lesion was identified in 25 of the 79 patients (31.6%). Fourteen of the 25 patients (56%) had a single lesion in one eye, 6 (24%) had \( \geq 2 \) lesions in one eye, and 5 (20%) had \( \geq 1 \) lesion in each eye. All melanotic choroidal lesions identified in this study were <1 disc diameter in largest basal diameter and completely flat (i.e., not detectably thicker than normal choroid by B-scan ultrasonography). No classic choroidal nevus was identified in any of these patients.

CONCLUSIONS: Because our study identified a similar frequency of melanotic choroidal lesions as the prior studies reported by Gass, we conclude that Gass is likely to have counted small melanotic choroidal lesions without appreciable thickness as choroidal nevi. We prefer to regard lesions of this type as acquired focal aggregates of normal choroidal melanocytes (choroidal melanocytic clusters) and reserve the term melanocytic choroidal nevus for small melanotic fundus lesions having a largest basal diameter >1 disc diameter but \( \leq 5 \) mm and a maximal thickness greater than that of normal choroid at that site but \( \leq 1 \) mm (by B-scan ultrasonography).
Fine Needle Aspiration Biopsy for Cytopathologic Diagnosis of Posterior Segment Tumors in 494 Consecutive Patients

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PURPOSE: To evaluate fine needle aspiration biopsy (FNAB) for cytopathology in patients with posterior segment tumors for yield, diagnostic accuracy, and complications.

METHODS: Retrospective, nonrandomized, single center case series of 494 consecutive patients with diagnostically challenging posterior segment tumors who underwent FNAB for cytopathology.

RESULTS: The median patient age was 63 years. The most common referring diagnosis was choroidal melanoma (41%), choroidal metastasis (15%), choroidal nevus (4%), and choroidal lymphoma (3%). The median basal dimension of the lesion was 12 mm and median thickness was 5 mm. The majority of lesions were amelanotic (73%) and discrete/focal (91%). Fine needle aspiration biopsy was performed for cytopathology alone in 402 (81%) cases and for both cytopathology and cytogenetics in 94 (19%) cases. A pars plana transvitreal approach was used in the majority of cases (89%), and needle gauge was 22 (3%), 23 (1 mm in 209 (42%), or not present in 142 (29%) cases. Minimal vitreous hemorrhage (VH) was noted in 46 (9%) and substantial VH developed in 49 (10%) cases. Intraoperative hypotony was found in 81 (16%), requiring intravitreal injection of balanced salt solution. In the 406 patients with available follow-up at 5 months, persistent preretinal and/or subretinal hemorrhage was present in 14 (3%) and VH was present in 28 (6%) cases. Rhegmatogenous retinal detachment (RRD) occurred in 11 (3%) cases. Surgical intervention was performed for RRD in 5, combined RRD and VH in 4, and VH alone in 1 case. No patients developed lens damage, endophthalmitis, or extraocular tumor seeding.

CONCLUSIONS: Fine-needle aspiration biopsy is a reliable technique for cytopathologic identification of posterior segment tumors with clinically challenging diagnoses. Postoperative hemorrhage is transient, rarely requiring surgical intervention.
Universal Reflex Referral to VHL Comprehensive Clinical Care Center of Patients Presenting to Ophthalmologists Leads to Dramatic Improvement in Guideline-concordant Screening: Results of a Pilot Study

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PURPOSE: VHL affects many organ systems and requires treatment by multiple specialists. Thus, care is often fragmented. It is difficult for a physician seeing a VHL patient for the first time to ascertain which other specialists are ordering screening studies, and whether the patient’s screening is up-to-date and guideline-concordant. In 2017, Vanderbilt became one of a dozen CCCCs in the United States. We instituted a quality improvement initiative to improve guideline-concordant screening by referring all VHL patients presenting to our ophthalmology clinic to the Vanderbilt CCC for surveillance imaging, regardless of whether they were being followed by other specialists.

METHODS: Retrospective case series of patients presenting to Vanderbilt Eye Institute, both before institution of the CCC in 2017 as well as afterwards. Beginning in 2017, all patients were referred to the CCC medical or pediatric oncologist for evaluation and surveillance. Patients referred to ophthalmology from the CCC oncologists were excluded. Rates of CCC referral from ophthalmology to oncology were measured. Guideline-concordant screening status was determined for patients prior to seeing ophthalmology, as well as afterwards. These rates were determined in both the pre-2017 and post-2017 cohorts. Tumors identified on initial screening were recorded.

RESULTS: 100% of VHL patients presenting to ophthalmology were referred to CCC oncologists. Almost all patients were already followed by other specialists. Prior to creating the CCC in 2017, 0% of patients were guideline-concordant at the time they presented to ophthalmology, and 29% were concordant afterwards. After creating the CCC and the reflex referral initiative, 20% of patients were guideline-concordant at presentation, and 100% were concordant after seeing the CCC oncologist. 50% of patients referred from ophthalmology to CCC oncology had tumors requiring intervention at the time of initial screening imaging. These included renal cell carcinomas (>3cm), pheochromocytomas, metastatic rhabdoid tumors, and central nervous system hemangioblastomas.

CONCLUSIONS: Rates of guideline-concordant screening have historically been poor, even for patients being followed for VHL-related tumors by subspecialists. Universal reflex referral of VHL patients to a CCC dramatically improved guideline-concordant screening rates to 100%. Half of all patients have a (non-ocular) tumor requiring treatment at the time they present to ophthalmology, underscoring the importance of expeditious referral.
USA Health Policy Directions: A single payer like the UK’s NHS?

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Many Americans (more than a majority in some surveys) covet a health care system that functions like the U.K.’s National Health Service (NHS). They argue that everyone in the U.K. has easy health care access and the cost is zero. By a number of measures, the NHS outperforms the U.S. health care system in developed nations’ quality measures. What not to love? American healthcare costs exceeded $3.5 trillion last year or nearly 20% of our GDP. That equaled nearly $10,400 per American. By comparison, the U.K. cost was $4,192 per person. That difference would fund the interest on the national debt, all military, food and agriculture, transportation, education, energy, environment, and veterans benefits costs—with about $0.5 trillion left over. (No wonder single-payer systems put dollar signs in politicians’ and economists’ eyes!)

National (and a handful of state) politicians are looking to the U.K., Canada, and a few other countries in designing a single-payer health care system (SPS). California is not the only state where SPS is in front of the legislature or on a state initiative. Consider Vermont, Colorado, New York, and Michigan—among others.

Developed nations’ SPS’s vary considerably. In the United Kingdom, the government is the single direct payer. Its National Health System is the world’s largest health service and employs about 3% of the U.K.’s population! (However, about 11% of the population have supplementary private insurance and others pay cash to access the private sector—sometimes referred to as the “Harley Street” option.)

From the standpoint of its advocates, the NHS solves the twin goals of universal coverage and reducing costs. Most care is completely covered and those covered services don’t result in any out-of-pocket costs. Those opposed to the NHS point out that universal coverage isn’t actually universal access if the system is so resource-constrained that there are long waiting lists for care or if many services aren’t included. And they point out that the services are not free; they are supported by the tax base.

Most U.S. health policy wonks believe that within the next five years the U.S. will move closer to an SPS with an expansion of Medicare to a ‘Medicare-like’ system to a greater percentage of the American population and substantive new cost contraints. Is the U.K.’s NHS a model that could be grated onto the ‘American system?’
Phenotypic Spectrum of Pentosan Polysulfate-associated Maculopathy: Report of 35 Cases

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PURPOSE: We recently described a novel maculopathy observed in 6 patients with chronic exposure to pentosan polysulfate sodium (PPS), the only FDA-approved oral medication for interstitial cystitis (IC). In this study, we conducted a multi-institutional, retrospective review of patient records to further characterize this maculopathy. We hypothesized that it would affect patients with chronic PPS exposure, and predominantly manifest structural changes at the level of the retinal pigment epithelium.

METHODS: Medical and ophthalmic imaging records of patients diagnosed with PPS-associated maculopathy were reviewed at the Emory Eye Center (n=16), Casey Eye Institute (n=6), Kellogg Eye Center (n=11) and Northern California Retina Vitreous Associates (n=2). Clinical data including demographics, visual symptoms, history of IC and PPS exposure, and exam findings were retrieved. Multimodal ophthalmic imaging was evaluated to assess the phenotypic spectrum of disease.

RESULTS: Among 35 confirmed cases of PPS-associated maculopathy, 34 were female and the median age was 61 years (range, 38–79 years). Median PPS intake duration and daily dose were 14.5 years (range, 3–21.9) and 300 mg/day (range, 150–592 mg), respectively. The three leading symptoms were blurred vision while reading (48.6%), prolonged dark adaptation (43.8%) and metamorphopsia (11.4%). Median logMAR BCVA in both right and left eyes was 0.10 (Snellen equivalent, 20/25, OD range = 0 – 1.18, OS range = -0.12 – 1.30, p = 0.94). In all patients, pathology manifested bilaterally in the posterior pole. Fundus photography revealed hyperpigmented macular spots in 53.1% of eyes, and/or RPE atrophy, noted in 39.4%. Fundus autofluorescence permitted the best visualization of the macular changes, typically revealing a well-circumscribed pattern (56.1%) of densely-packed hyper- and hypoautofluorescent spots involving the fovea, but occasionally extending to the retinal periphery. Optical coherence tomography revealed foci of RPE nodularity associated with hyperreflectance on near infrared reflectance imaging.

CONCLUSIONS: PPS-associated maculopathy manifests in the setting of chronic exposure to the drug, and results in characteristic pigmentary changes suggesting a primary disturbance at the RPE and RPE-photoreceptor interface. Importantly, this condition may masquerade as other known conditions including age-related macular degeneration. We recommend drug cessation in affected patients.
Strength of Association between Pentosan Polysulfate Exposure and a Newly Described Maculopathy among Patients with Interstitial Cystitis

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PURPOSE: Interstitial cystitis (IC) is a chronic regional pain syndrome of the bladder and pelvis, for which only one oral medication has been approved by the United States Food and Drug Administration (FDA): pentosan polysulfate sodium (PPS). Recently, we described 6 cases of a unique pigmentary maculopathy in patients reporting chronic exposure to PPS. In this study, we evaluated risk factors for development of this condition among patients diagnosed with IC. We hypothesized that PPS would emerge as the sole predictor of this maculopathy.

METHODS: A retrospective cross-sectional study was performed. All patients of the Emory Eye Center harboring a diagnosis of IC between May 2014 and October 2018 were included in the study. Patient records were reviewed for documented exposure to PPS, and off-label IC therapies including hydroxyzine, tricyclic antidepressants, gabapentin, cyclobenzaprine, methenamine, phenazopyridine, and oxybutynin. Histories of hydroxychloroquine use and cigarette smoking were also reviewed. Masked graders assessed posterior segment images of all patients for resemblance to the characteristic maculopathy according to predetermined criteria. Fisher’s exact tests and independent two-sample T-tests were used to study the association of categorical and continuous variables with the outcome. We adjusted for multiple comparisons using the Holm-Bonferroni correction.

RESULTS: 219 patients were included in the study. Reviewers diagnosed 14 cases of the characteristic maculopathy amongst a total of 80 patients with documented PPS exposure. No cases were diagnosed in the remaining 139 unexposed patients. PPS was the sole statistically significant predictor of the novel maculopathy amongst all covariates evaluated (odds ratio: 11.25, 95% CI: 3.69 – 34.33, p<0.0001). Among the 14 affected patients, median duration of PPS intake and cumulative exposure among were 18.3 years (range, 3 – 21.9 years) and 2.3 kg (range, 0.58 – 2.98 kg), respectively.

CONCLUSIONS: These findings strongly implicate PPS, and no other IC-related exposure, in the development of a vision-threatening maculopathy. At this time, we recommend cessation of PPS intake in all affected individuals. Future investigations will seek to elucidate the mechanism of disease and inform screening guidelines.
Novel Multi-modal Image Analysis to Quantify Pentosan Polysulfate Sodium (Elmiron) Retinal Toxicity Demonstrates an Exponential Dose-response Curve

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PURPOSE: To develop a novel multi-modal image analysis to quantify Pentosan Polysulfate Sodium (PPS, Elmiron) retinal toxicity and to investigate the mathematic correlation between the cumulative dose and the magnitude of retinal toxicity.

METHODS: A cross-section, observational study was performed using the Epic electronic healthcare record system. The records of all UMass Memorial Healthcare patients were searched for patients using PPS longer than 3 years, with a minimum daily consumption of 100 mg. Patients with any maculopathy, including macular degeneration, macular dystrophy, or known drug-induced maculopathy were excluded. Additionally, patients with refractive error greater than ±3 diopters, history of prior ocular surgery or a coexisting ocular disease, or patients with any media opacities were excluded. All patients were invited to undergo a comprehensive ophthalmic evaluation and multimodal imaging. Imaging modalities included wide field funduscopic color photography, infra-red autofluorescence (IRA), wide field autofluorescence (AF), optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Qualitative and quantitative analysis of images were performed. The quantitative analysis included the calculation of the ratio between AF intensity signal in the fovea and in perifovea in all study eyes (AFI ratio), IRA entropy, the ratio between the thickness of the fovea and the thickness of the perifovea area (FT ratio), and vascular density of the different layers of vasculature on OCTA. This study was approved by the Institutional Review Board of the University of Massachusetts Medical School, Worcester.

RESULTS: Thirty-four eyes of 17 patients (14 females, 3 males) were included. Average age was 52.82± 10.6, average BMI was 28.38± 5.71, the cumulative average PPS years exposure was 11.82±6.84 years, the average cumulative PPS grams exposure was 1121.84±1006.71 grams, the average logMAR VA was 0.061±0.09.

Qualitative analysis showed significant changes only in 3 patients who were exposed to highest doses of PPS, including subtle retinal pigment epithelium changes, central pattern of hypo-autofluorescence accompanied by scattered hyper-autofluorescent areas on AF, and a ‘flying saucer’ macular OCT configuration.

AFI ratio and IRA entropy were exponentially correlated with PPS standardized cumulative dose $f= 0.3\exp(-0.02*x)$, R=0.88, $R^2=0.95$, P<0.05. FT ratio was significantly correlated with PPS standardized cumulative dose $f= 0.3\exp(-0.02*x)$, R=0.9, $R^2=0.089$, P<0.002. The changes in vascular density and vascular intensity of the superficial plexus layer, deep plexus layer, choriocapillaris layer and choroid were found not to correlate with cumulative PPS dose.

CONCLUSIONS: This study is the first to demonstrate the exponential dose-response correlation between exposure to PPS and retinal toxicity. The novel image analysis techniques that were developed present an opportunity and a tool to further investigate, better understand and quantify the correlations between chronic exposure to systemic medications and retinal toxicity.
Outer Hemorrhagic Henle Maculopathy (OHHM): Clinical Features and Pathogenesis of a New Syndrome

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PURPOSE: To describe the clinical presentation and multimodal imaging characteristics of deep retinal hemorrhages primarily located in Henle’s fiber layer around the fovea. The spectrum of etiologies and theories of pathogenesis are presented.

METHODS: This study is a multicenter, retrospective, descriptive case series of patients with retinal hemorrhage localized to Henle’s fiber layer in the perifoveal region and contributed by retinal specialists worldwide. Clinical diagnosis, systemic and ocular risk factors, visual acuity at presentation and follow-up and multimodal imaging including color fundus photography and cross sectional and en face optical coherence tomography (OCT) findings were collected and analyzed for each patient.

RESULTS: Retinal hemorrhages primarily localized to Henle’s fiber layer were featured in 23 patients with the following etiologies: acute blunt traumatic injury to the head (n=2), eye (n=1), or trunk (n=1), intracranial aneurysm rupture (Terson’s syndrome, n=3), general anesthesia (n=1), epidural anesthesia (n=1), hypertension with anemia (n=1), decompression retinopathy (n=1), post vitrectomy with intraocular expansile gas (n=1), retinal vein occlusion (n=7), myopic degeneration (n=2), macular telangiectasia type 2 (n=1) and aneurysmal type 1 neovascularization (n=1). The defining clinical features included deep retinal hemorrhage with a feathery margin and petaloid pattern radiating from the center of the fovea. OCT demonstrated characteristic hyperreflectivity of the hemorrhage that was delineated by obliquely oriented Henle’s fibers. Spontaneous resolution of the hemorrhage in the Henle layer occurred in the 15 patients by 3 months for which follow-up was available.

CONCLUSIONS: The characteristic presentation of deep, petaloid shaped, retinal hemorrhage with a feathery margin primarily localized in Henle’s fiber layer represents a unique syndrome associated with various disorders. We propose the anatomic term “Outer Hemorrhagic Henle’s maculopathy” (OHHM) to describe this presentation which may result from elevated retinal venous pressure due to systemic or local retinovascular disorders affecting the deep capillary plexus or from choroidal vascular abnormalities.
The epithelial-mesenchymal transition (EMT) is a key process in fibrogenic diseases where transdifferentiated myofibroblasts produce excessive amounts of extracellular matrix, resulting in organ dysfunction. Idiopathic epiretinal membrane (iERM) is a vision-threatening disorder characterized by fibrocellular proliferation and contraction on the central retina. Müller glial cells, which regulate retinal physiology and structure, are the major cellular components in the iERM tissue; however, the pathological role of this cell type remains incompletely understood. Here we revealed the involvement of Müller glial-mesenchymal transition (GMT), as an alternative to EMT, in the pathogenesis of iERM lacking epithelial contribution in nature.

METHODS: The human Müller glial cell line (MIO-M1) was used to analyze EMT-like changes in response to cytokines. The expression of EMT-related molecular markers were assessed by real-time quantitative PCR, immunoblot analyses, and immunocytochemistry. EMT-related cell motility was examined by cell migration, invasion, and proliferation assays. Human surgical samples were evaluated by immunohistochemistry.

RESULTS: Of various pro-fibrotic cytokines, transforming growth factor (TGF)-β1 stimulation to human Müller glial cells exclusively increased mRNA and protein levels of several EMT-related molecular markers, together with the transcription factor SNAIL but not SLUG or TWIST. TGF-β1-stimulated Müller cells also exhibited EMT-related cell motility, while reducing the expression of glutamine synthetase (GS), a Müller glial marker. Notably, all of these TGF-β1-induced EMT features were reversed by SNAI1 knockdown in Müller cells. iERM patient specimens demonstrated co-immunolocalization of SNAIL with TGF-β1, GS, and smooth muscle protein 22.

CONCLUSIONS: Our data implicated a critical role of the TGF-β-SNAIL axis in Müller GMT to promote iERM formation.
Primary Retinal Vascular Abnormalities in Neurofibromatosis Type 1 (NF1): a NF1 Related Capillary Hemangioma

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PURPOSE: To evaluate the prevalence, clinical features, and diagnostic implications of primary retinal vascular abnormalities (RVA) associated to neurofibromatosis Type 1 (NF1) in a large cohort of young patients.

METHODS: Six hundred and twenty-four (624) young (<18 years) patients affected by NF1 were consecutively enrolled, and followed on a yearly basis. At baseline, each patient underwent genetic, dermatologic, and ophthalmologic examination, to evaluate the presence/absence of each NIH standard diagnostic criterion. The presence of RVA was diagnosed by means of infrared confocal scanning laser ophthalmoscopy images, by two masked observers. Three hundred (300) healthy subjects were enrolled as control group. Fluorescein angiography, indocyanine green angiography, and optical coherence tomography angiography (OCT A) were also performed in eyes with RVA.

RESULTS: Primary retinal vascular abnormalities were detected in 34 patients (6.3%) with NF1 and in none of the healthy subjects. These retinal vascular abnormalities appeared in all cases as well-defined, small, tortuous retinal vessels with a spiral aspect, originating from small tributaries of retinal veins. The presence of RVA was not correlated with the presence of any other specific ocular or systemic NF1 features (P> 0.05, for all). On optical coherence tomography angiography, RVA appeared as a complex of isolated tortuous vessels in the superficial capillary plexus in all cases, associated with localized anomalous crowded and congested capillary network in the deep vascular plexus, in 75% of cases. No FA or ICGA leakage was related to RVA. No RVA changes were observed during follow-up, performed using both infrared imaging and OCT angiography. The agreement for RVA detection between operators was complete (ICC: 1.0)

CONCLUSIONS: Primary retinal vascular abnormalities are present in a limited proportion of young patients affected by NF1, and can be considered as an additional distinctive sign of NF1. These vascular abnormalities have clinical and angiographic, including OCT A, characteristics which allow to classify them as a primary specific disease related type of retinal capillary hemangioma. These observations open new insights in the diagnostic criteria for NF1 and in the classification of different retinal lesions in NF1.

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PURPOSE: von Hippel-Lindau (VHL) affects >10 organ systems, but the most common manifestation is the retinal capillary hemangioblastoma. Active surveillance improves patient outcomes, and guidelines for retinal screening, as well as for other organ systems, have been developed. The majority of previous guidelines, including those previously developed by the VHL Alliance, have been based on expert opinion, rather than systematic review of the literature. Beginning in late 2018, the VHL Alliance spearheaded an effort that assembled an international consortium of 50+ VHL experts tasked with developing new surveillance guidelines for each organ system. This abstract reports on the results of the ophthalmology subcommittee, and focuses not just on the new approach and newly-expanded areas covered by the guidelines, but also reports, for the first time in a public setting, the new retinal screening guidelines for 2020.

METHODS: The ophthalmology subcommittee was tasked with an expanded scope of topics (covered below under Results), with systematic review of the literature (graded according to evidence level), and with developing the new retinal screening guidelines.

RESULTS: The approach to developing the new 2020 surveillance guidelines was based on systematic review of the literature, rather than only expert opinion as with previous guidelines. Expert consensus was used where only low-level evidence was available. The scope was expanded to address several questions beyond just the frequency of examination, including: Age at which to initiate surveillance, frequency of surveillance of not-previously-affected individuals by age group, special situations such as puberty and pregnancy in which the frequency is altered, age at which routine surveillance may cease, the use of anesthesia in evaluating young children, the use of advanced and widefield imaging modalities, guidelines for managing tiny presymptomatic retinal lesions, and frequency of secondary surveillance of patients with a history of ocular involvement.

CONCLUSIONS: The specific 2020 VHL retinal screening guidelines are presented in detail here for the first time. These new evidence-based guidelines result in more-intensive evaluation of young children, increased frequency during the first several decades of life, recommendations for increased use of widefield imaging, and more proactive/early treatment of smaller lesions.
Results of a Phase 1/2 Trial of an Optimized Gene Therapy in Adults and Children with Retinal Dystrophy Associated with Bi-allelic Variants in RPE65

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PURPOSE: In this Phase 1/2 trial we investigated an AAV2/5-RPE65 gene therapy optimized for transduction efficiency, potency and stability (NCT02781480). Foveal detachment and a volume of up to 1.0 mL was investigated to permit coverage of the entire potentially treatable retina including central vision.

METHODS: Fifteen subjects received subretinal administration of AAV2/5-RPE65 in the more affected eye. Nine adults (age 16-24) were dosed in a dose escalation phase, with 3 subjects per dose (1x10^11, 3x10^11 and 1x10^12 vg/ml). In the expansion phase, six children (age 5-12) were treated at 1x10^11 vg/ml. Outcome measures included safety, functional vision (mobility testing), retinal sensitivity (static perimetry), visual acuity (ETDRS) and contrast sensitivity (Pelli-Robson).

RESULTS: AAV2/5-RPE65 was generally well-tolerated, with a safety profile that was consistent with other approved and investigational ocular gene therapies. Subretinal injection targeting the central retina, including the fovea, was demonstrated to be safe and well tolerated. Retinal thinning was not observed in this study in either adults or children. After 6 months, across all study cohorts, improvement from baseline in the treated eye compared to the untreated eye was demonstrated in vision-guided mobility testing (p<.002); and in the adults and children dosed at 1x10^11 (n=9), after 6 months, improvement from baseline in the treated eye compared to the untreated eye was also demonstrated in retinal sensitivity (p<.008); visual acuity (p<0.016) and contrast sensitivity (p<0.016). Greater improvement in retinal sensitivity was observed in children than adults, most likely due to the increased preservation of the retina in younger patients.

CONCLUSIONS: 1x10^11 was determined to be the optimal dose for future clinical use due to the safety and activity profile observed among patients treated with this titer. We demonstrate that the unmet need of targeting central vision can be safely addressed by delivery of an optimized vector subretinally to include the fovea. Six months after receiving subretinal injection of AAV2/5-RPE65 gene therapy, statistically significant improvement from baseline in the treated eyes compared to the untreated eyes was demonstrated in measures of functional vision, visual function and retinal function.
Novel Anti-VEGF Antibody Biopolymer Conjugate KSI-301 with Potential for Extended Durability in Retinal Vascular Diseases: Late-Breaking Results from a Phase 1b Study in Patients with wAMD, DME and RVO

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PURPOSE: Antibody Biopolymer Conjugates (ABC Medicines) are a new class of molecules designed for extended intraocular durability, consisting of an antibody stably linked to an optically clear, high molecular weight phosphorylcholine biopolymer. KSI-301 is an anti-VEGF ABC that demonstrates in preclinical data high retinal tissue bioavailability, high binding affinity and anti-VEGF potency, extended intraocular half-life, and rapid systemic clearance, and is delivered via intravitreal injection. In a Phase 1a study in DME, KSI-301 demonstrated safety and durable bioactivity.

METHODS: The Phase 1b study evaluates safety and efficacy of multiple doses of KSI-301 in wAMD, DME/DR, and RVO. The Phase 1b study of KSI-301 is an open-label study to investigate the bioactivity and safety of KSI-301 following multiple intravitreal administrations in treatment-naïve subjects with wAMD, DME/DR and RVO. The study evaluates two dose levels, 2.5 mg and 5 mg. Subjects receive 3 initial injections every 4 weeks. Protocol-guided retreatment starts at Week 12. Approximately 30 subjects are being enrolled in each cohort.

RESULTS: The phase 1b study is on-going with 80 subjects enrolled. As of July 27, 2019, ocular safety of KSI-301 has been encouraging with no reports of intraocular inflammation and no drug-related adverse events after 200 doses given. Initial results have been presented for the first 35 patients that reached 12 weeks of follow-up. Rapid, high-magnitude responses were observed in all cohorts. The median improvement in ETDRS BCVA score was +8 letters in wAMD (n=17, baseline 66 letters), +9.5 letters in DME (n=8, baseline 69.5 letters) and +26.5 letters in RVO (n=10, baseline 52.5 letters). The median improvement in OCT CST was -96 microns in wAMD (baseline 380 microns), -197 microns in DME (baseline 491) and -209 microns in RVO (baseline 513). This presentation will include late-breaking data (expected full enrollment, 230+ doses given, and data beyond the loading phase to Week 16 or beyond).

CONCLUSIONS: Novel ABC Medicines have been designed for ophthalmic use with a goal of meaningfully improved treatment durability. In the Phase 1b multiple-dose study, KSI-301 has demonstrated strong efficacy and excellent safety in wAMD, DME/DR, and RVO. This presentation will include late-breaking data.
Results of a Phase 1, Open-label, Dose-escalation Study of THR-149 for the Treatment of Diabetic Macular Oedema (DME)

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PURPOSE: THR-149 is a novel bicyclic inhibitor of plasma kallikrein (PKal), a serine protease implicated in the development of DME. Here, we present safety and preliminary efficacy data from a Phase 1 dose-escalation study of THR-149 in subjects with DME, including first presentation of selected exploratory endpoints.

METHODS: Subjects were enrolled according to an open-label, 3+3 dose-escalation design, and followed for 3 months after a single intravitreal injection of THR-149. All subjects had centre-involved DME with a history of response to anti-VEGF and/or corticosteroid treatment in the study eye, CST of 320 µm on OCT, and BCVA ETDRS letter score of 23–62. The primary endpoint was incidence of dose-limiting toxicities (DLTs). Secondary endpoints included incidence of (serious) AEs ([S]AEs). Key exploratory endpoints included change from Baseline (BL) in BCVA and CST, THR-149 plasma levels by Day 7, and biomarker levels in anterior chamber aqueous humour by Day 7. Post-hoc analysis was performed to determine correlation between BL parameters and efficacy outcomes.

RESULTS: Twelve subjects were treated at 5 sites in the United States; 3 received 0.005 mg, 3 received 0.021 mg, and 6 received 0.125 mg THR-149. No DLTs or ocular SAEs were reported. Across all doses, the mean BCVA change from BL increased rapidly and was highest at Day 14 (+7.5 letters), with a mean of +6.4 letters at Month 3. Mean CST change from BL after an initial decrease at Day 1, increased and was +30.4 µm at Month 3. At Day 7, THR-149 was undetectable in the plasma of all subjects. At BL, PKal levels in aqueous humour samples ranged from 314 to 5621 pg/mL; however, no correlation was found with BCVA or CST outcomes. Post-hoc analysis indicated that subjects with better BCVA at BL and a smaller macular volume tended to have more improvement in BCVA after treatment.

CONCLUSIONS: THR-149 is safe and well tolerated. Preliminary efficacy data indicate improvements in mean BCVA throughout the study. Mean CST change from baseline was minimal and not clinically meaningful. Presence and level of PKal at baseline were not shown to be predictive of clinical efficacy outcomes.
Suprachoroidal Injection of CLS-TA in Uveitis Maintains Efficacy Outcomes Through 48-weeks: Results of the MAGNOLIA Phase 3 Extension Study

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PURPOSE: To determine if patients treated with suprachoroidal injections of triamcinolone acetonide CLS-TA at Baseline & Week 12 (W12) in the PEACHTREE study maintain efficacy outcomes through week 48.

METHODS: Subjects with macular edema associated with uveitis of any anatomic subtype (anterior, intermediate, posterior, or panuveitis) treated with CLS-TA at baseline and W12 in the PEACHTREE study were followed for an additional 24 weeks in MAGNOLIA, a prospective, non-interventional, masked, observational, extension trial. The total evaluation period was 48 weeks. Subjects who completed PEACHTREE and did not receive rescue medication were eligible for MAGNOLIA. In addition, only a subset of PEACHTREE sites were selected to participate in MAGNOLIA. The primary outcome in MAGNOLIA was the time to rescue therapy relative to Day 0 of PEACHTREE. Secondary outcomes included incidence of adverse events grouped by organ system. No further injections of CLS-TA were administered after PEACHTREE W12. The baseline characteristics of patients enrolled into MAGNOLIA were compared to patients who were eligible but did not enroll to ensure generalizability.

RESULTS: Of the 61 potential subjects from PEACHTREE from sites where the MAGNOLIA extension study was offered, 33 qualified and participated. Of the 28 subjects from the PEACHTREE CLS-TA arm, 14 patients (50%) completed MAGNOLIA without receiving any additional medication through W48 (36 weeks after the last treatment in PEACHTREE in W12). 5 subjects were incidentally enrolled into MAGNOLIA from the PEACHTREE sham arm to maintain blinding in PEACHTREE and were not included in this analysis. Mean time to rescue therapy in MAGNOLIA was 344 days. Patients gained a mean of 16 letters through W24 and 12 letters through W48. No SAEs related to study treatment were observed; all safety events including new reports of IOP elevations and cataract progression will be reported. Baseline characteristics of MAGNOLIA patients were similar to eligible patients who did not enroll (p>0.05 on all covariates).

CONCLUSIONS: CLS-TA-treated patients were able to maintain efficacy outcomes through week 48 in the MAGNOLIA extension study. Half of patients did not require additional treatment 36 weeks after their last injection of CLS-TA.
**Suprachoroidal Triamcinolone Acetonide Suspension (CLS-TA) and Intraocular Pressure: Results from the Phase 3 PEACHTREE Clinical Trial for Uveitis**

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**PURPOSE:** To evaluate intraocular pressure (IOP) in noninfectious uveitis (NIU) patients following suprachoroidal injection of CLS-TA (triamcinolone acetonide suspension), which in principal can more precisely target chorioretinal tissues while limiting exposure to the anterior segment of the eye.

**METHODS:** 160 participants were randomized 3:2 to receive suprachoroidal injections of CLS-TA or sham at baseline and week 12, and rescue therapy if needed. Pre-injection IOP was assessed every 4 weeks through week 24. Prespecified IOP endpoints included: >10mmHg increase in IOP from baseline, >30mmHg IOP at any visit, IOP medication use, surgical intervention for IOP, and mean IOP. The primary analysis included events that occurred in all patients randomized to each arm, regardless of if they received rescue treatment. A post hoc analysis was also conducted that compared patients who only received CLS-TA to patients who only received rescue treatment.

**RESULTS:** By week 24, 13% of the patients in the CLS-TA arm and 72% in the control arm required rescue therapy. Rescue therapies consisted primarily of topical (51%) and intravitreal (31%) corticosteroids. A similar proportion of CLS-TA and sham patients experienced a >10mmHg increase in IOP from baseline (15.8% vs 17.2%; p>.05) or an IOP >30mmHg at any visit (5.3% vs 7.8%; p>.05). A similar proportion were treated with IOP-lowering medication (7.3% vs 9.4%; p>.05). No patients required surgical intervention for IOP elevation. Mean IOP was low throughout the study in both arms and remained low through week 24 (15.0 mmHg vs 14.7 mmHg; p>.05). The post hoc analysis found that patients who only received CLS-TA experienced lower rates of IOP events than patients who only received rescue therapy. In this analysis, CLS-TA patients experienced lower rates of >10mmHg increases in IOP from baseline (12.2% vs 23.9%), IOP >30mmHg at any visit (4.9% vs 10.9%) and use of IOP lowering medications (7.2% vs 13%).

**CONCLUSIONS:** Suprachoroidal injections of CLS-TA did not significantly increase IOP relative to sham control (+/- rescue therapy) in the Phase 3 PEACHTREE study. Patients who only received CLS-TA experienced lower rates of IOP events relative to patients that only received rescue therapy.
Duration of Effect for Long-acting Injectable Fluocinolone Acetonide Implant for Noninfectious Uveitis

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PURPOSE: To determine the length of time to disease recurrence after implantation with the long-acting, injectable 0.18mg fluocinolone acetonide implant (FAi) in noninfectious intermediate uveitis, posterior uveitis, and panuveitis.

METHODS: This was a longitudinal, follow-up study of patients who had completed a two-year, prospective, interventional, investigator-sponsored, investigational new drug (IND) study with FAi. Records of patients who had office visits with the principal investigator (GJJ) for at least 12 months after initial study completion were reviewed. Uveitis recurrence was defined as: 2 step increase in anterior chamber cell or 2 step increase in vitreous haze requiring the need for additional anti-inflammatory therapy. Cystoid macular edema (CME) was defined as increased macular thickening of 10% or more in central subfield thickness or appearance of new intra-retinal cysts on optical coherence tomography (OCT).

RESULTS: Of the 16 participants from the initial IND study, 12 eyes from 12 participants (mean age 43 years, 25 – 64 years; 10/12 female) were included for the longitudinal follow-up study. Patients were followed for a mean of 34.2 months (range, 12.0 – 56.9 months) with an average of 9.3 visits (range, 2 – 18 visits). Five eyes of 5 participants (42%) had a uveitis recurrence after FAi, with a mean time to first recurrence of 36.1 months (range, 22.8 – 61.1 months) after FAi implantation. Two eyes of 2 participants (16%) had CME alone without increase in inflammation, with a mean time to occurrence of 36.9 months (range, 36.1 – 42.1 months) after FAi implantation. Five eyes of 5 patients (42%) did not have a documented recurrence of uveitis or CME. These patients had a mean follow-up of 29.8 months (range, 12.3 – 52.9 months) with an average of 6 office visits (range 1 to 15). In total, 4 eyes (33%) had intraocular pressure elevations above 21mmHg with 2 eventually undergoing incisional glaucoma surgery.

CONCLUSIONS: Real-world data suggests that the injectable FAi for noninfectious uveitis lasts on average 3 years. These long-term data support the safety and efficacy of FAi for control of noninfectious uveitis.
The Use of Adjunctive Anti-inflammatory Medications: Results from a 3 Year Study of a Fluocinolone Acetonide Intravitreal Insert in Chronic Non-infectious Uveitis Affecting the Posterior Segment

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PURPOSE: Repeated use of systemic and local anti-inflammatory therapies are often required to manage patients with Chronic Non-Infectious Uveitis Affecting the Posterior Segment (NIPU). This study evaluated the effect that one 0.18 mg fluocinolone acetonide intravitreal insert (FAi) delivering microdoses of steroid had on the need for additional anti-inflammatory therapies during 36 months.

METHODS: Subjects with a > 1-year history of recurrent NIPU, who had experienced at least 2 separate recurrences requiring ≥ 3 months of systemic therapy or ≥ 2 intra- or periocular steroid injections, were randomized to treatment with FAi or sham. Treatment of recurrent intraocular inflammation was per the investigator’s discretion. When possible, systemic therapy was used only if local therapy failed. Adjunctive medication use was compared annually during the 3-year clinical trial (NCT #01694186 and #02746991).

RESULTS: The rate of recurrence was significantly reduced in the FAi versus sham-treated eyes (56% vs 93%, p<0.001). Local treatments (Intraocular or peri-ocular steroid injections) were used 23 times to treat inflammation in 17/87 (19.5%) FAi-treated eyes and 99 times to treat 29/42 (69.0%) sham eyes during the 3-year study. These treatment rates represented an increase for both FAi and sham compared to year 1 (6.9% and 61.9% respectively) and year 2 (16.1% and 66.7% respectively). For systemic treatment, in the first year, 17/87 (19.5%) of the FAi patients received a total of 34 systemic treatments while 17/42 (40.5%) of the sham patients received 30 treatments. Systemic treatment rates increased to 34.5% and 50% respectively by 3 years.

CONCLUSIONS: Treatment with a single intravitreal injection of the FAi reduced the 3-year rate of recurrence and significantly reduced the need for adjunctive local and systemic therapies in this group of patients.
Minimizing Uveitic Recurrences: Results from a 36M Study of Fluocinolone Acetonide Intravitreal Insert in Subjects with Chronic Non-infectious Uveitis Affecting the Posterior Segment

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PURPOSE: Cumulative damage from repeated inflammatory episodes can result in permanent vision loss in patients with non-infectious posterior uveitis (NIPU). The cumulative number of recurrences of uveitis over a 3 year period was compared among eyes treated with the fluocinolone acetonide intravitreal insert (FAi) and those treated with a sham injection in a prospective, randomized, double-masked phase 3 clinical trial.

METHODS: Subjects with a > 1-year history of recurrent NIPU, who had experienced at least 2 separate recurrences requiring >/= 3 months of systemic therapy or >/=2 intra- or periocular steroid injections, were randomized to treatment with FAi or sham. Cumulative recurrence of uveitis, defined as 1) >/= +2 increase in vitreous haze; or 2) >/= 15-letter loss of VA; or imputed in case of missing data or for rescue treatment of ocular inflammation, was compared annually during the 3-year clinical trial.

RESULTS: Uveitis recurrence rate, was significantly reduced in the FAi versus sham injected eyes (56% vs 93%, p1) recurrences were observed in 21.8% (19/87) of the FAi treated eyes and 73.8% (31/42) of the sham treated eyes. The 3-year cumulative recurrence totals were increased from 40 (1y) and 81 (2y) in FAi treated eyes and from 77 (1y) and 126 (2y) in sham treated eyes. Adverse events included elevated IOP requiring medical treatment (42% FAi vs 33% sham) and cataract extractions (74% FAi vs 24% sham).

CONCLUSIONS: Treatment with the FAi not only resulted in a reduced the 3-year rate of uveitic recurrences but also reduced the cumulative number of inflammatory episodes in eyes that did relapse. FAi is a viable strategy in reducing recurrence in chronic or recurrent NIPU.
Patient Comfort and Antimicrobial Efficacy of Aqueous Chlorhexidine Compared to Povidone Iodine as an Ocular Surface Disinfectant Prior to Intravitreal Injection: A Randomized Clinical Trial

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**PURPOSE:** Topical povidone iodine (PI) is widely used as an ocular surface antiseptic for intravitreal injections (IVI). While PI is generally well-tolerated, it can be associated with ocular discomfort. Aqueous chlorhexidine (AC) has been described as a better-tolerated antimicrobial for ophthalmic procedures. We compared patient pain scores, ocular surface characteristics, and antimicrobial properties between povidone iodine 5% and aqueous chlorhexidine 0.1% during IVI.

**METHODS:** A prospective single-center, masked study was conducted of patients receiving same-day bilateral IVI of anti-VEGF medications using PI and AC for ocular surface decontamination. Each patient had one eye randomized to either PI or AC, while the second eye received the other agent. Both eyes received topical proparacaine 0.5%. After IVI, each eye was assessed using a standardized quantitative grading system of corneal epitheliopathy (ocular staining score, OSS). Participants rated their pain (Wong-Baker) scale 0-10) for each eye one minute after PI or AC instillation and one day after the procedure. Each eye was evaluated using microbial swab cultures both prior to instillation of topical disinfectant and following IVI.

**RESULTS:** One hundred eyes of 50 patients were included. The average patient age was 68 years (range 39-92) and 30/50 (60%) were male. Compared to AC, eyes receiving PI had a significantly greater mean pain score immediately after injection (1.44 vs 0.44, p<0.001), but not on post-procedure day one (1.04 vs 0.48, p=0.06). Eyes that received PI had a significantly higher OSS indicating worse corneal epitheliopathy (4.22 vs 3.1, p<0.001). There was no significant difference in rates of positive microbial cultures between groups. There was no difference in rates of adverse events between groups (p=0.99) and no cases of endophthalmitis occurred.

**CONCLUSIONS:** PI demonstrated greater ocular surface discomfort and corneal epitheliopathy compared to AC during same-day bilateral IVI. The disinfecting agents otherwise demonstrated no difference in positive microbial cultures or adverse events. AC may be a better-tolerated alternative to PI for antimicrobial prophylaxis during IVI.
Toxic Posterior Segment Syndrome: Clinical Characteristics of 48 Eyes

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PURPOSE: To describe the clinical features of toxic posterior segment syndrome (TPSS), a toxic maculopathy that may occur after an intraocular injection of compounded triamcinolone and moxifloxacin.

METHODS: This retrospective case series included 48 eyes of 47 patients. Patients were identified by query of the electronic medical record system. All patients received the same batch of compounded triamcinolone and moxifloxacin from a local compounding pharmacy during their cataract surgery. The findings on presentation, clinical course, and outcomes were reviewed for a comprehensive analysis. Main outcome measures included best-corrected visual acuity (BCVA), subjective nature of the visual disturbance, qualitative examination and imaging features, treatment regimens, and final visual and anatomic outcomes.

RESULTS: Characteristic findings of TPSS include unremarkable postoperative day 1 examination; delayed-onset painless central vision loss within the first week, often followed by continued deterioration of central vision for one to two months; varying degrees of subfoveal blurring and disruption of the outer retinal layers on OCT; electroretinogram with reduced rod and cone responses; and varying degrees of optic disc pallor. All eyes received the same batch of compounded intraocular triamcinolone and moxifloxacin via intracameral bolus, transzonular injection into the vitreous, or pars plana intravitreal injection. Patients were referred to our practice 14 to 35 days after surgery. Follow-up period ranged from one to 12 months. The majority of patients (85%) were treated with oral and topical corticosteroids. Visual outcomes were variable, ranging from hand movements to 20/25, with minimal to no improvement over time. In all patients, outer retinal disruption improved gradually over time.

CONCLUSIONS: TPSS is a rare, visually debilitating condition that can develop after an intraocular injection of compounded triamcinolone and moxifloxacin during cataract surgery. Disease course and findings suggest that TPSS is a progressive toxic maculopathy. With extended follow up, subfoveal outer retinal disruption improves; however, despite treatment with corticosteroids, vision does not tend to improve.
Real-world Rates of Suspected Endophthalmitis Following Intravitreal Injections in the United States

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**PURPOSE:** To compare real-world rates of suspected endophthalmitis following intravitreal injections (IVT) of aflibercept, bevacizumab, ranibizumab (both conventional and pre-filled preparation), dexamethasone implant, and triamcinolone.

**METHODS:** Retrospective study of aggregated, longitudinal electronic medical records obtained from Vestrum Health Retina Database, a geographically diverse sample of US retina providers. Inclusion criteria were a diagnosis of suspected endophthalmitis based on billing codes between January 2013 and March of 2018. Primary outcome was the rate of acute endophthalmitis post IVT. Secondary outcomes included vision recovery as well as rates of retinal detachment and vitrectomy. Statistical comparisons between groups were performed using Chi-Square testing.

**RESULTS:** Overall, following 2,860,153 IVTs, 935 cases (0.033%) of suspected endophthalmitis were reported. Number of IVTs and rate of suspected endophthalmitis by drugs were: aflibercept (915,786, 0.046%); bevacizumab (1,002,405, 0.024%); conventional ranibizumab (728,865, 0.026%); pre-filled ranibizumab (128,075, 0.02%); dexamethasone implant (28,188 injections, 0.053%); triamcinolone (56,194, 0.114%). Rates of suspected endophthalmitis were statistically lower for both bevacizumab and ranibizumab (conventional and pre-filled) compared to aflibercept, dexamethasone implant, and triamcinolone (P < 0.05). Triamcinolone had a statistically higher rate of suspected endophthalmitis compared to all other drugs (p ≤ 5 letters). Corresponding proportions for vision within 15 letters of baseline vision was 47%, 67%, and 73% respectively. Overall, the rate of retinal detachment was 5% and vitrectomy was 34%.

**CONCLUSIONS:** The current study represents one of the largest reviews of real-world rates of suspected endophthalmitis and associated outcomes. Overall the rates were low and similar to reported rates in clinical trials. A significantly higher rate was observed with triamcinolone as compared to the other drugs. The majority of patients were able to regain vision within the first three months following the suspected endophthalmitis.
Endogenous Endophthalmitis: Empiric Antibacterial and Antifungal Management

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PURPOSE: Endogenous endophthalmitis (EE) occurs as a complication of sepsis when pathologic organisms disseminate hematogenously through the blood-ocular barrier. Prior studies have found that EE has a more indolent presentation than exogenous endophthalmitis in that exam findings are less acute, and diagnosis is made several days after symptoms onset, resulting in errors leading to an inaccurate or delayed diagnosis. We are presenting a case series of all cases of endogenous endophthalmitis managed at a tertiary care center over a three-year period. This study sought to compare the clinical features and courses between bacterial and fungal cases of EE. Our aim was to identify features that may aid ophthalmologists in accurately diagnosing and instituting appropriate targeted medical and surgical intervention in a timely manner.

METHODS: Records of patients with a clinical diagnosis of EE at the University of Pittsburgh Medical Center (UPMC) from September 2015 to September 2018 were reviewed. Exclusion criteria included history of ocular trauma, intra-ocular surgery or intra-ocular injection within 6 months prior to presentation, or a primary external ocular infection. Data collected included demographics, past medical and ocular history, clinical examination, culture data, treatment modalities and timing, final corrected visual acuity and mortality. All ophthalmic samples were analyzed by the Charles T. Campbell Ophthalmic Microbiology Laboratory at UPMC. Statistics were performed using SPSS, and a p-value of <0.05 was regarded as statistically significant.

RESULTS: Thirty-five eyes of twenty-six patients were clinically diagnosed with EE during a three-year period at a single institution. Twenty-four cases were attributed to a bacterial pathogen (69%), and ten cases were attributed to a fungal pathogen (29%). Fifteen patients (58%) were male and eleven (42%) were female. The average age at diagnosis was 52.3 years (19 to 86 years). All patients were immunocompromised, and 77% patients were septic at the time of diagnosis (p<0.05). As such, based on clinical features alone, the pathogenic organism was incorrectly predicted on 28% of cases. Additionally, given the indolent nature of EE, 20% of cases were misdiagnosed as non-infectious uveitis on initial presentation. Complications including final visual acuity < 20/200, retinal detachment, enucleation or death within six months of diagnosis were not statistically significant between bacterial and fungal cases.

CONCLUSIONS: The presentation of EE differs remarkably from that of exogenous endophthalmitis. No clinical feature reliably differentiated between bacterial and fungal sources, highlighting the importance of obtaining blood and intra-ocular cultures. Without a high index of suspicion and an understanding of the patient’s overall health status, the indolent presentation of EE may lead to misdiagnosing this vision-threatening condition. Many of these patients are critically ill and not optimal candidates for vitrectomy. Failing to institute appropriate empiric therapy is associated with poor clinical outcomes. As a result, we recommend empiric coverage for bacterial and fungal organisms in cases of suspected EE while awaiting culture results.
Domination of Enterococcal Isolates in Postoperative Endophthalmitis Associated with Selection Pressure of Fluoroquinolone: 10-years Multicenter Study and Co-culture Experimental Study

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PURPOSE: To investigate microorganisms profile isolated from postoperative endophthalmitis and their antibiotic sensitivity, and the possible mechanism of Enterococcus spp. domination as a causative isolate through in vitro and vivo experiments.

METHODS: Medical records of patients who were diagnosed with and treated for postoperative endophthalmitis at eight resident training institutions in Busan, Gyeongsangnam-do area between January 2004 and December 2015 were included. Causative microorganisms, initial and final visual acuity, and antibiotics susceptibility were reviewed. Enterococcus faecalis (E. faecalis) and Staphylococcus epidermidis (S. epidermidis) which were isolated from cul-de-sac of out-patient clinic were tested for fluoroquinolone antibiotic susceptibility test by serial dilution method. In vitro and vivo, Co-culture model of E. faecalis and S. epidermidis were made and their survival assay through colony counting after administration of 4th generation fluoroquinolone was performed.

RESULTS: Total number of infectious endophthalmitis was 423 cases. Among them, postoperative endophthalmitis was 254 cases (60%, 254/423), which were consisted with post-cataract (227 cases), post-vitrectomy (17 cases), and post-filtration (10 cases). Culture positive rate was 49.0 % (122/249). The most common isolate was E. faecalis (29.1%), followed by S. epidermidis (16.4%) and other coagulase negative staphylococci (CNS, 12.7%). Initial and final visual acuity (LogMAR) of E. faecalis was 2.29 and 1.65, CNS was 1.89 and 0.93. In terms of conjunctival flora, resistance of S. epidermidis on ciprofloxacin, levofloxacin, and moxifloxacin was 23.17%, 23.39%, and 17.07%, the resistance of E. faecalis was 37.5%, 37.7%, and 37.5%, respectively. In vitro co-culture model with standard microorganisms, viability of E. faecalis (ATCC29212) and S. epidermidis (ATCC12228) after administration of various concentrations of moxifloxacin (0.016-8.0 /ml) showed that the number of E. faecalis colony was significantly more than that of S. epidermidis from the 0.0625 µml. In animal co-culture model, the number of E. faecalis colony was significantly more than that of S. epidermidis after administration of topical moxifloxacin (2.5 mg/ml).

CONCLUSIONS: E. faecalis was the most common causative isolate of postoperative endophthalmitis during the past 10 years in South Korea, which might be associated with selection pressure of fluoroquinolone.
**PCR versus Conventional Culture for Detection of Endophthalmitis Pathogens**  
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Andrew Packer, MD

**PURPOSE:** To compare the sensitivity of polymerase chain reaction (PCR) versus conventional culture (Cx) methods in identifying pathogens responsible for endophthalmitis.

**METHODS:** Retrospective consecutive case series of patients undergoing vitrectomy for various endophthalmitis indications (both before and after receiving intravitreal antibiotics). Minimally diluted vitreous specimens were acquired with a 25-gauge vitrectomy probe. The first 1-2cc of vitreous was submitted immediately for gram stain and Cx, and the second 1-2cc was flash frozen and stored at -80°C. If the first specimen demonstrated no growth after 48 hours, the second specimen was submitted for broad-range PCR targeting 16S bacterial rRNA, 28S fungal rRNA, and Internal Transcribed Spacer fungal DNA targets.

**RESULTS:** Eight vitrectomy specimens with no growth after 48 hours underwent PCR testing. Four specimens (50%) were PCR-positive for likely pathogenic organisms, with final Cx results corroborating the species identification in 2 cases. There was positive likelihood of species identification by PCR, whether or not the patient received intravitreal antibiotics (Abx) prior to vitrectomy; versus a zero likelihood of species identification by Cx after receiving intravitreal Abx. The identification of neutrophils on gram stain was associated with an increased likelihood of pathogen identification by PCR (positive likelihood ratio = 3.0; positive predictive value = 75%).

**CONCLUSIONS:** Using PCR, we were able to identify likely pathogens in several cases of culture-negative endophthalmitis, including those receiving intravitreal Abx prior to vitrectomy. PCR may have greater sensitivity than conventional Cx methods to detect endophthalmitis pathogens in vitreous specimens with no growth after 48 hours.
LONDON GHERKIN AT DUSK

POSTERS

THURSDAY, SEPTEMBER 12, EMPIRE ROOM
**POSTER #1**

**Short-term Outcomes of Eyes Switched from Intravitreal Aflibercept (IVA) to Ranibizumab (IVR)**

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_Haddonfield, NJ_

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**PURPOSE:** In 2018, cases of inflammation were reported after aflibercept (IVA), which resulted in a change of treatment to ranibizumab (IVR). Our purpose was to evaluate outcomes after switching from IVA to IVR in wet age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO).

**METHODS:** Retrospective cohort study. Eyes switched from IVA to IVR in 2018 were included. Data was gathered from three (B3), two (B2), and one (B1) visit before switch, switch visit, and first (P1), second (P2), and third (P3) post-switch visit. Eyes were excluded if interval between switch-P1 was longer than B1-switch.

**RESULTS:** 324 eyes (266 patients) were eligible (140 AMD, 102 DME, 82 RVO eyes). For all conditions, there was no significant change in central foveal thickness (CFT) from B3 to switch visit.

- For AMD, mean CFT at P1, P2 and P3 visits was significantly increased compared to switch visit (189±83µm, p=0.01; 194±93µm, p=0.002; 194±78µm, p=0.01). Mean LogMAR Snellen VA worsened at P1 (0.50±0.47, p=0.14) and P2 (0.53±0.49, p=0.02) visits with stabilization at P3 (0.51±0.44, p=0.23) visit.
- For DME, there was a statistically significant increase in CFT at P1 visit (325±234µm, p=0.006) compared to switch visit, but no difference at P2 or P3 visits (268±103µm, p=0.32; 284±118µm, p=0.11). There was no statistically significant change in mean LogMAR VA between switch and P1, P2 or P3 visits (0.43±0.38, p=0.95; 0.38 ±0.30, p=0.12; 0.41 ±0.37, p=0.69).
- For RVO, the mean CFT significantly increased at P1 and P2 compared to switch visit (308±186µm, p<0.001; 287±175µm, p=0.005). By P3 visit, mean CFT was similar to switch visit (255±118µm, p=0.12). Mean LogMAR VA worsened significantly from switch visit to P1, P2, and P3 visits (0.62±0.55, p=0.04; 0.65±0.63, p=0.02; 0.58±0.54, p=0.03). Subgroup analysis of BRVO revealed no significant change in CFT or VA post-switch in contrast to CRVO.

**CONCLUSIONS:** With short-term follow-up, we observed transiently worsened macular edema in DME and RVO, and persistently worsened macular edema in AMD post-switch. Snellen VA was persistently decreased only in RVO, but not in AMD or DME post-switch.
Prepapillary Vascular Loops — A Collaborative Study

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PURPOSE: Prepapillary vascular loops are rare asymptomatic congenital vascular anomalies first described in 1871 by Leibrich. These blood vessels extend from the optic nerve head into the vitreous cavity and back to optic disk or retina. The present study aims at analyzing several ophthalmic characteristics of congenital prepapillary vascular loop.

METHODS: Collaborative multinational retrospective study.

RESULTS: 33 cases (13 men, 20 women) (41 eyes) divided into 23 arterial and 10 venous loops, multiple loops in 6 cases, and a mean number of looping turns of 3 (range 1-7). Other findings included cilioretinal artery (10 cases), diffuse retinal artery tortuosity (3 cases), vitreopapillary traction in fellow eye (2 cases), amaurosis (1 case), branch retinal artery occlusion (1 case), and vitreous hemorrhage (3 cases).

CONCLUSIONS: This series allowed us to divide loops into 3 different etiologic types: Type 1 along Cloquet canal with or without vitreous traction, Type 2 as part of diffuse retinal vascular tortuosity, Type 3 multiple loop resembling angioma.
Optical Coherence Tomography Angiography Findings in Purtscher-like Retinopathy in Systemic Lupus Erythematosus

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Kazuhiro Kimura, MD, PhD

**PURPOSE:** To report clinical features of Purtscher-like Retinopathy using optical coherence tomography angiography (OCTA).

**METHODS:** Case report.

**RESULTS:** We hereby reported a 43-year-old Asian female in Systemic Lupus Erythematosus who complained of decreased right vision two days prior to her visit to our outpatient clinic. Her best-corrected visual acuity was 2/200 and 20/20 in her right eye and left eye, respectively. Anterior segments were normal, and Ophthalmoscopy revealed lateral, nearly symmetric retinopathy with multiple flame hemorrhages. Optical coherence tomography angiography (OCTA) revealed flow voids in both the superficial capillary plexus and deep capillary plexus. One month after the intravitreal bevacizumab, OCTA revealed the recovery of flow voids in deep capillary plexus. However, the remaining flow voids and enlarged foveal avascular zone in the superficial capillary plexus were observed using OCTA. Fluorescein angiography (FA) showed multifocal filling defects and an irregularly enlarged foveal avascular zone. OCT images showed thinning of the inner retinal layer. Her best-corrected visual acuity in the right eye was recovered to 20/40 at her final visit.

**CONCLUSIONS:** With the ability to delineate superficial capillary plexus and deep capillary plexus separately, OCTA offers a valid alternative to the standard invasive FA, for evaluating vascular perfusion in all capillary plexuses, and for monitoring retinal microvascular flow changes during Purtscher-like Retinopathy, without dye injection.
Survey of Intravitreal Injection Practice Patterns among Retina Specialists

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PURPOSE: Intravitreal injection therapy (IVT) is the most commonly performed procedure in ophthalmology. There are comparatively few data to guide selection of best practice patterns to deliver intravitreal therapies. This study was conducted with the aim of determining current trends in IVT delivery among retina specialists.

METHODS: An online, 31-question, multiple-choice survey was created using the Qualtrics interface (Provo, UT) and sent to 1677 retina specialists. The survey consisted of 3 sections: general questions, procedure technique, and post-procedure technique. Results were tabulated, and the data were analyzed using the Qualtrics platform. Statistical analysis was performed in SAS.

RESULTS: A total of 264 retina specialists completed the survey. 70% of respondents work in private practice, with most giving injections during their regular clinic. Approximately 60% of respondents give 20 or more injections in a typical day, and 69% reported giving bilateral, same day injections. The majority use an assistant to aid in injection preparation. Almost 75% of respondents use an eyelid speculum, and over 97% prefer a 30G or 32G needle for IVT delivery. Lidocaine gel is the most frequently used IVT anesthesia (31%), followed by subconjunctival lidocaine (28%). Most respondents (52%) wait 5-10 or 10+ minutes for their anesthetic of choice to take effect. 74% of respondents have patients request a different or supplemental form of anesthesia. All respondents use povidone-iodine for antisepsis, and 54% wait 30 seconds or more after the last povidone-iodine application to administer IVT. Approximately 33% reported receiving patient calls (frequently, 3%; sometimes, 30%) 24-48 hours post-IVT due to pain or foreign body sensation. Corneal toxicity was felt to be primarily responsible for post-IVT pain (76%) and over 84% believe Betadine contributes to post-IVT corneal toxicity. Almost 10% of retina specialists report having had a needlestick injury.

CONCLUSIONS: There is consensus on a few aspects of IVT delivery including the use of povidone-iodine, eyelid speculum, and small gauge needle. Most respondents report the occurrence of post-IVT pain in at least some patients, and this is predominantly attributed to povidone-iodine-induced corneal toxicity. There is a lack of consensus on ocular anesthesia choice, with most practitioners having at least some patients request alternative anesthesia options. Needlestick injuries are a common occurrence for physicians delivering IVT.
Delayed Onset Retinal Detachment in Patients Receiving Chronic Anti-Vascular Endothelial Intravitreal Injection Therapy

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PURPOSE: To describe the incidence and clinical features of patients who developed retinal detachment greater than one week after anti-VEGF injections.

METHODS: A billing database search was performed for all patients who received an intravitreal injection (CPT code 67028) and underwent a repair of retinal detachment by pneumatic retinopexy (67110), scleral buckling (67107) or vitrectomy (67108). A retrospective chart review was then performed of all charts identified. Of the 67,028 total intravitreal injections given by five physicians in a private practice setting from 2013 to 2017, three patients developed delayed onset retinal detachments. The clinical history of each patient, location of retinal detachment and causative retinal break, surgical procedure used to repair the detachment, and final anatomic and visual outcomes were obtained.

RESULTS: The incidence of retinal detachment in our series was 0.0044%. Patient ages ranged from 57 to 76 years. The number of injections ranged from 8 to 19 injections. One patient had previously been treated for endophthalmitis with intravitreous ceftazidime and vancomycin. All patients were phakic. Indications for anti-VEGF treatment included vascular occlusion and exudative macular degeneration. Presenting visual acuity ranged from 20/32 to 20/250, and two patients had macula-off retinal detachments. The time to presentation ranged from 3 to 90 weeks. The status of the vitreous differed in the three patients, with one patient having a partial hyaloid separation and two with posterior vitreous detachments. In all three patients, retinal tears were superior. All patients were treated with pneumatic retinopexy initially. One patient required a repeat pneumatic retinopexy. Another patient eventually required vitrectomy with gas fluid exchange and endolaser. Two patients regained vision to the level prior to their detachments. One patient had a final visual acuity of 5/200, significantly worse than previously. In two patients, injections were resumed while injections were held in the third patient due to lack of recurrent macular edema.

CONCLUSIONS: Anti-VEGF injections continue to have a very low rate of severe complications. In our series, retinal breaks were seen superior whereas injections were all delivered inferior temporal. The status of the vitreous may impact the nature of delayed-onset retinal detachments.
Outcomes and Complications of In-office Laser Demarcation of Peripheral Rhegmatogenous Retinal Detachments

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PURPOSE: To evaluate the outcomes of in-office laser demarcation for the treatment of limited retinal detachments (RD).

METHODS: This was a retrospective, single-center analysis of eyes that underwent laser demarcation for peripheral RD of at least 1 clock hour in size. Patients were excluded if they had prior surgery for retinal detachment or follow up less than 3 months. Patient demographics, best-corrected visual acuity (VA), RD size and location, retinal break type, lens status, posterior vitreous detachment (PVD), and presence of vitreous hemorrhage (VH) were recorded. Progression of RD requiring surgery, subretinal fluid (SRF) extension requiring additional laser, VH requiring surgery, and epiretinal membrane (ERM) requiring surgery was recorded. Fischer exact test and multiple logistic regression was used to characterize the association of RD anatomy to treatment complications.

RESULTS: 112 eyes of 107 patients were analyzed with 20 ± 12 months of follow up. The mean patient age was 53 ± 15 years and 97 (87%) were phakic. VA at baseline and last follow up were equal (20/29). The causative break was a flap tear in 66 (63%) eyes and a retinal hole in 38 (37%) eyes. 95 (85%) eyes were successfully treated without an additional procedure. 9 (8%) eyes underwent pars plana vitrectomy or scleral buckle for progressive RD, 6 (5%) had extension of SRF treated with additional laser, 4 (4%) developed VH requiring surgery, and 5 (5%) developed visually significant ERM requiring surgery. Progression of RD occurred within one week in 7 of 13 (54%) eyes and within 3 months in 10 (77%) eyes. Presence of VH (OR=4.7, p=0.007), PVD (OR=4.6, p=0.05), and flap tear (OR=3.9, p=0.04) were associated with complications in univariate analysis. In multivariate analysis, only the presence of VH (OR=4.0, p=0.04) and RD in the inferior 6 clock hours (OR=6.2, p=0.01) were associated with complications.

CONCLUSIONS: Laser demarcation is successful in treating peripheral RDs. RD characteristics less conducive to laser treatment include presence of VH and inferior RD. Patients should be followed closely after treatment to detect post-laser progression of RD.
Optimizing the Visual Performance of a 3D Viewing System

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**PURPOSE:** To determine the ideal way to setup a 3D viewing system for maximal visual performance during vitreoretinal surgery.

**METHODS:** A 3D viewing system was tested to evaluated the best visual performance with respect to lateral resolution, depth of field and depth resolution when the following surgeon-controlled variables are altered; TV viewing distance, Camera Aperture and Microscope Zoom. Multiple subjects were tested using industry standard devices to measure visual performance.

**RESULTS:** Maximal lateral resolution was obtained at a TV viewing distance of 1.2m which was subtly better than 1.5m and substantially better than 2.0m. Increasing microscope magnification improved lateral resolution and a camera aperture of 30% was slightly better than 50% or 75%. Maximal depth of field was obtained at a camera aperture of 30% with minimal microscope magnification. TV viewing distance did not seem to alter depth of field scores in the ranges tested. Depth resolution was maximized at high magnifications with a closer TV viewing distance.

**CONCLUSIONS:** Visual performance on a 3D viewing system can be maximized by placing the TV at a viewing distance of 1.2m and using a camera aperture of 30%. For maximal lateral resolution the microscope zoom should be maximized, while for maximal depth of field the microscope zoom should be minimized.
Chandelier Assisted Scleral Buckling for Primary Uncomplicated Rhegmatogenous Retinal Detachment

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PURPOSE: To report our experience in chandelier assisted scleral buckling in uncomplicated primary rhegmatogenous retinal detachments (RRD).

METHODS: Retrospective case series of 282 eyes that underwent chandelier assisted scleral buckling and were followed for a mean of 13.5 months.

RESULTS: There were 160 male patients. The average age was 42.6 years old. There were 263 eyes that were phakic, 18 pseudophakic and 2 aphakic. Two third of eyes presented with the macula detached. Eyes had an average of 1.6 breaks. The single operation anatomic success rate was 85.1% (240/282). The pre-op visual acuity improved from 1.21 to 0.76 logMAR at 6 months. Complications included a case of scleral laceration, choroidal hemorrhage, 3 epiretinal membranes, 1 macular fold and 4 buckle exposure.

CONCLUSIONS: Chandelier assisted scleral buckling compares favorably with conventional scleral buckling for primary uncomplicated primary RRD.
Clinical Characteristics Predictive of Successful Pneumatic Retinopexy for Rhegmatogenous Retinal Detachment

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PURPOSE: To identify characteristics that predict successful anatomical attachment following pneumatic retinopexy (PR) for rhegmatogenous retinal detachment (RRD).

METHODS: A retrospective review was performed on patients who underwent PR for RRD between January 1, 2015 and December 31, 2018 at single center. Statistical analysis was performed using Fisher’s exact test, Wilcoxon rank sum, and analysis of variance.

RESULTS: Three hundred and forty patient charts were reviewed. Two hundred twenty-nine (67%) of patients experienced complete reattachment without the need for surgery and were classified as “success”. One hundred twelve (33%) of patients required additional surgery for retinal repair. The average age of patients was 60.3 ±9.5 years in the success group versus 58.0 ±12.0 years in the failure group (p = 0.29). There was no statistical significance in number of retinal breaks (p = 0.78), quadrants of detachment (p = 0.77), location of lowest retinal tear (p = 0.32), or volume of intraocular perfluoropropane gas used (p = 0.75). Post procedural laser retinopexy was performed in 10% of the success group and 9% of the failure group (p = 1.00). Seventy-nine percent of the success group and 76% of the failure group were phakic (p = 0.80). The average pre-procedural visual acuity was 0.3 logMAR in the success group versus 0.45 logMAR in the failure group (p = 0.06). Presence of vitreous hemorrhage was 16% in the success group and 18% in the failure group (p = 0.11). The prevalence of proliferative vitreoretinopathy (PVR) following pneumatic procedure was 0% in those with success versus 12% in those with failure (p = 0.01).

CONCLUSIONS: Our study supports pneumatic retinopexy as a reasonable option for initial RD repair with good anatomical outcomes.
Biocompatibility of Silicone Oils: The Role of Exogenous and Endogenous Surfactants

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PURPOSE: Silicone Oils (SOs), which are considered biocompatible intraocular tamponade, can cause serious complications in the presence of surfactant. This phenomenon is influenced by their physical and chemical properties and, particularly, by the presence of “impurities” (exogenous surfactants) as residuals from manufacturing process and by proteins produced by the eye (endogenous surfactants). This study aimed to evaluate the different concentration of exogenous surfactants in 10 commercially available SOs, as well as the variation of interfacial tension (IT) between SOs and aqueous solutions by adding endogenous surfactants.

METHODS: We assessed the type of SOs polymer, the molecular weight distribution (MWD) and low molecular weight components (LMWC) by spectroscopy and conventional size exclusion chromatography, respectively. Due to the low MW, the content of LMWC with M 1,000 g/mol was determined by gas chromatography-mass spectrometry. IT and the interfacial dilatational viscoelasticity (DV) were measured at 35°C for the interface between SO and serum proteins (albumin and gamma-globulins).

RESULTS: The SOs present on the market differed significantly in terms of both MWD and relative LMWC fractions. Specifically, the relative fraction of all LMWC (M 10,000 g/mol) ranged from 2.31 to 9.40% and the content of LMWC with M 1,000 g/mol also varied significantly (range: 51-1,151 ppm). The experiments show that when proteins are dissolved in the aqueous solution the equilibrium IT decreases significantly for physiologically realistic concentrations. Moreover, the DV modulus achieves values that are significantly larger than those observed for LMWC molecules, even for small proteins concentration.

CONCLUSIONS: Commercially available SOs differ significantly in molecular and rheological features. These compounds contain a significant amount of LMWC, “exogenous impurities” generated during the synthesis process, potentially inducing ocular inflammation and toxicity. Moreover, common serum proteins, produced by the eye and by our surgery, are responsible for further change of IT and promotion of droplets formation, which, in addition, are expected to be stable against coalescence, owing to the large values of the DV modulus. Both exogenous and endogenous surfactants play an important role in the generation of inflammation and emulsion. Both the choice of the SO and our surgery are responsible for such adverse event.
Utilizing Spectral Domain Optical Coherence Tomography to Identify Posterior Vitreous Detachment in Patients with Retinal Detachment: Analysis of the Primary Retinal Detachment Outcomes (PRO) Study

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PURPOSE: To compare posterior vitreous detachment (PVD) identification rate between clinical examination vs. spectral domain optical coherence tomography (SD-OCT) in patients with retinal detachment (RD).

METHODS: Data from the Primary Retinal detachment Outcomes (PRO) study was utilized to conduct secondary analysis for this retrospective cross-sectional study. PVD status was identified by reviewing 31 raster scans on a 30 x 30 degree capture mode (roughly 8.9 x 7.4 mm) for separation of the posterior hyaloid face from the optic nerve. Statistical analysis was performed to compare SD-OCT identified PVD with PVD identified on slit lamp biomicroscopy. PVD identification by imaging vs. clinical exam was then analyzed for macula on RD and macula off RD subgroups, and PVD status and surgical choice was compared.

RESULTS: A total of 507 patients were included in the study. There was a statistically significant (p<0.001) difference in PVD identification rate between clinical examination and SD-OCT imaging in patients with RD. PVD was found by clinical exam in 261 (51.5%) patients vs. 298 (66.8%) identified by SD-OCT. A total of 116 (22.9%) were graded not to have a PVD on clinical examination vs. 66 (14.8%) being negative for PVD on SD-OCT. More patients were graded to have unknown PVD status on clinical exam vs. imaging, 130 (25.6%) vs. 82 (18.4%) respectively. In patients with macula on RD, 84 (60.4%) were found to have PVD on clinical examination vs. 97 (80.8%) by imaging. Similarly, SD-OCT imaging identified PVD more often in macular off RD patients; 116 (54.5%) compared to 110 (47.8%) on clinical examination. Patients with macula off RD had higher rates of unknown PVD status, on both clinical exam and SD-OCT, compared to those with macula on RD. There was a statistically significant (p<0.001) difference in surgical choice based on PVD status with scleral buckle being the most common surgery in those without PVD and vitrectomy in those with PVD.

CONCLUSIONS: Knowledge about the posterior hyaloid anatomy is important before undergoing RD repair. PVD status influences surgical choice and SD-OCT can better identify PVD than clinical examination in patients with both macula on and macula off RD.
Full Thickness and Basement Membrane-only Transplant of Dehydrated Amniotic Membrane for Macular Holes, Penetrating Trauma and Retinal Detachments

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PURPOSE: To describe a novel method of amniotic membrane transplantation and its applications to vitreoretinal surgery.

METHODS: Dehydrated amniotic membrane was used either as a full thickness graft or in which the basement membrane was separated from the stroma and draped over the pathology. The graft was used as a retinal plug or epiretinal covering for macular holes, full thickness penetrating injury, or retina breaks in detachments. In retina detachments, the graft was fixated over the break as a “patch” with fibrin glue and short-term tamponade with 16-18% SF6 was used.

RESULTS: 8 eyes were included: 4 macular holes, 1 penetrating trauma, and 3 tractional-rhegmatogenous detachments. 2 of the macular holes had full thickness amniotic membrane graft as a plug. The other 2 had basement membrane only graft as a cover (draped over the hole). The penetrating trauma and rhegmatogenous detachment cases had full thickness graft as covers. All macular holes closed and all detachments stayed attached with resolution of gas within 2 weeks.

CONCLUSIONS: Dehydrated amniotic membrane graft is an alternative option for complex macular holes and allows for separation of stroma from basement membrane for a basement membrane-only amniotic graft cover for macular holes. When use to cover retina breaks in detachments, dehydrated amniotic membrane grafts allows for reattachment with shorter duration gas, and potentially air-only tamponade.
Retinal Detachment After TASER Trauma

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PURPOSE: To report the retinal injuries sustained after TASER trauma to the eyes and ocular adnexa, and the outcomes after management of this complex trauma.

METHODS: Multicenter, retrospective, consecutive, case series and literature review. Seventeen eyes of 16 patients with TASER-related injuries. Spearman's Correlation Coefficient was used to assess the association between the extent of TASER injury (zone of injury; penetrating vs perforating) and patient outcomes (retinal status; visual acuity, VA).

RESULTS: Median age was 26 years old. Males (94%) were more likely than females to have TASER trauma. In all cases of TASER injuries to the eyes and ocular adnexa, there was a 63% (10 of 16) incidence of retinal detachment (RD). Among cases with open globe injury (71%, n=12), there was a high rate of Zone 3 injuries (100%) and a high incidence of RD (73%, 8 of 11, one previously eviscerated eye excluded). Among cases of open globe injury with RD, 87% (7 of 8) were detached on presentation and 13% (1 of 8) detached within 1 week. Among cases with closed globe injury (n=5), there was 1 exudative RD and 1 retinal dialysis with RD. Of 10 cases with RD (8 open globe injury, 2 closed globe injury), 1 (10%) was exudative and resolved with monitoring; 1 (10%) was localized and underwent cryopexy/pneumatic; 3 (30%) underwent vitrectomy, and 5 (50%) with poor prognosis did not undergo vitreoretinal surgery. Three of 3 (100%) TASER-related RDs that underwent repair with vitrectomy re-detached secondary to proliferative vitreoretinopathy (PVR). Re-detachment cases required additional vitrectomy, membrane peeling, endolaser, silicone oil, and 2 cases also received a scleral buckle. All 3 remained attached after the second surgery. There was a 50% rate of loss to follow-up after incarceration. VA on presentation was significantly correlated with final VA ($\geq 0.783$, p=0.02).

CONCLUSIONS: Ocular TASER injuries represent a complex trauma with a high propensity for Zone 3 injury and retinal detachment. PVR formation represents a major challenge in the post-operative course of patients with TASER-related RD. The visual prognosis is guarded, and multiple surgeries may be required to achieve long-term retinal attachment.
**PURPOSE:** To present effects of the inverted internal limiting membrane (ILM) flap technique in full-thickness macular holes (FTMH) coexisting with dry age-related macular degeneration (AMD).

**METHODS:** A retrospective observational case series. Our database was retrospectively reviewed in order to spot patients with the simultaneous diagnosis of drusen and full-thickness macular hole. 18 of 12 patients (mean age 68 years) were included. Vitrectomy with the inverted ILM flap technique was performed. Inclusion criteria were: full-thickness macular hole, drusen, vitrectomy performed and spectral domain optical coherence tomography (SD OCT) or swept source OCT before surgery, then one week (±3 days), one month (±1 week), three (±1 month), six (±1 month), twelve (±2 months) and 18 months- 12 years after surgery. Main outcome measures: closure of macular hole and visual acuity at the final control.

**RESULTS:** Mean minimum macular hole diameter: 493 µm. Mean maximum macular hole diameter: 1072 µm. Macular hole was closed in sixteen eyes after first surgery and in all eyes after second surgery. Improvement of visual acuity was statistically significant (P = 0.05), but there was no statistically significant correlation observed between initial macular hole diameters and final visual acuity (P > 0.1).

**CONCLUSIONS:** The inverted ILM flap technique improves anatomical and functional results in eyes with coexisting drusen and FTMH. Final Development of CNV or geographic atrophy is possible in rare cases.
A Case of Macular Hole with Multiple Recurrences and Spontaneous Closures; A Condition Behind the Disease

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PURPOSE: An idiopathic macular hole that causes substantial reduction in central visual acuity is believed to involve no obvious underlying diseases; thus, it is suspected to form due to the presence of idiopathic tractional forces at the vitreoretinal interface. Importantly, it is effectively treated with pars plana vitrectomy (PPV), which removes the mechanical forces. However, while it is exceedingly rare, a macular hole can develop in eyes after PPV; fresh or postoperative macular holes can close spontaneously without surgical removal of traction. Thus, another mechanism might be involved, although it has not become evident.

METHODS: A 67-year-old woman experienced four episodes of distorted and/or blurred vision. She was diagnosed with recurrent macular hole formation. For each episode, she either underwent surgery or was placed under observation.

RESULTS: The macular hole was twice closed with PPV and twice without. The second PPV procedure, which was performed at the time of second recurrence, confirmed the absence of the epiretinal membrane and internal limiting membrane that cause tractional forces at the vitreoretinal interface in the macular area. At the time of the third recurrence, fluorescein angiographies (FAs) revealed the presence of mild and diffuse inflammation throughout the peripheral retina, although there were no other findings indicative of ocular inflammation during the general eye examination conducted for every episode of macular hole formation. After the initiation of topical steroid treatment, inflammation (as recorded on FA) was reduced, and the macular hole subsequently closed. Development and resolution of perifoveal cystoid change and retinal protrusion were observed in every episode in optical coherence tomography (OCT) images. A bridging element in an OCT image was observed during the fourth closure of the macular hole.

CONCLUSIONS: Dynamic changes in FA and OCT images unraveled the pathogenesis of a macular hole that was originally diagnosed as idiopathic; mild inflammation in the peripheral retina was demonstrated. FA is typically not used for the diagnosis and management of macular hole formation; however, its use in this case helped determine a new mechanism in an otherwise idiopathic disease.
Grid Deformation Analysis of the Macula and Postoperative Metamorphopsia after Macular Hole Surgery

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PURPOSE: Postoperative metamorphopsia was reportedly related to deformation of the macula after macular hole surgery with the internal limiting membrane peeling. However, the mechanism is still under debate. The purpose of the present study was to investigate the correlation between postoperative metamorphopsia and macular deformation by analyzing the deformation of the grid overlaid on the fundus photograph.

METHODS: Consecutive eyes that underwent pars plana vitrectomy for idiopathic macular hole and achieved hole closure were analyzed retrospectively. The fundus photographs were taken before and at 6 months. Postoperative vertical and horizontal metamorphopsia was assessed using M-chart. Two photos were overlapped matching the major arcade vessels. The 6x6 mm grid having crossing lines at 1mm interval was overlaid on the preoperative photo. Each node was anchored at the photo, which was deformed by moving the node to match the retinal vasculatures to those of the postoperative photo (Figure 1). Differences in the coordinates of the nodes were calculated and analyzed to find correlation with M-score. Parafoveal deformation was defined as differences in coordinates between the center node and the first adjacent nodes, and perifoveal deformation as between the first and second nodes.

RESULTS: In 33 eyes, the average displacements of the nodes were 25.92 um to the disc and 14.03 um inferiorly. On the vertical lines of the grid, the average difference in X-coordinates between the adjacent nodes was 81.62 um, and on the horizontal line, the average difference in Y-coordinates was 47.01 um. Horizontal M-score was correlated with the superior perifoveal horizontal deformation of the vertical line on the fovea (p=0.013), and vertical M-score was correlated with the temporal perifoveal vertical deformation of the horizontal line on the fovea (p=0.007).

CONCLUSIONS: Postoperative metamorphopsia after macular hole surgery was correlated with perifoveal deformation of the macula.
Surgical Outcomes of Traumatic Retinal Detachment Repair in Patients with Self-injurious Behavior

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PURPOSE: Self-injurious behavior (SIB) is a well-described feature in patients with cognitive developmental delay and can lead to sensory impairment including loss of vision from traumatic retinal detachment (RD). Visual prognosis is often poor despite technically sound surgery due to ongoing ocular trauma and inability to cooperate with conventional postoperative care, which may lead to proliferative vitreoretinopathy, redetachment, and phthisis bulbi. The management of these patients, both intraoperative and postoperative, is profoundly challenging and can be isolating for families and physicians who are co-managing these patients. We provide the largest series to date of surgical outcomes in patients with retinal detachment due to SIB.

METHODS: We report a multicenter, retrospective, interventional case series of patients with retinal detachment due to SIB.

RESULTS: The study included 95 eyes from 68 patients, with median age of 12 and median postoperative followup of 1024 days. The most common cause of SIB was autism spectrum disorder, and the most common behaviors were face hitting or slapping (54%) or intense eye rubbing (19.5%). Of the patients with RD, 42.6% had bilateral retinal detachment at time of presentation. As the primary surgery, eyes with RD underwent vitrectomy (28.4%), scleral buckle (18.9%), combined buckle/vitrectomy (31.6%) or no treatment (16.8%) and 5 eyes without RD underwent prophylactic scleral buckle. Eyes underwent 1.6 surgeries on average, and the re-detachment rate was 49.5% and the final attachment rate was 72%. None of the eyes with prophylactic buckle developed an RD. Factors predicting worse final outcome included funnel RD (p=9.6x10-5) or PVR (p=5.7x10-9). Factors predicting final attachment were the use of a scleral buckle in the primary surgery (p=0.04) and the use of silicone oil (p=0.003). The final attachment rate correlated with more improvement in visual acuity in eyes with RD (p=0.028), suggesting both anatomic and functional benefit to repair.

CONCLUSIONS: Overall, patients with SIB who present with RD have a higher risk of bilaterality, redetachment and ultimate non-attachment likely due to ongoing trauma, but surgery in these patients can lead to anatomic and functional success. Based on these data, these challenging cases may be more successful with scleral buckle and/or silicone oil tamponade.
Identifying Gaps in Patient Access to Diabetic Screening Eye Examinations in Ontario: A Provincially Representative Cross-Sectional Study

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PURPOSE: In 2016, there were an estimated 3.5 million Canadians with diabetes. This represented a 46% increase from 2008. It is estimated that the prevalence could increase to 4.9 million by 2026. The risk of blindness in diabetics is up to 25-times higher than non-diabetics. Diabetes is the leading cause of acquired blindness in Canadians under the age of 50, and diabetic retinopathy affects an estimated 500,000 Canadians. Meanwhile, the percentage of Ontario residents age 40–65 years with diabetes who received a general eye examination within a 2-year period from 1998 to 2010 demonstrates a significant decrease from 70% to 55%, regardless of level of income. Early identification of diabetic retinopathy with screening eye examinations allows for secondary prevention of the complications of diabetic eye disease. To better understand the need for resource allotment in diabetic screening across populations in Ontario, we undertook a study of key demographics and geographics characteristic of both screened and unscreened patients in the province.

METHODS: Ontario Health Insurance Plan (OHIP) records were derived from both physician and optometry billing, matched with patients age > 19 with prevalent diabetes between 2011–2013. Data was cross-correlated with demographic covariates including age, sex, income quintile, immigrant-status, as well as geographic co-variates such as rurality and patient Local Health Integration Networks.

RESULTS: Of almost 1,146,000 patients included in the analysis, approximately 406,000 were unscreened. Of note, this included 234,000 (43%) of adults age 40-64 years. Approximately 818,000 diabetic patients lived in large cities, and 301,000 (37%) were unscreened. However, when Toronto was analyzed as a large urban area with the highest density of unscreened prevalence, autocorrelation between percentage of eye exams among diabetics age >40 and low-income measure revealed large areas of Toronto Central correlated for low exam rates and low-income. The majority (13/22) of Community Health Centres are present in these areas.

CONCLUSIONS: Large cross-sectional population statistics for diabetes prevalence and ophthalmic examinations provides a geographic and socioeconomic profile for populations of middle-age adults in large urban areas at-risk for developing diabetic retinopathy, who might benefit from interventions to improve the rates of screening eye exams.
Morphofunctional Analysis of the Retina in Type 1 Diabetic Patients without Complications after 30 Years of Disease

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PURPOSE: To investigate sub-clinical structural and/or vascular retinal changes in patients with long-term (>30 years) type 1 diabetes mellitus (T1DM) and without history of systemic/ocular complications (“happy few” patients).

METHODS: Cross-sectional study. Twelve patients without micro/macrovascular complications associated with long-standing T1DM — i.e. diabetic retinopathy — and twelve healthy subjects were consecutively included in this study. Patients and controls underwent a complete ophthalmologic evaluation, including optical coherence tomography angiography (OCT-A), structural OCT and assessment of retinal sensitivity using microperimetry.

RESULTS: Mean age of diabetic patients was 52±12 years, mean duration of disease was 35±3 years (range 30–40 years), and mean HbA1c level was 7.3±2.8% (range 6.2–8.3%). No statistically significant differences were disclosed comparing patients and controls for age, sex, best-corrected visual acuity, central macular thickness, and choroidal thickness. Using OCT-A, we did not find any significant difference in foveal avascular zone area, perfusion density, vessel length density and vessel tortuosity between diabetic and control group in both superficial and deep capillary plexuses. Moreover, no significant differences were disclosed between diabetic patients and controls analyzing macular and peripapillary retinal nerve fiber layer and ganglion cell complex thickness using structural OCT. No differences were disclosed in retinal sensitivity by microperimetry.

CONCLUSIONS: The new diagnostic tools are able to identify diabetic patients who have been completely spared from diabetic retinal complications. The finding of these “happy few” patients could help better understanding and targeting future treatments for diabetes, and it may allow creating personalized screening intervals providing new perspectives for patient management.
Alteration in the Number of Microaneurysms in Diabetic Macular Edema after Anti-Vascular Endothelial Growth Factor Therapy

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PURPOSE: We evaluated the number of microaneurysms (MAs) on fluorescein angiography (FA) and indocyanine green angiography (IA) in diabetic macular edema (DME) after intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs.

METHODS: Twenty-one eyes of 16 patients with DME were included in this retrospective study. Those patients received an initial loading dose of 3 monthly injections anti-VEGF agents and thereafter, received in a pro re nata regimen at least 12 months of follow-up. FA and IA images using Heidelberg SPECTRALIS HRA+OCT were obtained for all patients before the injections and after 6 months of injection. MAs in the perifoveal capillary network in the FA and IA images were quantified.

RESULTS: At baseline, patients had 5.3±2.6 MAs in early phase FA, 3.8±2.2 leaky MAs in late phase FA and 2.8±1.8 MAs in late phase IA, respectively. At 6 months, patients had 2.5±2.1 MAs in early phase FA, 1.5±2.0 leaky MAs in late phase FA and 1.1±1.2 MAs in late phase IA. All type MAs decreased significantly from baseline (P<0.0001). One month after 3 initial anti-VEGF injections, DME persisted in 42.8% (9/21 eyes). There was no significant correlation between the persistence of DME and the number of MAs at baseline by both FA and IA. However, only the number of MAs in late phase IA was significantly higher in recurrent DME group (12 eyes) compared to non-recurrent DME group (5 eyes) (3.4±1.8 vs 1.2±0.7 (P=0.0185)) during the follow-up period.

CONCLUSIONS: Intravitreal injection of anti-VEGF agents decreases the number of MAs in patients with DME. Refractory MAs participating in the recurrence of DME may be more precisely detected by IA than FA.
Retinal Degeneration in Oguchi Disease

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**PURPOSE:** Oguchi disease is a rare retinal disease characterized by autosomal-recessive form of congenital stationary night blindness and golden-yellow reflex of the fundus that disappears in the long dark-adaptation (Mizuo-Nakamura phenomenon). The purpose of the present study was to determine the frequency of retinal degeneration in our patients with Oguchi disease using ERG and OCT.

**METHODS:** Eight patients with Oguchi disease were included in this study. In addition to routine ophthalmological examinations, full-field, focal, or multifocal ERGs were recorded. OCT was performed by spectral-domain OCT.

**RESULTS:** Five of eight patients had normal visual acuity, normal visual field, and normal SD-OCT findings associated with normal cone ERG responses. Two patients had normal visual acuities, but showed a paracentral scotoma associated with RPE atrophy along the vascular arcade in both eyes. The ellipsoid zone defects are also seen in these patients. One patient showed reduced visual acuities and severe macular degeneration in both eyes, associated with thinning of outer retina at the macula area in SD-OCT. These three patients had reduced cone ERGs and SAGgene mutations.

**CONCLUSIONS:** Three of eight patients with Oguchi disease had retinal degeneration at paracentral or macular area. These results supported the idea that progressive retinal degeneration can occur in Oguchi disease with SAGgene mutations.
Verscian Canonical Splice Site Mutation is associated with V Vitreoretinal Degeneration and Disrupts a Matrix Metalloproteinase Proteolytic Site

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PURPOSE: To gain insight into the pathophysiology of vitreoretinal degeneration, the clinical course of three family members with Versican Vitreoretinopathy (VVR) is described, and a canonical splice site mutation in the gene encoding for versican (VCAN) protein was biochemically analyzed.

METHODS: A retrospective chart review, human eye histopathology, Sanger DNA sequencing, protein structural modeling and in vitro proteolysis assays were performed.

RESULTS: The proband (II:1), mother (I:2), and younger sibling (II:2) suffered retinal degeneration with foveal sparing and retinal detachments with proliferative vitreoretinopathy, features which were confirmed on histopathologic analysis. All affected members carried a heterozygous adenine to guanine variant (c.4004-2A>G) predicted to result in exon 8 skipping or the deletion of 13 amino acids at the beginning of the GAG chain (VCAN p.1335-1347). This deleted region corresponded to a putative MMP cleavage site, validated using FRET-based proteolysis assays. Proteomic network analysis identified 10 interacting partners in the human vitreous and retina linked to retinal detachment and degeneration.

CONCLUSIONS: VVR causes significant ocular disease including retinal detachment and retinal dystrophy. The intronic Commutation removes an MMP cleavage site which alters versican structure and results in abnormal vitreous modeling. Disruption of a versican protein network may underlie clinicopathological disease features and point to targeted therapies.
Genotypic Profile and Phenotype Correlations of ABCA4-associated Retinopathy in Koreans

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**PURPOSE:** This study was conducted to analyze the clinical features of pathogenic variants of ABCA4 in Korean patients with inherited retinal dystrophies (IRDs).

**METHODS:** We enrolled subjects with IRDs who visited a tertiary referral hospital and identified the pathogenic variants of ABCA4 by targeted gene panel sequencing and whole exome sequencing. We analyzed the clinical characteristics and phenotypic spectrum according to genotypes.

**RESULTS:** In total, 11 subjects with IRDs from 9 families who showed pathogenic variants in ABCA4 were included. Eight subjects with Stargardt disease in 7 families, two subjects with cone-rod dystrophy in one family, and one subject with early-onset retinitis pigmentosa (RP) were included. Two heterozygous mutations were identified in eight families and one variant was found in a patient with fundus flavimaculatus. Two variants p.Gln294Ter and p.Gln636Lys were associated with severe phenotypes, such as early-onset RP and cone-rod dystrophy. Four novel pathogenic variants, p.Gln636Lys, p.Ile1114del, p.Thr1117Ala, and p.Asn1588Tyr, were identified. p.Gln294Ter, p.Leu1157Ter, and p.Lys2049ArgfsTer12 were repeatedly detected in Koreans with ABCA4-associated retinopathy.

**CONCLUSIONS:** Various pathogenic variants of ABCA4, including four novel variants, were identified and ABCA4-associated retinopathies exhibited various phenotypes and disease severities in a Korean IRD cohort.
Multimodal Imaging of Macular Neovascularization in Stargardt Disease

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PURPOSE: Choroidal neovascularization (CNV) is a rare complication in recessive Stargardt Disease (STGD1). STGD1 is also an important consideration in the differential diagnosis of Age-related Macular Degeneration (AMD). We report an elderly patient with macular neovascularization associated with Late-onset STGD1, who was treated with intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) in both eyes.

METHODS: A 66-year-old man presented in our office for decreased vision in his right eye due to a hemorrhagic detachment of the macula from a CNV in 2009. STGD1 was clinically suspected on the basis of central atrophy in the macula, pisciform retinal flecks, and sparing of the peripapillary area. In 2017, a new macular hemorrhage was recorded in the left eye at age 75. Retinal findings and CNV were assessed with a multimodal imaging approach, including quantitative fundus autofluorescence (qAF) and swept-source optical coherence tomography angiography (SS-OCTA).

RESULTS: His best corrected visual acuity (BCVA) at presentation was 20/20 in the left eye. qAF imaging highlighted hyperautofluorescent retinal flecks and low qAF levels due to atrophy in both eyes, before the molecular diagnostic report confirmed two pathogenic mutations in the ABCA4 gene. A small ridge of CNV was detected by SS-OCTA, between two lobules of atrophy. This CNV was treated with several intravitreal injections of anti-VEGF medication in a prolonged treat & extend schedule. However, a six-month follow-up recorded a BCVA of 20/200 from a subfoveal CNV in this eye.

CONCLUSIONS: By a wise use of diagnostic studies, the real identity of this AMD masquerader can be revealed. The quantification of fundus autofluorescence can be used to guide clinical diagnosis and genetic testing in ABCA4-related diseases and define genotype/phenotype correlations. OCTA also allows for differentiation between RPE atrophy secondary to STGD1 versus AMD. Late-onset STGD1 might increase susceptibility to AMD-like features over the years.
Effect of Intravitreal Bevacizumab on the Retinal Ganglion Cell Layer

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PURPOSE: Inhibition of vascular endothelial growth factor (VEGF) has revolutionized management of neovascular diseases in the eye. However, there are some reports indicating that the use of anti-VEGF may provoke or worsen glaucoma, a disease that primarily affects the inner retinal layers, particularly the ganglion cell layer (GCL). While some studies have evaluated the GCL in age-related macular degeneration (ARMD) patients treated with anti-VEGF agents we are not aware of any published studies on the GCL in patients with vein occlusions or diabetic retinopathy that were similarly treated.

METHODS: In this retrospective study, we investigated the effect of intravitreal bevacizumab injections on the ganglion cell layer through spectral domain OCT GCL volumetric analysis, a relatively new imaging modality. Inclusion criteria included patients with unilateral or bilateral diagnosis of ARMD, diabetic macular edema or venous occlusive disease. They had three successive injections of bevacizumab in one eye. They had OCT with GCL volumetric analysis before each injection and at the visit after the third injection. Patients who had any non-bevacizumab injection, retinal laser or retinal surgery were excluded. Demographics, visual acuity, intraocular pressure were also measured.

RESULTS: Initial 50 eyes of 25 patients were included. The change in the GCL thickness (in microns) compared to baseline after each of the three injections was -0.03, -0.047, and -0.048. This compared to the change in the fellow eye of -0.002, -0.001, and -0.002. The GCL volume was significantly decreased after the second and third injections when compared to baseline. The GCL volume was also significantly decreased after the second injection when compared to the fellow eye. The intraocular pressure did not show a correlation with the GCL changes.

CONCLUSIONS: The thinning of the GCL after intravitreal bevacizumab is independent of the intraocular pressure and may represent direct damage to those inner retinal layer cells. An additional 25 patients will be analyzed to see if the initial results are confirmed.

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PURPOSE: Arteriosclerosis is “the root of all evil” not only for ocular diseases but also for systemic diseases. Early detection and intervention for arteriosclerosis can lead to prevent cardiovascular diseases and reduce its mortality. We previously developed auto-Doppler optical coherence tomography flowmeter (auto-DOCT flowmeter) which can measure retinal blood flow (RBF) easily and accurately within 3 seconds. Our studies suggested that one of RBF parameters from auto-DOCT flowmeter can reflect the condition of arteriosclerosis in healthy subject. In the study, we investigated the relationship between the conventional method to evaluate arteriosclerosis and a parameter from DOCT flowmeter.

METHODS: 26 eyes of 26 consecutive patients with hypertension with a mean age of 66.5 years (27 to 94) were assessed using auto-DOCT flowmeter. The superotemporal artery in an eye was used for measuring RBF using auto-DOCT flowmeter. The pulsatility ratio (PR), which is expressed as PSV (the peak velocity during systole)/EDV (the end diastolic velocity), is an indicator of increased vascular resistance to flow and/or decreased vascular compliance. A degree of arteriosclerosis was evaluated by cardio-ankle vascular index, CAVI. Pearson’s correlation coefficient was employed to compare PR with CAVI. P values < 0.05 were considered statistically significant.

RESULTS: Mean PR and CAVI were 4.1 ± 1.1 and 7.6 ± 1.6, respectively. Pearson’s correlation analysis showed a strong correlation between PR and CAVI (R= 0.71, P< 0.0001).

CONCLUSIONS: PR was highly correlated with CAVI, suggesting that auto-DOCT quantitatively evaluate the degree of arteriosclerosis and can replace the conventional method to assess arteriosclerosis. This approach will be a useful test for screening the degree of arteriosclerosis.
**Optical Coherence Tomography Angiography Redefining Rare Retinal Disease**

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**PURPOSE:** To describe how optical coherence tomography angiography (OCTA) has added to our knowledge of the pathogenesis and clinical features of rare retinal disease.

**METHODS:** Patients with crystalline retinopathies, persistent placoid maculopathy, presumed solitary circumscribed retinal astrocytic proliferation (pSCRAP), extensive macular atrophy with pseudodrusen (EMAP), and dissociated optic nerve fiber layer underwent multimodal imaging including OCTA and images were analyzed.

**RESULTS:** In cases of Sjogren-Larsson syndrome maculopathy, OCTA demonstrated retinal capillary plexus abnormalities similar to tamoxifen maculopathy and macular telangiectasia type 2 which suggest a common pathogenesis involving Muller cells. OCTA imaging of persistent placoid maculopathy reveals flow voids in areas of choroidal inflammation that can be adequately monitored during treatment and obviates the need for indocyanine green angiography. The location of the pSCRAP lesion on OCTA appears to arise from the deep or sub-retina and has no internal vascularity which argues for updated nomenclature. Marked choriocapillaris atrophy is noted on OCTA in EMAP and signs of dissociated optic nerve fiber layer are easily appreciated on the en face OCTA image.

**CONCLUSIONS:** Multimodal imaging that includes OCTA greatly enhances our understanding of the pathogenesis and clinical features of rare retinal disease and is often one of the few imaging modalities needed to diagnose and monitor select patients.
An AI-assisted Decision Support Tool for Retinal Video Angiography

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PURPOSE: To present a novel computer aided decision support tool in analyzing, quantifying, and evaluating retinal blood vessel structure from fluorescein angiogram (FA) videos.

METHODS: The authors propose a novel pipeline-based architecture that consists of three phases: image registration for large motion removal from FA videos, followed by retinal vessel segmentation, and, lastly, segmentation-guided video magnification. In the image registration phase, individual frames of the FA video are spatio-temporally aligned using a wavelet-based registration approach to compensate for global camera and patient motion. Following this, in the second phase, a capsule-based neural network architecture is utilized to perform segmentation of retinal vessels. The authors show this novel application of a capsule network architecture outperforms state-of-the-art convolutional neural networks (CNN) in terms of qualitative and quantitative results, as well as network parameter efficiency. Lastly, in the final phase, Eulerian video magnification is applied to magnify subtle changes in the retinal video produced by blood flow through the retinal vessels. The magnification is applied only to the segmented vessels, thus maximizing information while minimizing the high levels of noise present in FA videos, enabling ophthalmologists to more easily identify potential regions of pathology.

RESULTS: A prospective study was conducted with institutional review board (IRB) approval at the University of Central Florida in collaboration with Central Florida Retina, Orlando, FL. The collected FA video dataset consists of 1402 frames collected from 10 normal subjects. Experimental results for retinal vessel segmentation show the proposed method obtains a dice coefficient of 85.94%, outperforming the state-of-the-art CNN U-Net. Qualitative analysis of the wavelet-based registered, vessel-segmented, Eulerian-magnified FA videos performed by expert ophthalmologists supports the claim that the proposed pipeline can be helpful for providing a better analysis of blood flow dynamics.

CONCLUSIONS: The analysis of blood flow in FA videos provides key information to ophthalmologists for diagnosing retinal vascular pathology. The authors introduced a novel computational tool, combining a wavelet-based video registration method with a deep learning capsule-based retinal vessel segmentation algorithm and an Eulerian video magnification technique to quantitatively and qualitatively analyze blood flow dynamics in fluorescein angiogram videos.
Inner Retinal Fenestration for Pediatric Optic Disc Pit Maculopathy

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PURPOSE: To evaluate the efficacy of vitrectomy with inner retinal fenestrations as a surgical technique for the treatment of optic disc pit maculopathy in the pediatric population.

METHODS: This retrospective, interventional case series included pediatric patients with optic disc pit maculopathy treated at two tertiary hospitals in London by a single surgeon (SCW). All patients underwent pars plana vitrectomy with the creation of two inner retinal fenestrations and endogas tamponade. These partial-thickness retinotomies were made radial to the optic disc pit in the papillomacular bundle using a 25-gauge MVR blade. Anatomic and visual outcomes were determined by optical coherence tomography and best-corrected visual acuity (BCVA), respectively.

RESULTS: A total of six patients were included. Average age was 12.0±3.5 years. Preoperatively, all eyes demonstrated subretinal and intraretinal fluid in the central macula. Patients were followed for a mean of 22.7±16.1 months with a range of 6-48 months. Mean preoperative BCVA was logMAR 0.71±0.29 (20/100). Mean postoperative BCVA was 0.55±0.30 (20/70) at two weeks, 0.40±0.37 (20/50) at three months, 0.28±0.36 (20/40+2) at six months, and 0.20±0.32 (20/32) at one year. Visual gains were significant at six (p=0.05) and twelve months postoperatively (p=0.03). Progressive resolution of intraretinal and subretinal fluid was observed in all eyes (Figure 1). Recurrence of macular detachment or intraretinal fluid was not observed.

CONCLUSIONS: Inner retinal fenestration is an effective technique that resolves fluid and restores vision in pediatric patients with optic disc pit maculopathy. These results support the hypothesis that allowing an egress of fluid into the vitreous cavity can achieve long-lasting amelioration of the pathologic findings often associated with this condition.
Ocular Manifestations of Cutis Marmorata Telangiectatica Congenita (CMTC)

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PURPOSE: To describe the range of ocular manifestations in cutis marmorata telangiectatica congenita (CMTC).

METHODS: Multi-center retrospective non-consecutive case-series of patients with a diagnosis of CMTC referred for ophthalmologic evaluation between January 1, 2015 and December 31, 2018. Evaluation of ocular findings at presentation, systemic manifestations suggestive of a diagnosis of CMTC, genetic testing, and visual outcomes after treatment. Main outcome measures included visual acuity, findings on ophthalmoscopy, and results of fluorescein angiography.

RESULTS: 9 patients with CMTC diagnosed clinically based on stereotypical cutaneous vascular malformations were included. The median age of presentation was 8 weeks (range 2 weeks – 4 years). 6 patients were female and 3 were male. Avascular retina was identified on dilated fundus examination and/or on fluorescein angiography in 11 eyes of 6 patients. Retinal neovascularization was present bilaterally in 2 patients at presentation. One patient demonstrated retinal venous tortuosity, and another patient had mild straightening of nasal retinal vessels in both eyes. There were two patients (two eyes) with retinal detachment. Both were managed surgically. One infant presented with retinal detachment, while the other child presented with extensive neovascularization and later progressed to combined tractional-rhegmatogenous detachment. A unique constellation of lacy peripheral capillary anomalies with prominent terminal vascular bulbs was noted in 3 patients. Granular pigment abnormalities were noted in the macula in 5 patients. There were 2 patients with glaucoma, one requiring surgical intervention. Two patients demonstrated features of Adams-Oliver Syndrome, with genetic testing identifying a Notch1 mutation in one patient.

CONCLUSIONS: Retinal vascular abnormalities in CMTC may occur more frequently than previously recognized. Given the variability of ocular involvement and the potential for rapidly progressive retinal vascular abnormalities and development of retinal detachment, complete ophthalmologic evaluation including measurement of intraocular pressure, gonioscopy, dilated fundus examination and fluorescein angiography is recommended in infants with suspected CMTC shortly after birth. The distinct pattern of lacy capillary anomalies with prominent terminal bulbs seen in CMTC has not been described in other syndromes of vascular dysgenesis. Therefore, ophthalmic examination may be a valuable modality to distinguish CMTC from other disorders presenting with similar dermatologic and systemic manifestations.
Pediatric Gene Therapy Experience at the Bascom Palmer Eye Institute

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**PURPOSE:** To discuss the pediatric retina surgical techniques and experience in gene therapy at the Bascom Palmer Eye Institute.

**METHODS:** IRB approved retrospective review of pediatric gene therapy cases at the Bascom Palmer Eye Institute. Analysis of cases and surgical techniques.

**RESULTS:** Surgical techniques in pediatric surgery have changed with the advancement in technology and experience of the surgical team. We will discuss the state-of-the-art techniques for subretinal surgery in the pediatric population for gene therapy.

**CONCLUSIONS:** Experience has maximized surgery, instrumentation and technique in the pediatric population for gene therapy.
Bevacizumab or Laser for Aggressive Posterior Retinopathy of Prematurity

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PURPOSE: To report rate of reactivation and structural outcome after laser or bevacizumab treatment for aggressive posterior Retinopathy of Prematurity (APROP).

METHODS: Retrospective chart review was conducted on consecutive infants with APROP treated with 1) laser or 2) bevacizumab, followed by fluorescein angiography (FA) and prophylactic laser to persistent avascular retina.

RESULTS: 36 eyes of 19 patients were included. Mean gestational age was 24.5 weeks with mean birth weight of 632g in the bevacizumab group and 24.7 weeks and 777g in the laser group. Unfavorable outcome occurred in 1 of 22 eyes treated with bevacizumab and in 5 of 14 eyes in the laser group (p=0.002). Reactivation requiring retreatment was common in both groups, 9/22 after bevacizumab and 6/14 after laser (NS).

CONCLUSIONS: Regardless of initial treatment, reactivation requiring retreatment is common in eyes with APROP. Unfavorable structural outcome was significantly more common after initial laser treatment than after initial bevacizumab treatment.
Adopting Contrast Sensitivity Screening in a Driver's License Program: Results from a Pilot Study of 352 Subjects

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PURPOSE: Contrast sensitivity (CS) measurement provides details about functional vision not captured by visual acuity testing, however, it is not commonly tested when obtaining a driver’s license. Impairment in CS occurs in many ocular pathologies, including macular degeneration. This study sought to assess CS impairment in a random sample of drivers.

METHODS: 352 drivers at 6 licensing centers were enrolled. Subjects were screened using portions of the Functional Acuity Contrast Test (FACT). 5 blocks of increasing spatial frequency were tested, each containing 4 images with decreasing contrast. Failure was defined as more than 2 errors in a block of 4. Demographic data, visual testing data, and accident history were collected. Logistic regression was used to assess for predictors of testing errors.

RESULTS: 112 subjects under 35 years old, 126 between 35 and 50 years old, and 114 over 50 years old were studied. At higher spatial frequencies, those over 50 had on average 1.51-4.38 times the number of errors as compared to the other two age groups. Failure rates at these frequencies were as follows: 3.16% and 3.53% of those under 35, 7.02% and 15.09% between 35 and 50, and 15.38% and 29.07% of those over 50. In terms of accidents, 8.93% under 35, 11.11% between 35 and 50, and 7.89% over 50 had an incident within the last three years. Age, corrected vision, and visual field deficits were associated with errors at higher spatial frequencies. Recent accident history was not associated with errors on CS testing.

CONCLUSIONS: At higher spatial frequencies, drivers older than 50 had a significantly higher number of errors and failures on this screening test. Recent accident history was not associated with a higher number of errors, though the study was not sufficiently powered in terms of accident history. Our study found that a significant portion of drivers have issues with CS, especially over the age of 50. To our knowledge, no states in the U.S. evaluate CS as part of a routine qualification for a driver’s license, but some countries mandate such testing (Germany).
Cellular Automata: A Conceptual Framework for Perfect Drusen Symmetry

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PURPOSE: The general symmetry of anatomical features present in both retinas of the same patient is well recognized by any practitioner of ophthalmology. But striking examples of exact spatial symmetry of retinal pigment epithelial features, in particular drusen and reticular pseudo-drusen present in the monolayer of -3.5 million RPE cells in two eyes that develop independently of each other, cannot be explained by Mendelian genetic or epigenetic factors.

METHODS: The concept of “cellular automata”, popularized by Stephen Wolfram in *A New Kind of Science*, describes algorithmic models with simple rules in which the initial state of a “cell” can change over time, depending upon its local spatial organization and the state of its nearest neighbors. From a few simple rules, remarkable biological dynamics and complexity may emerge, patterns that have recently been identified throughout nature.

RESULTS: Different models of cellular automata will be presented, and how such models are predicted to manifest as symmetric drusen phenotypes in the hexagonal tiling of the retinal pigment epithelium of the eye will be discussed and presented in video format.

CONCLUSIONS: This paper presents a theoretical approach to understanding perfect phenotypic symmetry between the two eyes through the concept of cellular automata.
Opioid Prescribing Patterns Among Retina Specialists in the United States

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PURPOSE: The use of opioids in the United States has grown considerably. Increases in opioid-related deaths and complications have prompted clinicians in all fields to scrutinize their prescribing patterns. We sought to determine the opioid prescribing patterns among retina specialists.

METHODS: An observational, retrospective, cohort study was conducted of American Society of Retina Specialists (ASRS) members’ prescribing patterns in the 2013–2016 Medicare Part D Prescriber database. ASRS members within the United States were profiled from the ASRS member directory as of April 2019. The Centers for Medicare and Medicaid Services Medicare Part D Prescriber Public Use Files for 2013, 2014, 2015, and 2016 were accessed. Data were collected and analyzed regarding the prescribing patterns for opioid drugs for all participating ASRS members. The mean number of opioid prescriptions written annually by retina specialists, prescriber rates compared with all prescriptions written, and geographic distribution of opioid prescriptions written per retina specialists were analyzed.

RESULTS: The authors identified 1,815 surgeons in the 2019 ASRS directory. Members had written a total of 14,127 prescriptions in 2016 with 66% of members writing at least 1 opioid prescription. On average, members wrote 11 opioid prescriptions per year. Almost a quarter (24%) wrote >10 prescriptions annually. A minority wrote >50 prescriptions per year (5%). Among those writing >10 prescriptions annually, 16 opioid prescriptions were given annually with a mean supply of 4 days. Using multivariable analysis, the factors associated with increased number of opioid prescriptions were male gender (B=3.86, P < 0.001) and a practice location in the South (B=5.61, P < 0.001). The total number of opioid prescriptions including refills written by members also decreased by 18% from 2013 to 2016 (P<0.001).

CONCLUSIONS: ASRS members prescribed opioids at a rate (3%) lower than the national mean of all prescribers (6.8%). Male gender and a practice location in the South were correlated to number of prescriptions. The present opioid abuse epidemic should prompt physicians to reconsider their prescribing protocols given the high risk for dependency.
Distribution and Practice Patterns of Retina Providers Across the United States

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PURPOSE: Medical retina care in the United States may be provided by fellowship-trained retina specialists or by comprehensive ophthalmologists. Despite the growing national burden of retinal disease, the distribution and practice patterns of various retina providers has not been well studied. A deeper understanding of these differences is essential when considering strategies to ensure high quality retina care. Combining large national datasets, new insights regarding retina care delivery are now possible.

METHODS: This retrospective, cross-sectional study utilized 2016 Medicare dataset to identify ophthalmologists who performed intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections and/or posterior segment laser (common procedure terminology [CPT] J2778, J3590, J0178, 67228, 67210) +/- YAG capsulotomy (CPT 66821). Ophthalmologists offering retina-only services were labeled “retina specialists” and those who additionally offered comprehensive services were labeled “hybrid providers.” This dataset was merged with Internal Revenue Service, Census Bureau, and Centers for Disease Control datasets to characterize county-level income, age distribution, and diabetes burden. Statistical outcomes were assessed using multivariate logistic regression, chi-square, and two-tailed t-tests. Geospatial analyses were also performed.

RESULTS: 3329 retina providers—2295 specialists and 1034 hybrid providers—were identified. There was no difference in regional distribution of retina providers overall. On geospatial analysis, the distribution of retina providers nationally was similar to prior studies evaluating access to ophthalmology care. Relative to specialists, hybrid providers were more likely to practice in Pacific (p<0.001) and West North Central (p=0.003) regions and in areas with older population (p<0.001). Hybrid providers provided 15% and 23% of anti-VEGF and laser services, respectively. On average, beneficiaries received more sessions of focal laser beneficiary (1.40 vs. 1.33, p<0.001) and fewer injections Aflibercept (4.27 vs. 4.52, p<0.001) when treated by a hybrid provider. Hybrid providers utilized anti-VEGF injections with differing frequency (p<0.001) and were more likely to use Bevacizumab (37% vs. 29%) and less likely to use Ranibizumab (20% vs. 28%, p<0.001).

CONCLUSIONS: No regional bias in availability of retina providers was identified but there were regional and practice differences between specialists and hybrid providers. Further studies are needed to understand the causes of these differences and their impact on retina care delivery.
Choroidal Circulation in Radiation Retinopathy

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PURPOSE: Radiation retinopathy is a major cause of blindness in patients treated with radiation against various malignancies; however, the mechanisms underlying intraocular circulatory disturbances are largely unknown. The aim of this study is to examine choroidal circulation in patients who underwent radiotherapy.

METHODS: Seventy patients treated with external beam radiation therapy (EBRT) because of malignancies in the periocular and facial regions were retrospectively studied. Four and 3 out of 7 patients underwent total dosage of 30 Gy and 50-60 Gy EBRT, respectively, the irradiated fields of which contained the retina. Patients were divided into low and high dose groups according to the total dosage, respectively. Choroidal circulation was determined by laser speckle flowgraphy, in which mean blur rate (MBR) was obtained as a relative value of choroidal circulation in the macula. Central choroidal thickness (CCT) was calculated based on findings of enhanced depth imaging-optical coherence tomography before, and 3 and 6 months after irradiation.

RESULTS: Fundus showed no significant changes in patients with low dose; however, soft exudates, retinal hemorrhages, and retinal avascular areas were noted in irradiated eyes of the high dose group. MBR did not change significantly in 3 out of 4 patients with low dose group, whilst one patient having abnormality of retinal pigment epithelium (RPE) before irradiation revealed 20 % reduction of MBR as well as thinning of CCT (from 288 to 238 µm) 6 months after the radiation. In contrast, MBR showed low in the irradiated eyes (10.1±2.0) with high dose compared with that in non-irradiated eye (12.4±2.4) of all the patients. There was no significant difference in CCT between eyes with high dose before and after radiation.

CONCLUSIONS: These data suggest that choroidal circulation was involved in patients treated with high-dose radiotherapy.
Retinal Vascular Abnormalities in Phakomatosis Pigmentovascularis; Implications for G-protein Involvement in Retinal Vascular Development

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PURPOSE: To describe the spectrum of retinal vascular abnormalities in patients with phakomatosis pigmentovascularis (PPV).

METHODS: Observational case series.

RESULTS: Three patients with PPV are presented. One of the patients was a carrier of a somatic GNA11 R183C pathogenic variant consistent with PPV. Evaluation of all patients (n=6 eyes of 3 patients) with widefield fluorescein angiography illustrated several retinal vascular abnormalities, including peripheral retinal non-perfusion (n=3 eyes), peripheral vascular leakage (n=3 eyes), aberrant retinal vessels (n=1 eyes), vascular tortuosity (n=1 eyes), and disruption of the foveal avascular zone including fovea plana (n=3 eyes). In addition, two eyes demonstrated peripheral retinal vascular straightening and leakage similar to the features of familial exudative vitreoretinopathy.

CONCLUSIONS: Fluorescein angiography, especially with wide field capability, reveals numerous retinal vascular abnormalities in patients with phakomatosis pigmentovascularis. Considering the association of GNA11 pathogenic variants with PPV and allied disorders, these observations may suggest a role of G-proteins in retinal vascular development.
Intra-operative Cytology on Choroidal Tumors

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PURPOSE: The purpose of the study is to determine the effect of intra-operative cytology on the frequency of insufficient results.

METHODS: The study was a retrospective review of 23 consecutive needle biopsies performed at Mayo Clinic Florida. The surgery was attended by a cytology technician in all cases and a Diffquick direct smear was made on all aspirates. Diffquick direct smears were reviewed intra-operatively by a cytology technician and the surgeon and assessed for adequacy by microscopy. If the specimen was judged as not adequate by the surgeon a repeat aspirate was performed.

RESULTS: All 23 specimens received a final interpretation by a cytologist, and none were judged as insufficient to give a diagnosis. 18 of the specimens were designated as adequate after a single aspiration. 3 cases required a second aspiration and 2 cases required a third aspiration. A determination of benign or malignant was made in all cases. 14 cases were diagnosed as melanoma, 4 cases were diagnosed as carcinoma, 3 cases were diagnosed as benign nevus and 2 cases were diagnosed as lymphoma.

CONCLUSIONS: Intraoperative cytology can reduce the number of biopsies that yield “not sufficient” as a result by allowing for repeat biopsy if the specimen the first or second aspiration is judged to be inadequate without the need for a cytologist in the operating room.
Whole Genome Sequencing of Circulating Cell-free DNA in Patients with Uveal Melanoma

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PURPOSE: To explore the potential application of ultra-low pass whole genome sequencing of cell-free DNA in patients with uveal melanoma

METHODS: Ultra-low pass whole genome sequencing (ULP-WGS) was performed on cell-free DNA extracted from 29 plasma samples. The samples were collected from 14 patients with metastatic uveal melanoma and 2 patients with primary uveal melanoma who had received proton irradiation and had no metastatic disease. Tumor content was quantified using the computational tool ichorCNA (Adalsteinsson, et al. Nature Communications 2017;8(1):1324).

RESULTS: Circulating tumor DNA was detectable in 13/14 patients with metastatic disease but was not detected in the 2 patients without metastatic disease. The fraction of cell free DNA derived from tumor DNA (tumor fraction) appeared to correlate with clinical outcome. Copy number variation was consistently detected in samples with a wide range of tumor fractions ranging from 0.04 - 0.58.

CONCLUSIONS: Circulating tumor DNA in patients with metastatic uveal melanoma can be detected by ultra-low pass whole genome sequencing and correlates with disease status. A custom sequencing panel targeting recurring copy number variants in uveal melanoma could serve as a blood-based biomarker assay with the potential for predicting clinical outcomes in both adjuvant and metastatic disease settings.
Central Serous Chorioretinopathy Treated with Targeted Navigated Laser Photocoagulation

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PURPOSE: Central serous chorioretinopathy (CSC) is a common cause of central vision loss that is characterized by the development of serous retinal detachments. This consecutive interventional case series studies the visual and anatomic outcomes of CSC patients treated with angiography-guided laser treatment (AGLT).

METHODS: Angiography-guided navigated laser treatment used to treat angiographically leaking hot spots in CSC between 11/01/2012 and 04/17/2019 at two study sites in a large retina practice. Demographic and clinical information, including visual acuity (VA) and central retinal thickness (CRT) of these subjects were collected and analyzed using Student’s T-test and ANOVA. The optical coherence tomography (OCT) images of the subjects were also examined for the height of subretinal fluid (SRFH) and pigment epithelial detachments (PED).

RESULTS: The 57 patients (61 eyes) who received AGLT for CSC had a mean LogMAR VA score of 0.345 (between 20/40 and 20/50 Snellen equivalent), CRT of 409 microns, and maximal SRFH of 222 microns at baseline. Of the 52 eyes that completed follow up, 25 (48.1%) eyes followed up within a month after AGLT and reported an average CRT reduction of 141 microns (P < 0.001) and SRFH reduction of 166 microns (P = 0.002). Within three months, 48 eyes (92.3%) reported an average CRT reduction of 126 microns (P < 0.001) and SRF reduction of 151 microns (P < 0.001). Of 52 patients, 34 (65.4%) had completely resolved SRF within five months of follow up after receiving AGLT. VA significantly improved by an average of 0.111 to a mean LogMAR VA score of 0.219 (around 20/32 Snellen equivalent; P < 0.001), CRT was reduced by 135 microns to a mean of 283 microns, and SRFH diminished by 157 microns to a mean of 71.8 microns within five months of follow up.

CONCLUSIONS: Angiography-guided navigated laser treatment to fluorescein leakage hot spots appears to be effective and safe for the resolution of CSC sub-retinal fluid in the study eyes. More investigation is necessary to determine the efficacy of AGLT compared to the natural course of the disease.
Experience in Initial Management of Central Serous Retinopathy with Spironolactone

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PURPOSE: There have been several studies evaluating the use of mineralocorticoid antagonists for the treatment of central serous retinopathy (CSR). These studies generally exclusively treat cases of chronic CSR after an initial observation period. Additionally, eplerenone tends to be the agent of choice in these reports. The purpose of this study is to report our experience managing all presenting macular involving central serous retinopathy patients with a course of oral spironolactone.

METHODS: A retrospective, consecutive case series of patients with active macular involving CSR managed with oral spironolactone from 2015 through 2018 is reported herein. All new CSR patients evaluated over this timeframe were identified. Exclusion criteria included: follow up less than 3 months, documented chronicity of findings greater than 2 months, choroidal neovascular membrane, prior treatment of any kind, and sole extramacular involvement. OCT imaging and fluorescein angiography data was reviewed in all patients. We assessed for central retinal thickness, visual acuity, treatment failure, recurrence rates, and adverse events at 1 month, 3 months, 6 months, 1 year and at final follow up visit if available.

RESULTS: We identified 30 eyes of 27 patients who were treatment naïve at initial presentation. The median VA at presentation was 20/30 (range: CF to 20/20) which statistically improved by final follow up. There was 90% rate of resolution of subretinal fluid at a median time of 111 days. Early recurrence of subretinal fluid was associated with a treatment time of 62 days, in comparison to 86 days in the nonrecurrent group. 23% of eyes eventually required PDT, which was associated with larger central retinal thickness at presentation and early date of presentation in the study period. There was an adverse event rate of 20%, most being intolerance due to abdominal pain, but there were two cases of hyperkalemia requiring hospitalization.

CONCLUSIONS: Spironolactone is a viable management option for CSR in select patients. A three-month course inclusive of tapering is advisable to prevent early recurrence. Hyperkalemia is a risk in predictable clinical scenarios, including kidney disease and those taking ACE inhibitors or angiotensin receptor blockers.
Use of Alcohol Swabs and Nonsterile Gloves in Preparation of Anti-VEGF Medication for Intravitreal Injection

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PURPOSE: Intravitreal injections have surged with the administration of vascular endothelial growth factor (VEGF) inhibitors in the treatment of retinal disease. Though a generally safe procedure, intravitreal injection does carry a risk of endophthalmitis, and a wide variety of techniques are used to prevent infection. Current recommendations include cleansing of the medication vial’s rubber septum with an alcohol pad and use of gloves during the injection procedure. This project seeks to evaluate the efficacy of these techniques in reducing contamination of the medication vial for intravitreal injection at our institution.

METHODS: An IRB waiver was obtained for this quality improvement project. Physicians preparing a patient for injection with aflibercept aspirated the medication according to their current practice patterns, either with an alcohol pad and nonsterile gloves or with neither. The septum of the medication vial was cultured after aspiration, with 152 vials sampled per group, powered for a 5% difference between groups.

RESULTS: Overall culture positivity was 0.7%. Of the 152 vials sampled after the use of an alcohol pad and nonsterile gloves, 2 were positive (1.3%; Bacillus and Staphylococcus). Of the 152 vials sampled without alcohol or glove use, 0 were positive (0%; p > 0.05). No patient that received injections in this series went on to develop endophthalmitis.

CONCLUSIONS: Contamination of the aflibercept septum is rare, occurring in 0.7% of vials sampled after medication aspiration in this group. Use of gloves and alcohol cleansing, according to physician preference at our institution, was not significantly associated with risk of contamination. Despite two vials with positive culture, no patients developed endophthalmitis.
Staphylococcus Warneri Endophthalmitis Following Intravitreal Anti-VEGF Injection

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**PURPOSE:** To describe two cases of S. warneri endophthalmitis after intravitreal anti-VEGF injection

**METHODS:** Retrospective review of small case series

**RESULTS:** Six days after intravitreal avastin injection, two eyes presented with redness, pain, “hand motions” visual acuity and anterior and posterior segment inflammation consistent with endophthalmitis. Both underwent vitrectomy and intravitreal antibiotic injection. Gram stains revealed polymorphonucleocytes. Final cultures were reported as negative at three days. One culture was read at 5 days and was reported as staphylococcal species, probable contaminant. PCR of both vitreous specimens identified S. warneri. No organism was identified by culture or PCR of the remaining avastin. Six months later, final visual acuity was reduced by 2 Snellen lines in one eye and had returned to baseline in the other.

**CONCLUSIONS:** Staphylococcus warneri, a coagulase negative staphylococcus (CoNS), is a commensal of the skin and nasal mucosa. Clinical infections are infrequent and occur predominantly in immunocompromised individuals, neonates and those with indwelling catheters, shunts or orthopedic implants. Diagnosis may be challenging as the organism’s slow growth and low virulence may result in cultures reported as contaminant or negative. The potential role of S. warneri in “sterile endophthalmitis” after IVAV warrants further investigation. To our knowledge, this is the first report of S. warneri endophthalmitis.
2A Case of Poor Visual Acuity due to Iridocyclitis and Choroiditis associated with Past Langerhans Cell Histiocytosis

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PURPOSE: Langerhans cell histiocytosis (LCH) is a disease characterized by abnormal proliferation of Langerhans cells in skin, bone, lymph nodes, and other organs. Intraocular involvement in LCH is rare but can result in iridocyclitis and choroiditis. We now report a case of posterior synechia and extensive retinal degeneration associated with a medical history of LCH.

METHODS: Case report

RESULTS: A 6-year-old girl, who had been treated for Langerhans cell histiocytosis at 4 months of age, presented at our hospital with poor vision in her left eye. Her best corrected visual acuity was 1.5 in the right eye and 0.09 in the left. The left eye showed posterior synechia from 3 to 6 o’clock in the pupil, with coarse retinal coloration and meandering retinal blood vessels. Optical coherence tomography (OCT) revealed disappearance of the ellipsoid zone in the entire left retina including the macula, and the electroretinogram was subnormal. No visual field constriction was apparent by Goldmann perimetry. Blood analysis and computed tomography did not reveal any potential cause of poor visual acuity. Given the history of LCH and the detection of posterior synechia and extensive retinal degeneration, we diagnosed the patient’s condition as iridocyclitis and choroiditis associated with LCH.

CONCLUSIONS: Iridocyclitis and choroiditis associated with past LCH can give rise to loss of vision.
Oculocardiac Reflex during Intravitreal Injection

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PURPOSE: To evaluate the occurrence of Oculocardiac Reflex during Intravitreal Injection.

METHODS: A total of 532 patients were enrolled in this study. Intravitreal injections were performed on one eye in every patient. Their heart rate was measured with a pulse oximeter before, during and after injection. Oculocardiac reflex was defined as a 20% decrease or more of basal heart rate.

RESULTS: The population enrolled comprised 270 women and 262 men. The mean age was 63.8 years ranging from 29 to 89 years. A decrease in heart rate of 20% or more occurred in 3.3% of patients during the intravitreal injection. A 95% confidence interval was found to be between (1.85% and 4.92%). All patients including the 3.3% with oculocardiac reflex were asymptomatic. The drop in heart rate recovered in all patients within 5 seconds after injection.

CONCLUSIONS: Oculocardiac reflex occurs mainly during strabismus surgery and has been described during different ophthalmic procedures when mechanical manipulation of the eye, eyelids or orbit are involved. There are no reports in the literature concerning oculocardiac reflex during intravitreal injection. This may be due to the fact that generally, heart rate is not monitored during intravitreal injection and if a drop in heart rate occurs, it goes unnoticed. Our study shows that 3.3% of 532 patients presented oculocardiac reflex during intravitreal injection. All patients were asymptomatic. Recovery time was less than 5 seconds.
EROS STATUE AT PICCADILLY CIRCUS IN LONDON
The Retina Society sincerely thanks our corporate supporters at every level for their contributions to our meeting. In addition, we are deeply grateful for their ongoing commitment to provide innovative and sophisticated equipment, pharmaceuticals, and services for the care of patients with vitreoretinal diseases. We acknowledge our debt to their excellence, and are delighted to have such talented partners in the development of new vitreoretinal treatments.

SPECIAL THANKS TO OUR GOLD PATRON, SILVER PATRONS AND PATRONS FOR THEIR LEVEL OF SUPPORT:

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