

# AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 • VOL. 202 JUNE 2019

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### EDITORIAL

- xi **Envirotyping: the next leap forward in the practice of precision medicine?** *Ta Chen Chang and Justin Stoler*

Envirotyping, the computation of an individual's high-resolution socio-environmental exposure profile, could facilitate the next leap forward in the practice of precision medicine. Wearable technologies, increasingly sensor-rich "smart cities," the exponential growth of computational power and artificial intelligence deep-learning strategies may culminate envirotyping as a powerful approach in disease characterization.

### PERSPECTIVES

- 1 **The genetic influence on corticosteroid-induced ocular hypertension: a field positioned for discovery.**

*Weilin Chan, Janey L. Wiggs, and Lucia Sobrin*

This perspective summarizes the evidence that the risk of ocular hypertension secondary to corticosteroids is influenced by genetic risk factors. It proposes that recent advances in genetic sequencing and analysis, coupled with new knowledge of the genetic underpinnings of primary open-angle glaucoma and intraocular pressure in general, provide novel opportunities to elucidate the genetic basis of corticosteroid-induced ocular hypertension.

- 133 **Looking back: fluorescein angiography and optical coherence tomography and the first century of the *American Journal of Ophthalmology*.**

*Christopher F. Blodi*  
This Perspective is part of a series celebrating the 100<sup>th</sup> anniversary of the founding of the *American Journal of Ophthalmology* (Third Series). The narrative discusses the key role of the *Journal* in the development and advancement of fundus fluorescein angiography. The landmark

1967 supplement issue containing six detailed articles by J. Donald M. Gass, essentially beginning the subspecialty of medical retina, is highlighted. The role of optical coherence tomography is reviewed as well.

### ORIGINAL ARTICLES

- 6 **Identification and correction of restrictive strabismus after pterygium excision surgery.** *Sally L. Baxter, Brian J. Nguyen, Michael Kinori, Don O. Kikkawa, Shira L. Robbins, and David B. Granet*

Pterygium excision is a commonly performed ophthalmic surgery. Restrictive strabismus causing diplopia is a potential complication of pterygium excision. This retrospective case series describes the clinical characteristics and treatment approaches for 15 patients who developed diplopia after pterygium excision. After scar tissue release and ocular surface reconstruction, their diplopia improved without needing medial rectus recession. Given the high volume of pterygium excision, awareness of postoperative restrictive strabismus and the potential for correction is critical.

- 15 **Effect of keratoconus severity on clinical outcomes after deep anterior lamellar keratoplasty.** *Sepehr Feizi, Mohammad Ali Javadi, and Bahareh Kheiri*

The outcomes and complications of deep anterior lamellar keratoplasty for keratoconus were independent of keratoconus severity. Comparison of eyes with different keratoconus stages demonstrated that this technique of corneal transplantation was more effective in eyes with severe keratoconus compared with those with moderate keratoconus. Therefore, it is advisable to use other alternative treatments, such as contact lenses and intrastromal corneal

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ring segments, and present corneal transplantation as the last alternative to keratoconus-affected patients.

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• **23 The location of exon 4 mutations in RPI raises challenges for genetic counseling and gene therapy.** *Anika Nanda, Michelle E. McClements, Penny Clouston, Morag E. Shanks, and Robert E. MacLaren*

Mutations in *RPI* can lead to dominant or recessively inherited retinitis pigmentosa. This paper looks specifically at dominantly inherited mutations within exon 4 of *RPI*, which are likely to lead to truncated versions of the *RPI* protein. By understanding the length of protein that causes retinal degeneration, we may gain a better understanding of the disease mechanism, which may help in developing future gene therapy strategies.

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• **30 Longitudinal study of peripapillary thinning in sickle cell hemoglobinopathies.** *Alisa T. Thavikulwat, Dingcai Cao, Thasarat S. Vajaranant, and Jennifer I. Lim*

Patients with sickle cell hemoglobinopathies were followed with spectral-domain optical coherence tomography of the peripapillary retinal nerve fiber layer over an average of 4 years. Faster rates of global retinal nerve fiber layer thinning were associated with a history of stroke and absence of hypertension. These findings may help guide management and screening of African American patients with sickle cell hemoglobinopathies at risk for glaucomatous optic neuropathy.

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• **37 Clinical manifestations, prognosis, and vaccination status of patients with rubella virus-associated uveitis.** *Fahriye Groen-Hakan, Suzanne van de Laar, Annemiek A. van der Eijk-Baltissen, Ninette ten Dam – van Loon, Joke de Boer, and Aniki Rothova*

Many clinicians assume that rubella virus-associated uveitis always presents with the Fuchs uveitis syndrome phenotype. In this series of 127 patients with rubella virus-associated uveitis, a wider clinical spectrum of clinical signs

was found. Typical features included unilateral anterior uveitis and vitritis, whereas posterior synechiae and cystoid macular edema were typically absent. The most common clinical feature was vitritis, and secondary glaucoma was the most common cause of permanent visual loss.

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• **47 Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, all-age United States health care system.** *Reza Dana, John L. Bradley, Annie Guerin, Irina Pivneva, Ipek Özer Stillman, Amber M. Evans, and Debra A. Schaumberg*

A retrospective claims analysis of data from a very large, geographically/demographically diverse study population provide the first population-based evidence for a rise in annual incidence/prevalence of dry eye disease in the United States over the past decade.

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• **55 The heritability of pigment dispersion syndrome and pigmentary glaucoma.** *Anamika Tandon, Ze Zhang, John H. Fingert, Young H. Kwon, Kai Wang, and Wallace L.M. Alward*

Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) are mostly sporadic. The risk of a first-degree family member having PDS or PG is 10.10%, which is lower than previously reported. However, there are a few families with an apparent autosomal dominant inheritance. If one relied only upon slit-lamp examination, PDS/PG relatives were only at a 2.89 times higher risk than what has been reported in the general population.

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• **62 Predictive factors for the rate of visual field progression in the advanced imaging for glaucoma study.** *Xinbo Zhang, Richard K. Parrish II, David S. Greenfield, Brian A. Francis, Rohit Varma, Joel S. Schuman, Ou Tan, and David Huang, on behalf of the Advanced Imaging for Glaucoma Study Group*

In the advanced imaging for glaucoma prospective observational study, the speed of visual field progression was

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found to be correlated with the following baseline factors: focal loss measured by optical coherence tomography or visual field, central corneal thickness, and intraocular pressure.

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• **72 Visual and clinical outcome of macular edema complicating pediatric noninfectious uveitis.** *Maya Eiger-Moscovich, Oren Tomkins-Netzer, Radgonde Amer, Zohar Habot-Wilner, Ahmed Kasb, Ronit Friling, and Michal Kramer*

The clinical course and visual outcome of macular edema in 25 children (33 eyes) with noninfectious uveitis was investigated. The prognosis was found to be favorable despite the chronic course of pediatric uveitic macular edema, with no clear preference to the treatment regimen obtained.

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• **79 Correlation of outer retinal degeneration and choriocapillaris loss in Stargardt disease using en face optical coherence tomography and optical coherence tomography angiography.** *Talal Alabduljalil, Rachel C. Patel, Abdullah A. Alqahtani, Simon S. Gao, Michael J. Gale, Miao Zhang, Yali Jia, David Huang, Pei-Wen Chiang, Rui Chen, Jun Wang, Richard G. Weleber, Mark E. Pennesi, and Paul Yang*

Photoreceptor and retinal pigment epithelium (RPE) degeneration in Stargardt disease exhibits a strong relationship wherein the loss of the inner segment/outer segment (IS/OS) junction is 1.6-fold greater than the RPE atrophy, supporting the theory that photoreceptor degeneration precedes RPE. Degeneration of both the photoreceptor and the RPE contributed synergistically to choriocapillaris attenuation, but apparently intact areas also tended to have abnormal choriocapillaris. The findings and techniques in this study may be of utility in developing endpoints for clinical trials.

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• **91 Randomized trial of treat and extend ranibizumab with and without navigated laser versus monthly dosing for diabetic macular edema: TREX-DME 2-year outcomes.** *John F. Payne, Charles C. Wykoff, W. Lloyd Clark, Beau B. Bruce, David S. Boyer, and David M. Brown, for the TREX-DME Study Group*

This prospective, randomized trial assessing a treat and extend dosing algorithm of ranibizumab 0.3 mg with and without navigated focal laser treatment demonstrated comparable visual and anatomic improvements and decreased treatment burden compared with monthly dosing at 2 years.

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• **100 The small fatal choroidal melanoma study. A survey by the European Ophthalmic Oncology Group.** *Susanna Jouhi, Martine J. Jager, Stefan J.R. de Geus, Laurence Desjardins, Nils Andreas Eide, Jean-Daniel Grange, Jens Folke Kùlgaard, Stefan Seregard, Edoardo Midena, Raffaele Parrozzani, Jean-Pierre Caujolle, Iwona Rospond-Kubiak, and Tero T. Kivelä*

This cross-sectional, multisite study investigates the size at which choroidal melanomas can metastasize and the clinical characteristics of the smallest choroidal melanomas that actually metastasized. It found that choroidal melanomas less than 3.0 mm in largest diameter are very unlikely to metastasize. No clinical risk factor was uniformly observed in these small fatal lesions. These findings are relevant for the decision when to follow for growth, biopsy, or treat small suspicious choroidal pigmented lesions.

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• **109 Prevalence and clinical patterns of ocular complications associated with anti-PD-1/PD-11 anti-cancer immunotherapy.** *Karen Bitton, Jean-Marie Michot, Emmanuel Barreau, Olivier Lambotte, Oscar Haigh, Aurélien Marabelle, Anne-Laure Voisin, Christine Mateus, Anne-Laure Rémond, Chloé Couret, Stéphane Champiat, Marc Labetoulle, and Antoine Rousseau*

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Among 745 anti-PD-(L)1-treated patients for malignancy included in a prospective cohort, 3 developed moderate-to-severe ocular immune-related adverse events (irAEs), providing a prevalence of 0.4% and an incidence of 0.7 per 1000 patient-months. An additional 5 cases of moderate-to-severe ocular irAEs were reported through a national pharmacovigilance registry for anticancer immunotherapies. Of these 8 patients, 5 presented with intraocular inflammation, 2 with ocular surface disease, and 1 with orbital myopathy. Some of these complications occurred in parallel with life-threatening extraocular complications. Local and/or systemic corticosteroid treatment allowed resolution or control of the ocular symptoms in 7 of 8 cases. Ocular irAEs led to permanent discontinuation of anti-PD-(L)1 in 4 patients.

- **118 Brillouin spectroscopy of normal and keratoconus corneas.** *Theo G. Seiler, Peng Shao, Amira Eltony, Theo Seiler, and Seok-Hyun Yum*

Brillouin spectroscopy represents a no-touch technique to measure biomechanical properties of the cornea. The response of keratoconus corneas is statistically different from that of normal corneas, but the differential diagnosis is currently not possible because of minor specificity and sensitivity.

- **126 Effect of timolol on aqueous humor outflow facility in healthy human eyes.** *Arash Kazemi, Jay W. McLaren, Matthew G.J. Trese, Carol B. Toris, Vikas Gulati, Shan Fan, David M. Reed, Tyler Kristoff, Jesse Gilbert, Sayoko E. Moroi, and Arthur J. Sit*

This prospective multicenter study investigated the effect of timolol drops, an aqueous humor flow suppressant, on aqueous outflow facility in 200 healthy human eyes after 1 week of use. Outflow facility was measured by 2-minute pneumatonography. Timolol decreased outflow facility in healthy human eyes, and this effect was greater in eyes with higher baseline outflow facility. Older age was associated with lower outflow facility.

## CORRESPONDENCE

- **151 Treatment duration and side effect profile of long-term use of intravitreal preservative-free triamcinolone acetonide in uveitis.** *Gary D. Novack*
- **151 Concerns regarding Nd:YAG laser posterior capsulotomy in children.** *Devesh Kumawat, Pranita Sahay, and Anusha Sachan*
- **152 Reply.** *Se Hyun Choi, Yong Dae Kim, Young Suk Yu, Mee Kum Kim, and Hyuk Jin Choi*

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0002-9394(201906)202:C;1-8

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