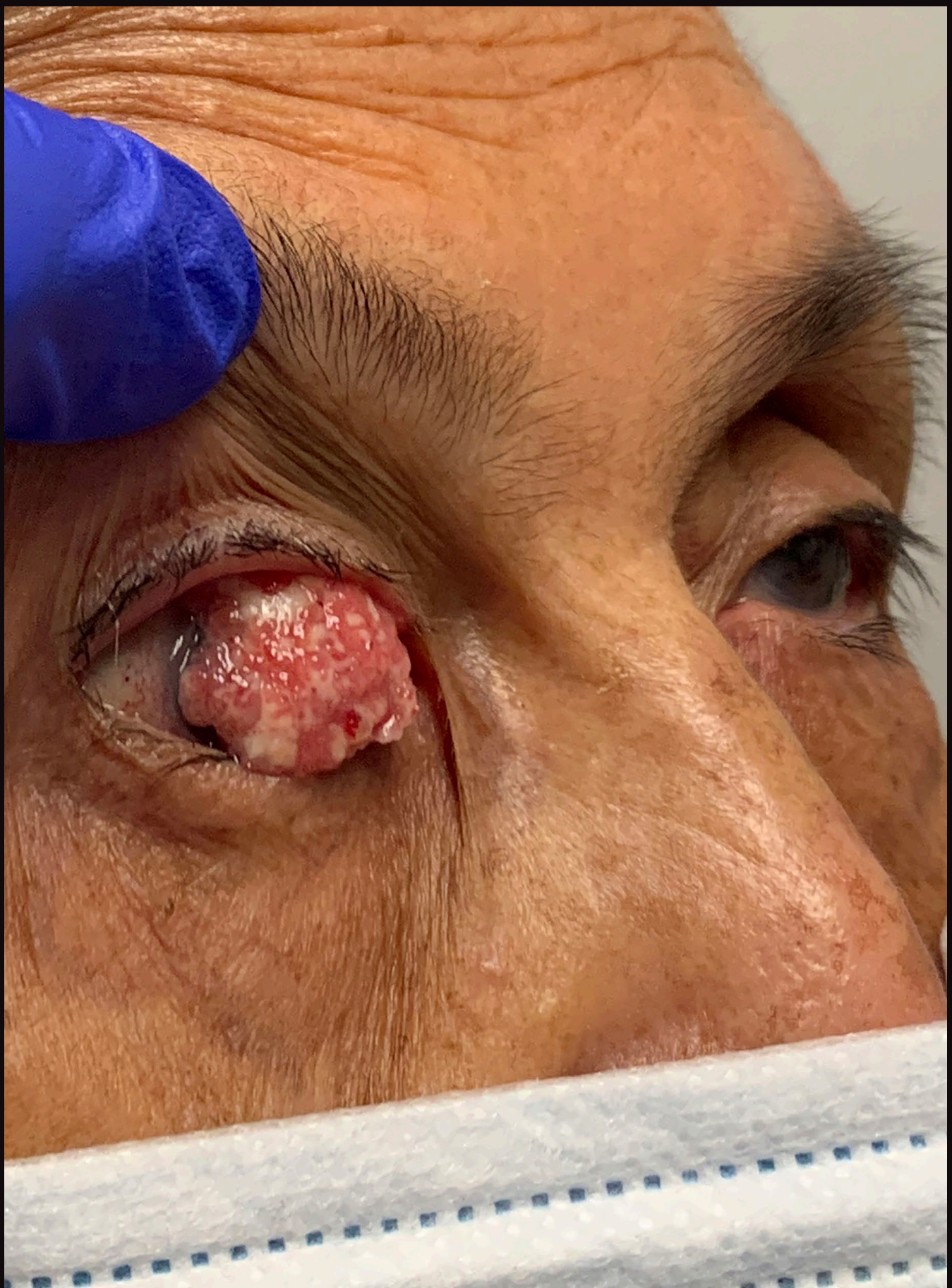


Jeremiah P. Tao, MD

Making Progress

Because the end of the year is a fitting time to take stock of recent clinical developments, *EyeNet* has asked three of its editorial board members to review their areas of expertise and to consider recent trends and news that have the greatest potential to shape their subspecialty over the next several years. Linda Tsai, MD, FACS, prognosticates on the future of comprehensive ophthalmology. Jeremiah Tao, MD, FACS, looks ahead in oculofacial plastic surgery. And Dan Gombos, MD, shares his thoughts on the near future of ocular oncology. Here are their perspectives.

Comprehensive Ophthalmology

Presbyopia Treatment Options Will Be Widely Accepted and Available

DR. TSAI

Presbyopia is the No. 1 cause of vision loss and affects more than 1.8 billion people worldwide. Becoming clinically relevant in patients who are between the ages of 40 and 50, presbyopia worsens with age. Often in low-income countries, the condition is not universally treated, which leads to significant functional and economic strain on society. In 2015, there were 826 million suspected cases of impairment due to lack of intervention or inadequate correction (estimated unmet need of 45%).[1] The good news? Presbyopia options allowing for spectacle independence will be widely accepted and available to all in the near future.

Classification

Presbyopia can be defined as the age-related, physiologic decrease of the eye's accommodative amplitude, which leads to insufficient near acuity when the patient is best-corrected for distance. This condition progresses along a spectrum in which newer classifications, such as "dysfunctional lens syndrome (DLS)" defined by Waring and Rocha in 2018, include age-related lenticular abnormalities in the later stages. DLS Stage 1 begins at approximately 40 years of age and is characterized by decreased near vision even with best-corrected distance VA and increasing higher-order aberrations. DLS Stage 2 adds contrast sensitivity reduction and increased light scatter symptoms resulting from early lens opacification. DLS Stage 3 is characterized by a visually significant cataract that affects daily activities as well as presbyopia.[2]

Improved Assessment of Needs

Future presbyopia management will be focused on the individual's specific visual needs and on personalizing therapeutic options. To this end, there will be a clearer algorithm for recommended treatments based on the patient's symptoms, exam findings, and objective data. Therapy will be tailored to the individual, and perhaps each eye, to optimize the range of clear focus for the patient's task requirements and to minimize adverse visual effects. Use of artificial intelligence (AI) will allow patients to experience simulations of what to expect after undergoing a therapy (e.g., cataract surgery with a multifocal IOL).

Current Therapies and Their Futures

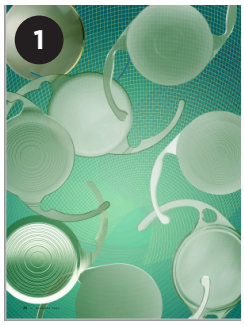
While presbyopia has been treated with limited success, none of the current therapies has become universally accepted as curative.

Pharmacologic therapy. Current pharmacologic options include two classes of medications. The first has been FDA-approved in the United States. It increases depth of focus through pupil modulation, by creating a pinhole effect under natural light conditions. The second is a lens-softening approach that uses lipoic acid and choline ester chloride to release the disulfide bonds thought to be responsible for progressive lens stiffening.[3] In an ideal future world, effective, reversible, low-cost pharmalogic therapy will be available to everyone. However, surgical options will likely be needed to achieve full spectacle independence for near work in older patients.

Corneal approach. Well-established corneal approaches to treat presbyopia include corneal inlays (refractive, reshaping, and small aperture inlays), presbyopia ablation profiles (central PresbyLASIK, peripheral PresbyLASIK, and laser blended vision), and targeted monovision in the nondominant eye. However, these approaches have limitations. Corneal inlays and corneal presbyopia ablations may have adverse effects such as glare, halos, and compromises in night vision. And corneal treatments that create monovision may not be tolerated by all patients. Additionally, these corneal-based procedures add inaccuracy to IOL calculations when patients eventually require cataract surgery.

Scleral procedures. Scleral microfibrils are cross-linked during the aging process and have been thought to decrease accommodative ability by increasing ocular rigidity. Polymethylmethacrylate I scleral expansion bands were attempted in the past, but this procedure had inconsistent results and complications of anterior ischemia and band extrusion. Laser scleral microporation uses an Er:YAG laser to create micropores in scleral tissue; this has been shown to have some effect on presbyopia as well as possible IOP-lowering effects.

Lenticular surgery. Cataract extraction is the most definitive treatment, as it is the only treatment for presbyopia that has progressed to DLS stage 3. It would be ideal if there existed an accommodating IOL that could mimic the 20 D range of childhood vision. However, data on the only FDA-approved accommodating IOL has been contradictory regarding the efficacy of intermediate and near visual acuities compared with monofocal IOLs. In the lab, liquid crystals controlled by an electric charge or other forms of optoelectronic lens technology are being developed.



IOLS. *To date, multifocal and extended depth-of-field lenses are the best solutions for presbyopes, but this may change over the next 10 years.*

Multifocal IOLs have been the most successful IOL technology to improve uncorrected near and distance VA and decrease spectacle dependence after cataract surgery. Many multifocal IOLs are currently available in the United States, and most work through ring-shaped diffractive zones that split light between two or more focal points. Extended depth-of-focus IOLs have gained popularity and use either a proprietary multifocal ring design or an aspheric defocus non-ring–based design to extend the depth of focus while decreasing patient-reported visual phenomena and decreased mesopic contrast sensitivity.[4] Nondiffractive IOL approaches including small aperture design and spherical aberration or a segmented refractive design to increase the depth of focus have not been found to be as effective as the multifocal technologies.

Future Climate

Options for spectacle independence at near are increasing. Nonetheless, no single treatment will be successful alone for all individuals, so future treatment plans will require a personalized combination of technologies for most patients. Pharmacologic options will target a younger population, or those with less of a need for near work. However, vehicles with longer drug delivery times must be developed for patient convenience and compliance.

And demand for spectacle independence is increasing, too. Many patients who in their youth turned to laser refractive surgery for spectacle independence for distance vision now require reading glasses, and they are eager to accept available surgical technology to obtain spectacle independence in their later years. The model of self-pay options spurred by laser refractive surgery and premium IOLs has become a standard in today's reimbursement environment and will continue to drive the presbyopia market, making the presbyopia focus of cataract surgery financially attractive to surgeons. However, patient expectations will be high, social media will be used to promote and criticize therapies, and companies will market more directly to patients.

As IOL options improve, it is possible that clear lens extraction will become a standard in coun-

Peter Bollinger

tries with developed economies. However, even with the advent of improved AI algorithms and improved surgical techniques, there will always be an inherent margin of error and surgical complication risk. With improved IOL calculation formulas, the ability to focus the eye at a preselected plane of vision has become an expectation. The next expectation of presbyopia therapies—spectacle independence—is one that will be met in the next decade.

1 Fricke TR et al. *Ophthalmology*. 2018:125(10):1492-1499.
2 Waring GO, Rocha KM. *Current Ophthalmol Rep*. 2018; 6(4):249-255.
3 Mercer RN et al. *J Refract Surg*. 2021;37(6 Suppl):S28-S34.
4 Schallhorn JM et al. *Ophthalmology*. 2021;128(10):1469-1482.

Oculofacial Plastic Surgery

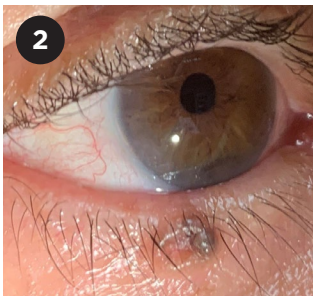
Trends That Could Shape Oculofacial Plastic Surgery in the Near Term

DR. TAO

Compared with the dramatic technology-driven transformations in intraocular surgery, oculofacial plastic surgery has remained mostly scalpel and suture, with few changes over time. After all, many of the procedures are among the oldest in medicine. Lacrimal surgery is on the list of the first recorded surgeries.[1] Likewise, thousands of years ago, Celsus and others described skin flaps and other eyelid surgeries that are similar to or the same as those offered today.[2] Although new periocular surgeries are hard to invent, several developments are reshaping the oculofacial plastic surgery specialty.

In the Clinic

Biologics. Targeted biologic agents will transform the management of many periorbital conditions. At the forefront is teprotumumab, a monoclonal antibody targeting the insulin-like growth factor 1 (IGF-1) receptor. Approved by the FDA in 2020 for the treatment of thyroid eye disease (TED), this agent is a long-awaited upgrade over nonspecific agents. It is especially preferred to corticosteroids, which have numerous side effects and limited efficacy. Many patients have received teprotumumab since its approval, yet how it best fits with existing treatments is uncertain. Importantly, meaningful durable clinical improvement has not been universal, and teprotumumab has not replaced surgery, especially for compressive optic neuropathy, or for moderate or severe proptosis or eyelid retraction. Also, adverse events, namely hearing loss, are concerning. Continued research will further define the indications and dosing for



CANCER? *Lower eyelid lesion suspicious for basal cell carcinoma.*

teprotumumab. Currently, it may be overprescribed owing to its broad TED FDA approval and because many prescribers are not trained to offer safe and effective orbit or eyelid surgery. The exorbitant price tag of teprotumumab (nearly $400,000 for a standard eight-infusion course) for this non–life threatening, commonly non–vision threatening, and often self-limited condition demands more evidence and further refinement of its indications.[3] Nevertheless, targeted therapies are here and will change how we manage not only TED but also other challenging diseases.

Cancer drugs. Novel treatments for malignancies add to the oculoplastic surgeon's therapeutic arsenal. In particular, the discovery of pharmacological agents that invoke one's own immune system to destroy malignant cells was a windfall. For some periocular malignancies (Fig. 2) where surgical excision or radiation can have significant risk to the eye, medications such as PD-1/PDL-1 or BRAF inhibitors can reduce morbidity and even mortality of some previously devastating cancers.[4]

Technology. Computers won't in the short term replace scalpel oculoplastic surgery but will impact the field. Artificial intelligence (AI) and deep learning (DL) will lessen diagnostic error in orbit and oculofacial disease. Skin carcinomas of the periocular region will be detected with smartphone imaging apps running AI algorithms. And patients with benign lesions—as well as their providers—will be reassured, thus saving not only stress but also time and cost.[5] Orbital imaging and other neuroradiology will similarly be interpreted with higher precision and less uncertainty using AI and DL.[6,7] Still, expect "clinical correlation recommended" to continue to appear gratuitously at the end of interpretation reports!

The Nonclinical Side

Business. Shifts in the business of medicine may change oculofacial plastic surgery. Trends of declining third-party payer reimbursements and increasing prior authorization requirements are not sustainable due to the increase in demands, hassles, and cost to the practice. The expected result is that more and more oculoplastic surgeons will opt out of accepting Medicare and other health

Jeremiah P. Tao, MD

insurance. Fee-for-service and concierge medicine are unsurprising upshots across diverse medical specialties, even primary care. For the oculofacial plastic surgeon already with cosmetic offerings, a conversion to complete cash-only practice is natural, seamless, and foreseeable. While this may limit access for some patients, the upside is that greater reimbursement and less administrative burden offers potentially higher quality, longer duration patient encounters that may bring back some of the joy of being a physician.

Recognition. Another uplifting trend is increasing recognition of oculofacial plastic surgery as a defined subspecialty within the house of medicine. The unique skills and proficiency of oculofacial plastic surgeons have been understood within ophthalmology and other smaller circles for over a half century, but many generalists and patients remain unaware that this expertise exists. Unfortunately, the important functions of the oculoplastic surgeon often become evident only when the eyes or periocular tissues are damaged, frequently by those without such focused training and ophthalmologic background. Key organizations, namely the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), the American Board of Ophthalmology (ABO), and the Academy, have raised awareness by advocating for patient safety and quality through high standards. In addition, the ASOPRS recently embarked on a marketing campaign to educate patients and referring providers about the unique training and skills of oculofacial surgeons. Wider recognition of oculofacial plastic surgery will reduce misinformation, delays, and the inability of patients to get to the right specialist.

Conclusion

In summary, the future of oculofacial plastic surgery looks bright, and the discipline is expanding in therapies and in recognition. While most oculoplastic surgeries won't soon be performed by robots, the discipline will thrive as a result of technologic and therapeutic innovations. The expertise and skills of the oculofacial plastic surgeon remains ever relevant as there is no one better to "clinically correlate" these advances with time-tested treatments for periorbital conditions.

1 Harish V, Benger RS. *Clin Exp Ophthalmol.* 2014;42(3):284-287.
2 Bartley GB. *Ophthalmology.* 2015;122(2):224-226.
3 Allen RC et al. *Ophthalmology.* 2021;128(8):1125-1128.
4 Habib LA et al. *Semin Ophthalmol.* 2019;34(4):327-333.
5 Esteva A et al. *Nature.* 2017;542(7639):115-118. Erratum in: *Nature.* 2017;546(7660):686.
6 Duong MT et al. *Neuroimaging Clin N Am.* 2020;30(4):505-516.
7 Lui YW et al. *Am J Neuroradiol.* 2020;41(8):E52-E59.

Ocular Oncology

Advances in Ocular Oncology

DR. GOMBOS

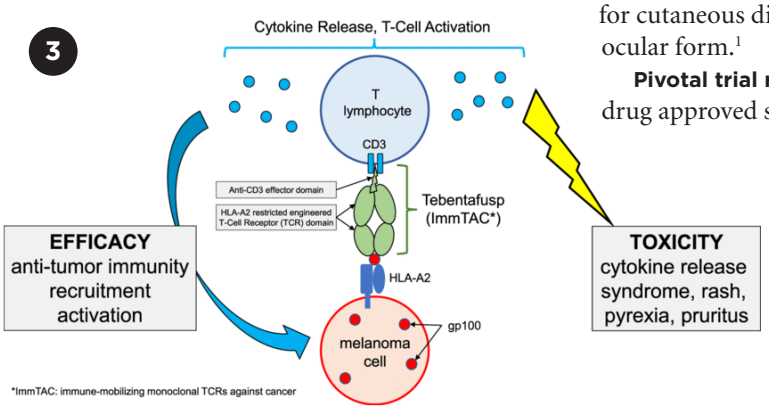
Ocular oncologists have several reasons to feel excited because promising new tools and techniques in therapy, diagnosis, and disease management are in development or have been introduced recently. Among these are a first-in-class drug for metastatic ocular melanoma, expanded use of liquid biopsy, and better-targeted treatments.

Breakthrough Therapy for Ocular Melanoma

Perhaps the most exciting recent news in the field was the approval of tebentafusp for metastatic ocular melanoma in 2022.

Ocular melanoma, the most common primary intraocular tumor in adults, is a particularly deadly disease: about half of patients with this form of melanoma experience metastasis, most frequently to the liver. Further, the median survival time in metastatic ocular melanoma is less than two years. The prior treatments for this disease were generally those used for cutaneous melanoma. But even though both forms of melanoma derive from melanocytes, their molecular behavior and metastatic targets are quite different, and the therapies for cutaneous disease are far less effective for the ocular form.[1]

Pivotal trial results. Tebentafusp is the first drug approved specifically for metastatic ocular melanoma. A landmark randomized clinical trial



NOVEL MECHANISM. *The fusion protein in tebentafusp creates a link between a T lymphocyte and a melanoma cell, enabling the T cell to destroy the cancer cell.*

compared tebentafusp against the standard-of-care therapies, specifically, single-agent pembrolizumab, ipilimumab, or dacarbazine. In this study, patients on standard therapy (the control group) had an overall median survival of 16 months, whereas the tebentafusp group had 21.7 months, an almost six-month improvement in overall survival.[1] Although this is not an out-of-the-park home run, it is a definite, significant incremental improvement over the existing therapeutic options.

Novel mechanism of action. Tebentafusp is also the first—and so far only—FDA-approved agent in its class, known as ImmTAC, or immune mobilizing monoclonal T-cell receptor against cancer. The mechanism of action is very interesting. The drug is a fusion protein (as indicated by the "-fusp" stem) that has a target domain and an effector domain. Basically, it acts by bringing a cytotoxic T cell up close to a melanoma cell and causing the release of cytotoxic agents to kill the cancer cell (Fig. 3).

Who might benefit? This drug presents a huge opportunity because we have learned over the years how to identify those patients at very high risk for metastatic disease. Various tools are available to assess risk, based on gene expression profiling, chromosomal status, and a new marker called PRAME, along with the eighth edition of the American Joint Committee on Cancer staging system for melanoma. And now, with this disease-specific treatment, we are better equipped to help the patients we have identified.

Caveats. However, tebentafusp is not available to all metastatic ocular melanoma patients. Only those patients who have a specific HLA haplotype (HLA-A*02:01) are eligible to receive the drug.

In addition, there is a significant amount of toxicity. In the pivotal trial, 44% of patients on tebentafusp had grade 3 or 4 systemic toxicity compared with 17% in the control group. The most common adverse events were pyrexia, chills, rash, and pruritus. It's not a trivial drug—it needs to be managed by someone who's an expert in ocular melanoma. Whenever possible, I think that these patients are best managed at a tertiary cancer center because if they're not eligible for one therapy, there may be other treatments or clinical trials available that might benefit them.

For more about tebentafusp, watch for the January *EyeNet*.

Liquid Biopsy for Intraocular Cancers

Looking ahead, I think that liquid biopsy will become increasingly important in diagnosing and managing intraocular cancer. This technique is already available for other cancers, including breast, lung, and gastrointestinal tumors. In liquid biopsy, a body fluid such as blood, aqueous, or cerebrospinal fluid is sampled rather than the actual tumor tissue. These fluid samples contain many tumor components, including circulating tumor cells, tumor DNA, and extracellular vesicles that may help not only to diagnose but also to predict the behavior of the cancer.[2]

A holy grail for retinoblastoma. Although this technique would be useful in many types of cancers, it has critical significance for retinoblastoma. We never perform a traditional intraocular biopsy in retinoblastoma for fear of spreading the tumor. Thus, finding an alternative method for diagnosing and characterizing retinoblastoma has been our equivalent of searching for the Holy Grail.

There is exciting research being done by Jesse Berry and colleagues at the University of Southern California,[3] and by David Abramson and colleagues at Memorial Sloan Kettering,[4] looking at either aqueous humor or blood. For example, Dr. Berry has done some very nice work using the aqueous to identify a tumor that is less likely to respond to therapy than other approaches, demonstrating that liquid biopsy may provide an opportunity for us to not only personalize the therapy in a more pragmatic fashion but to also monitor the response to therapy through ongoing sampling. Ultimately, this could reduce the need for enucleation and permit more eyes to be saved.

Other applications. Will we be able to do something similar for uveal melanoma? There's a lot of research on that as well.[5] We have already identified uveal melanoma cells circulating in the blood, but we still need to develop the platform to more fully utilize the wealth of molecular and target information. So, if I were putting my money on things, I'd bet that in three to five years we'll be seeing a lot of progress in liquid biopsies for eye cancers.

Targeted Therapies for Improved Survival

We are also seeing great progress in targeting therapies to improve management of metastatic lesions and thus increase both ocular and overall survival. For example, a patient may have a newly diagnosed lung cancer that involves the eye and the choroid. If that patient has the right PD-L1 pathway, we now have some therapies that can give the patient a much higher likelihood of survival.

I think that, increasingly, we're going to shy away from calling a cancer a lung cancer, for instance. Instead, we're going to ask, Does this cancer have a particular mutational pathway? And we already do that for some melanomas. For example, conjunctival melanomas are more like cutaneous

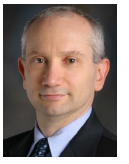
melanomas than they are uveal melanomas; thus, they may harbor a *BRAF* mutation. In that case, there are therapies that are highly targeted toward that mutation and can be very efficacious. It's all about knowing the right pathway.

Key Messages for Clinicians

The most important takeaway for our ophthalmology colleagues who are not specialists in oncology is to remain hopeful despite the currently poor prognosis for some ocular cancers: There is enormous potential for cures that we couldn't have dreamed of even five or 10 years ago. I would encourage clinicians to stay positive, to refer their patients to tertiary care centers where they can receive the most advanced therapies, and to support the role of prospective clinical trials. We've already learned so much from trials—and there's still much left to learn.

1 Nathan P et al. *N Engl J Med.* 2021;385(13):1196-1206.
2 Ghose N, Kaliki S. Liquid biopsy in retinoblastoma: a review. *Semin Ophthalmol.* 2022;1-7. Published online May 23, 2022.
3 Berry JL et al. *Ophthalmology.* 2020;127(4):552-554.
4 Abramson DH. Cell-free DNA (cfDNA) in the blood of retinoblastoma patients: The Robert M. Ellsworth Lecture. *Ophthalmic Genet.* 2022;1-5. Published online April 5, 2022.
5 Jin E, Burnier JV. *Ocul Oncol Pathol.* 2021;7(1):1-16.

Meet the Experts



Linda M. Tsai, MD, FACS Professor of ophthalmology and visual sciences at Washington University, St. Louis, Mo. *Relevant financial disclosures: None.*

Jeremiah P. Tao, MD, FACS Professor of ophthalmology and chief of oculofacial plastic surgery at the Gavin Herbert Eye Institute, University of California, Irvine. *Relevant financial disclosures: None.*

Dan S. Gombos, MD Professor and chief of the section of ophthalmology, department of head and neck surgery, University of Texas, MD Anderson Cancer Center, with joint appointments at the Baylor College of Medicine and the University of Texas Medical Branch; founding member and clinical codirector of the Retinoblastoma Center of Houston; and president of the International Society of Ocular Oncology. *Relevant financial disclosures: Castle Bioscience: C (unpaid).*

See disclosure key, page 8. For full disclosures, view this article at aao.org/eyenet.