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Editorial

Precision Medicine in Ophthalmology: Progress and Future Needs

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Precision medicine is a growing approach that has revolutionized patient care and treatment of disease. In 2019, the global precision medicine market was estimated to be worth 53.7–87.2 billion US dollars, and it is expected to more than double—reaching 146.8–278.6 billion US dollars—by 2030 [1]. In the US in 2023, the US Food and Drug Administration (FDA) approved 20 personalized medicines (38% of all newly approved molecular therapeutics) and 6 gene- or cell-based therapies. From 2015 to 2023, precision treatments accounted for more than one-quarter of new drug approvals each year. In addition, 12 companion diagnostic systems were approved in 2023, with the goal of targeting treatment to patients who can benefit most, avoiding the expenses and adverse effects for those patients who are less likely to benefit [2].

Ophthalmology has made significant strides in precision diagnostics and treatment. In 2012, the Collaborative Ocular Oncology Group published a study demonstrating a 97.2% rate of successful prognostication of posterior uveal melanoma using a 15 gene expression profiling assay in determining the likelihood of metastasis [3]. In addition to diagnostic and prognostic advances, major strides have been made in terms of precision treatment, specifically in the realm of gene therapy. In 2017, voretigene neparvovec-rzyl (Luxturna), an adeno-associated virus vector-based gene therapy, was approved by the FDA for the treatment of Leber congenital amaurosis, an inherited the gene encoding retinal pigment epithelium-specific 65 kDa protein. Numerous clinical trials are currently underway investigating gene therapies for other inherited retinal degenerations including retinitis pigmentosa, choroideremia, and X-linked juvenile retinoschisis [4]. Close collaboration among ophthalmologists, geneticists, and genetic counselors will facilitate the continued advancement of gene therapies. Simultaneously, given the sensitivity of genetic data, collaboration among healthcare providers, companies, and government officials will be necessary to ensure adequate data security and privacy.

Despite these advances, ophthalmology has fallen behind in the application of a precision approach to common eye diseases, particularly retinal diseases. Because of the retina's proximity to the vitreous humor, retinal disease represents a unique opportunity for the development of targeted therapy. The nearby vitreous contains abundant proteins, including many that play critical roles in retinal disease [5]. Furthermore, vitreous can be safely and easily biopsied in a clinic setting [6]. This combination of proximity to a tissue of interest, ease of access, and rich molecular milieu makes vitreous a suitable medium for liquid biopsy. Liquid biopsy, paired with molecular diagnostics, facilitates the optimal use of targeted therapies.

Ophthalmologists regularly administer molecular targeted therapy, most often in the form of intravitreal anti-vascular endothelial growth factor (VEGF) and anti-angiopoietin-2. An estimated 7 million intravitreal injections were administered in 2016 in the US, and more than 20 million were given worldwide [7]. Despite the large number of intravitreal injections of targeted drugs given regularly, there is currently no system in place to screen patients for the presence or absence of the molecules being targeted. Most commonly, anti-VEGF is used to treat age-related macular degeneration and diabetic retinopathy (DR), which affect more than 100 million patients worldwide [8,9] and are among the leading causes of vision loss in the US [10]. Unfortunately, a prior study has shown that as few as one in three of these patients responded well to this treatment at 1 year [11]. Seven years after treatment, only 23% of patients maintained a best corrected visual acuity of 20/40 or better [12]. In short, there is much room to improve treatment outcomes.

More than 30 years ago, Aiello *et al.* [13] demonstrated the significant range in vitreous VEGF concentrations among patients with active proliferative DR. Just over 20 years ago, the first anti-VEGF pharmaceutical was approved by the FDA for ophthalmic use. Despite the longstanding knowledge that many patients with neovascular retinal disease have low or normal vitreous VEGF concentrations, there is currently no companion diagnostic to screen patients for intravitreal VEGF levels prior to treatment. This results in excess cost and treatment-associated risks to patients who may have a low likelihood of treatment response. In addition to impeding optimized care for patients receiving treatment for neovascular retinal disease, the lack of companion diagnostics in ophthal-

mology thwarts drug development. Multiple large-scale, Phase 3 clinical trials for molecular targeted therapy have failed, including lampalizumab (Roche) targeting complement factor D and pegpleranib (Ophthotech/Novartis) targeting platelet-derived growth factor [14,15]. Specifically, the presence of molecular targets in these trials was not confirmed in the patients included in the trials, so the failure of these drugs may have been due to a lack of patient stratification to define appropriate treatment groups.

In conclusion, medicine is rapidly moving in the direction of precision diagnostics and treatments. Ophthalmology has made significant advancements in the realm of precision medicine, including tumor prognostic assays and gene therapy for inherited retinal dystrophies. However, there is much room for precision medicine to expand in ophthalmology, especially for the diagnosis and treatment of some of the most common eye diseases. Addressing the currents gaps in treatment workflows may help advance the application of precision medicine in ophthalmology. Although vitreous biopsy can be safely performed in a clinical setting, physicians remain hesitant to do so and typically take patients to the operating room for biopsy or forego biopsy altogether, posing a significant barrier to streamlined molecular analysis. Standardized instrumentation and protocols for liquid biopsy of vitreous humor may help increase the ease and willingness to complete vitreous biopsy. This will require novel device development and adequate clinical testing. Ultimately, better tissue availability for molecular analysis will accelerate the development of diagnostic assays and novel therapeutics. Together, these steps will bring ophthalmology into line with other medical fields in the advancement of precision medicine, with the critical and essential goal of improving patient care and treatment outcomes.

Author Contributions

SRW, TWG, and JMS conceived of the concepts. SRW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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