

Exploring Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema and Advances in Treatment

Judy E. Kim, MD, FARVO, FASRS

Introduction

Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are diseases affecting the choroidal and retinal vasculatures, respectively.¹ Vision loss associated with these conditions has a considerable socioeconomic impact and contributes to substantial reductions in quality of life for patients and burden for their caregivers.^{2,3}

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of these diseases and has been the primary treatment target.⁴ Years of experiences show that treatments directed at VEGF can improve visual acuity (VA) for patients with nAMD and DME. However, there remain unmet needs, as visual outcomes from treatments as applied in the real world fall short of the outcomes promised by pivotal clinical trials.^{5,6}

One possible reason is the significant burden of frequent and repeated treatment and monitoring that contributes to poor adherence to recommended dosing strategies.^{5,6} New therapies are emerging to address these limitations by improving the durability of treatment response to decrease treatment burden.^{5,6} Home monitoring strategies offer additional methods to decrease the overall burden of disease monitoring on patients and healthcare systems while improving personalized care.⁷

The purpose of this article is to review the pathophysiology, socioeconomic aspects of disease burden, and evolving therapies to optimize treatment strategies that aim to decrease the debilitating vision loss associated with nAMD and DME.

Understanding nAMD and DME

Neovascular AMD and DME are vascular diseases affecting the retina's central portion, known as the macula.¹ Both conditions result in central vision loss and are part of a group of retinal and choroidal vascular diseases that contribute to blindness worldwide.^{8,9} The etiologies of nAMD and DME differ, but their pathophysiologies involve, among other pathways, VEGF signaling and angiotensin/Tie2 signalling pathways, which are targets of current and emerging therapies.¹⁰

ABSTRACT

Retinal and choroidal vascular diseases are principal causes of blindness for adults in developed countries around the world. Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are 2 significant contributors to this global vision loss and confer substantial social and economic burdens on patients and society. Anti-vascular endothelial growth factor intravitreal injection therapy has dominated as the standard of care treatment for over 15 years, but poor adherence and high treatment burden have led to suboptimal visual outcomes in the real world compared with the clinical trial results. New treatments are emerging that expand the therapeutic targets and use innovative delivery mechanisms with longer durability to ease the treatment burden. Understanding the benefits and drawbacks of these therapies is key to designing new treatment pathways that improve visual outcomes while decreasing the treatment burden on patients and healthcare institutions.

Am J Manag Care. 2022;28:S35-S43

For author information and disclosures, see end of text.

nAMD

As the name suggests, AMD is a disease primarily occurring in older adults, with 10% to 13% of individuals older than 65 years affected in North America, Europe, Australia, and Asia.¹¹ Prevalence of AMD increases with age and is expected to continue to increase as the population ages. Global projections made in 2004 estimated a prevalence of 196 million people affected by 2020, further rising to 288 million in 2040. In the United States alone, the prevalence of AMD is expected to reach 22 million by the year 2050.¹² While nAMD, also known as exudative AMD or wet AMD, only makes up about 10% to 15% of cases of AMD, and non-neovascular AMD, also known as non-exudative AMD or dry AMD, makes up the remainder, nAMD makes up more than 80% of all AMD cases that result in severe VA loss or blindness.^{13,14}

While the exact mechanism responsible for the development of AMD is still under intense investigation, the various proposed mechanisms for the pathogenesis of AMD involve abnormalities in Bruch's membrane, a critical layer between the retina and the choroidal blood supply, along with the formation of drusen.¹ Considered to be a hallmark of AMD, drusen are small deposits in the Bruch's membrane visible on clinical examination of the retina and on retinal imaging with optical coherence tomography (OCT). Their exact origin and composition are still debated, but what is known is that the larger the drusen, the more advanced the dry AMD.^{13,15} As dry AMD progresses, some patients will develop choroidal neovascularization related to increased levels of VEGF.¹ These new vessels grow under the Bruch's membrane or penetrate through and grow under the retina or even into the retina. They are leaky and can bleed and disrupt retinal function through inflammation, exudation, and hemorrhage, hence the name "wet" or exudative AMD. This neovascularization primarily occurs in the macula, leading to central vision loss.¹⁶ Less commonly, neovascularization can occur near the optic nerve or even out in the peripheral retina.

DME

Diabetic retinopathy (DR) is a complication occurring in about one-third of people with diabetes mellitus (DM) and was estimated to affect about 93 million people worldwide in 2008. Of those with DR, approximately 21 million people experience DME, a form of DR that commonly leads to severe visual impairment.¹⁷⁻¹⁹ As the population living with DM increases, the incidence of DME is expected to grow as one of the leading causes of blindness in working-age adults.^{20,21}

The exact pathogenesis of DR is still debated but is thought to result from chronic hyperglycemia and hypoxia influencing vascular permeability and ischemia.^{21,22} Considerable variability exists in the progression of DR among patients, though DME could develop throughout any stage of DR.^{20,21} The hypoxic and inflammatory environment in the retina leads to upregulation of VEGF, resulting in vascular changes, such as the development of

microaneurysms and intraretinal microvascular abnormalities, aberrant angiogenesis, and breakdown of the blood-retinal barrier. Fluids and plasma proteins leak into the neural interstitium, leading to retinal edema and retinal thickening.^{21,23} This retinal edema with fluid in the macula is the defining diagnostic feature of DME and is best detected with OCT.²⁰

Similarities of nAMD and DME

Despite differing etiologies, nAMD and DME are both influenced by VEGF. The understanding of this pathology has grown in recent years, identifying additional factors including the Ang/Tie2 pathway. Ang-2 is a growth factor that enhances vascular response to VEGF, while Tie-2 is a tyrosine kinase receptor responsible for modulating neovascularization under normal physiologic conditions. In nAMD and DME, overexpression of Ang-2 prevents Tie-2 receptors from regulating angiogenesis, resulting in vascular destabilization and inflammation. The full mechanism of this interaction is highly complex, but the discovery of this pathway generated new therapeutic targets for the treatment of both diseases.^{8,10}

Another similarity between nAMD and DME is the substantial burden of the disease on patients and society. Vision loss drastically impacts a person's ability to complete activities of daily living (ADLs) and is associated with increased rates of falls, depression or anxiety, and other comorbidities.² The economic burden of visual impairment, including nAMD and DME, is considerable, with major costs including the need for ocular surgeries and procedures, hospitalization for disease-related complications, doctor's office visits, transportation, assistive devices, and caregiving services.³

Current Treatment Strategies

Numerous optometric and medical organizations have published clinical practice guidelines that uniformly recommend anti-VEGF therapy as a mainstay of treatment for both nAMD and DME, with limited alternative treatments and preventive measures to consider.^{11,13,17,20,24-26} As with the development of DM, the risk of vision loss from DR and DME is considered to be reduced with screening with annual dilated fundus examination or similar (eg, teleophthalmology), timely diagnosis, referrals, and treatment. Even after DME has been diagnosed, patients may benefit from optimization of glycemic control, hypertension, and dyslipidemia.^{20,26} Modifiable risk factors for developing nAMD include nutritional and lifestyle changes such as smoking cessation, reduced UV light exposure, control of hypertension, DM, and cardiovascular disease. Therefore, protection from UV rays, and therapy with antihypertensives and statins are recommended. Patients with intermediate dry AMD should be recommended to start on antioxidant supplements as shown in the Age-related Eye Disease Study.¹³

Nonpharmacologic treatment options are typically limited to the early stages of the disease or in specific instances where

intravitreal therapy is not appropriate. Focal/grid laser photocoagulation may be used to stop leakage from microaneurysms at a safe distance away from the fovea in patients with DME and in those with risk factors for poor adherence precluding frequent follow-up or injection regimen. Panretinal photocoagulation is considered for eyes with proliferative diabetic retinopathy (PDR) with or without DME, although intravitreal anti-VEGF therapy is the treatment of choice if there is concurrent PDR with foveal center-involving DME. Vitrectomy may also be used in select cases of non-clearing vitreous hemorrhage or traction retinal detachment resulting from PDR.^{20,26} For nAMD, laser photocoagulation to choroidal neovascularization, photodynamic therapy (PDT), transpupillary thermotherapy, retinal translocation surgery, submacular surgery, and even radiation therapy had been tried in the past, prior to current intravitreal anti-VEGF therapy becoming the standard of care.^{11,13}

Recommended Pharmacologic Therapies

The 3 VEGF inhibitors frequently used for the treatment of nAMD and DME include aflibercept, bevacizumab, and ranibizumab, though only 2 of them have FDA approval for these indications.^{13,20,25,26} The **Table**²⁷⁻⁴¹ compares these 3 agents along with newer anti-VEGF agents (brolucizumab, faricimab, and ranibizumab port delivery system [PDS]). Pegaptanib was the first anti-VEGF agent approved for nAMD in 2004 but it is no longer available, as it was phased out of usage with better performing anti-VEGF agents becoming available.¹³

Clinical treatment guidelines for both DME and nAMD recommend the use of aflibercept, ranibizumab, or off-label bevacizumab as first-line therapy to improve VA and prevent disease progression.^{13,20} There are limited head-to-head comparison trials with these agents and, as a result, it is difficult to make generalizations. One should not cross-compare clinical trials due to differences in

TABLE. Agents Used for the Treatment of DME and nAMD²⁷⁻⁴¹

	Aflibercept (Eylea)	Bevacizumab (Avastin)	Brolucizumab (Beovu)	Faricimab (Vabysmo)	Ranibizumab (Lucentis)	Ranibizumab PDS (Susvimo)
Pharmacology	VEGF-decoy receptor that binds VEGF-A, VEGF-B, and PLGF	Monoclonal antibody that binds VEGF-A	Antibody fragment that binds VEGF-A	Monoclonal antibody that binds both VEGF and Ang-2	Antibody fragment that binds VEGF-A	Antibody fragment that binds VEGF-A
Intravitreal half-life	4.8 days	5.6 days	4.4 days	7.5 days	3.2 days	25 weeks
Dosing for AMD	2 mg every 4 weeks for 3 months, then every 8 weeks thereafter ^a	1.25 mg every 4 weeks or as needed based on ophthalmologic assessment	6 mg every 4 weeks for 3 months, then every 8-12 weeks thereafter	6 mg every 4 weeks for 4 months, then every 8-16 weeks thereafter ^d	0.5 mg monthly ^c	Refill implant every 24 weeks ^e
Dosing for DME	2 mg every 4 weeks for 5 months, then every 8 weeks thereafter ^b	Same as nAMD	Not applicable	6 mg every 4 weeks for 4-6 months, then every 8 weeks thereafter ^d	0.3 mg monthly	Not applicable
Common ocular adverse effects	Conjunctival hemorrhage, blurred vision, eye pain, cataract, vitreous detachment or floaters, and increased intraocular pressure					
FDA-approved ophthalmic indications	nAMD, DME, DR, macular edema following RVO	None	nAMD	nAMD, DME	nAMD, DME, DR, mCNV, macular edema following RVO	nAMD
FDA-approved biosimilars	Ziv-aflibercept ^f	Bevacizumab-awwb ^f Bevacizumab-bvzr ^f	None	None	Ranibizumab-nuna ^g	Not applicable

DME, diabetic macular edema; DR, diabetic retinopathy; mCNV, myopic choroidal neovascularization; nAMD, neovascular age-related macular degeneration; PLGF, placental growth factor diabetic retinopathy; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

^aSelect patients may require monthly dosing beyond the initial 3 months. Others may be extended longer than every 8 weeks based on treat-and-extend dosing.

^bSelect patients may require monthly dosing beyond the initial 5 months. Others may not need injections once retinal edema resolves.

^cPatients may extend the dosing interval up to every 12 weeks after 3 to 4 monthly doses, if deemed appropriate based on treat-and-extend dosing.

^dSelect patients may require monthly dosing beyond the initial 4-6 months.

^eSupplemental injection with intravitreal ranibizumab may be administered if clinically necessary.

^fFDA approved for nonophthalmic indications.

^gFDA approved for ophthalmic indications.

trial enrollment criteria and designs. However, there do appear to be some differences in efficacy, such as the number of letter improvements, retinal drying effect seen on OCT, effect on VA based on baseline characteristics, or the duration of action between injections. For instance, when patients do not respond to off-label bevacizumab, they are often switched to ranibizumab or aflibercept in hopes of a better retinal drying effect or longer treatment interval. Protocol T from Diabetic Retinopathy Clinical Research Network compared these 3 anti-VEGF agents in eyes with vision loss due to macular center-involving DME and found that when vision loss was mild at baseline, all 3 agents had similar VA improvement, although aflibercept had a better drying effect. When the VA loss was greater at baseline, aflibercept was superior in achieving greater VA improvement compared with the other agents.³²

Off-label bevacizumab has been the most widely used agent due to a substantially lower drug cost per injection. This is due to vials of bevacizumab being aliquoted by compounding pharmacies, resulting in lower cost per syringe compared with on-label agents. Medicare fee-for-service plan data between 2008 and 2015 showed that the use of bevacizumab intravitreal injections instead of ranibizumab or aflibercept for patients undergoing treatment for nAMD resulted in a \$17.3 billion estimated savings.⁴²

Brolucizumab was approved for the treatment of nAMD in 2019, however, postmarketing safety reports of retinal vasculitis and vascular occlusions have limited its widespread use.⁴³ Prescribing information has been updated to highlight this risk in intraocular inflammation.³¹ The proposed advantages of this new agent include the concentrated formula made possible by the small molecule size, extended durability of response, and superior anatomical outcomes and fluid resolution compared with comparator anti-VEGF agent in the clinical trials.⁴⁴ While further safety review trials have demonstrated the rate of VA loss due to intraocular inflammation to be comparable with that of aflibercept, it is not widely used by retina specialists for nAMD.^{43,45} Interestingly, clinical trials for DME with brolucizumab are ongoing and appear to have a better safety profile. It remains to be seen whether those findings hold true in the future.

Intravitreal corticosteroid injections may be considered in the treatment of DME. While their use is more accepted in Europe due to lower drug cost and longer durability in some cases, it is not widespread in the United States due to the risk of increasing intraocular pressures and cataract formation. Agents studied for this indication include triamcinolone acetonide, fluocinolone acetonide, and dexamethasone, the latter 2 being available as an intravitreal implant.^{24,25} Implants are a promising advancement in therapy, as the effect of 1 fluocinolone acetonide implant can last up to 3 years. Steroid implants may reduce DME progression and stabilize symptoms in patients resistant to or contraindicated to receiving anti-VEGF therapies, such as patients who are pregnant

or had a recent stroke.^{25,46,47} Per international guidelines, data do not currently support the use of corticosteroid injections in nAMD, though ongoing research suggests that the combination of a dexamethasone implant with anti-VEGF therapy may restore foveal anatomy and decrease the frequency of injections.^{13,48}

Limitations of Current Treatment Options

Anti-VEGF agents have revolutionized the treatment of ophthalmic conditions, such as nAMD and DME, over the past 15 years by preventing and reversing vision loss.⁴ Unfortunately, the promising results of the clinical trials used to approve VEGF inhibitors are not consistently reproduced in real-world data. The treatment burden associated with frequent injections, physician visits, monitoring, insurance status, co-pays, other comorbidities of the patients, transportation needs, and time off from work are some possible reasons why patients receive significantly fewer injections in practice than in clinical trials. On average, real-world patients with DME or nAMD received about 3 to 5 injections per year of initial treatment, far from the near-monthly to every other month dosing used in clinical trials. These numbers drop further in subsequent years as patients are lost to follow-up. As a result, VA outcomes are inferior to those seen in clinical trials and initial improvements are not maintained over time.^{5,6}

Formulation and administration challenges have also been identified with intravitreal injections. Bevacizumab is manufactured in 25 mg/mL vials appropriate for use in its FDA-approved indications for treatment of various solid tumors, but must be split into single-use syringes by compounding pharmacies or hospital pharmacies for intravitreal administration. Inappropriate and/or unsanitary compounding practices have led to clusters of inflammation and infectious endophthalmitis.¹¹ Ranibizumab and aflibercept are available as prefilled syringes. Prefilled syringes are preferred over vial formulations, as they require less manipulation by clinical staff and help to lower incidence of vision loss related to endophthalmitis after administration.⁴⁹ Unfortunately, prefilled syringes do not eliminate inflammation risk, as clusters of sterile ocular inflammation have been linked to aflibercept.⁵⁰ Syringes also pose a risk of injection of silicone droplets that create floaters large enough to obstruct vision.^{51,52} Drugs with new modes of action and drug-delivery systems are being developed to address some of these limitations.

Novel and Emerging Therapies

Real-world data evaluating current treatment options for nAMD and DME highlight the need to decrease treatment burden and risks associated with frequent intravitreal injections by increasing treatment durability and safety.^{53,54} Emerging therapy options target factors other than VEGF and use alternative delivery systems to overcome these challenges.

Dual Targeted Therapies

Faricimab

Faricimab, approved in January 2022, is the first bispecific monoclonal antibody designed for the treatment of nAMD and DME. The bispecific design binds and neutralizes both VEGF and Ang-2, two important mediators of these diseases.^{10,41,55} This dual-targeted approach promises improved durability, as treatment intervals can be extended up to once every 4 months without loss of efficacy.⁵⁶

The phase 3, randomized, double-masked, active comparator-controlled trials, TENAYA and LUCERNE, compared intravitreal injections of faricimab with aflibercept in 1329 treatment-naïve patients with nAMD. Patients received either faricimab 6 mg given up to every 16 weeks or aflibercept 2 mg every 8 weeks after monthly loading doses. Faricimab frequency began at every 4 weeks and was increased to every 8, 12, or 16 weeks based on disease activity at weeks 20 and 24. The primary end point was mean change in best-corrected VA (BCVA) from baseline. In both trials, faricimab demonstrated noninferiority to aflibercept. In the TENAYA trial, mean gains in BCVA were 5.8 and 5.1 letters in the faricimab and aflibercept groups, respectively. Mean gains in BCVA in the LUCERNE trial were 6.6 in both the faricimab and aflibercept groups. In both studies, a larger proportion of patients in the faricimab group gained 10 or more or 15 or more letters from baseline compared with the aflibercept group and over 95% of patients in the faricimab group avoided losing 15 letters or more from their baseline vision. In the first year of treatment, about 45% of patients receiving faricimab were able to extend treatment to 16 weeks, with another 33% extending to every 12 weeks. Faricimab demonstrated no greater safety signals relative to aflibercept. Intraocular inflammation was low in both the faricimab group (2.0%) and the aflibercept group (1.2%). Serious ocular adverse effects (AEs) were also comparable between the treatment arms for both trials (faricimab, $n = 11$; aflibercept, $n = 13$).⁵⁷

Phase 3, randomized, double-masked, active comparator-controlled trials, YOSEMITE and RHINE, compared faricimab at 2 dosing frequencies with aflibercept in 1891 patients with treatment-naïve DME. Patients received faricimab 6 mg every 8 weeks after an initial 6 monthly doses, faricimab 6 mg up to every 16 weeks based on a personalized treatment interval (PTI) algorithm after 4 initial monthly doses, or aflibercept 2 mg every 8 weeks after 5 initial monthly doses. The primary end point was mean change in BCVA from baseline, and faricimab demonstrated noninferiority to aflibercept in both arms. In the YOSEMITE trial, mean BCVA change for the faricimab every 8 week, faricimab PTI, and aflibercept groups were 10.7, 11.6, and 10.9 letters, respectively. Mean BCVA change in the RHINE trial for the faricimab every 8 week, faricimab PTI, and aflibercept groups were 11.8, 10.8, and 10.3 letters, respectively. Also, about 52% of faricimab recipients were able to extend up to 4 months between treatments and an additional

20% reached a treatment frequency of every 3 months. Absence of DME and intraretinal fluid was more common in patients treated with faricimab compared with aflibercept in both YOSEMITE and RHINE trials. Overall, no greater safety signals were identified compared with aflibercept. Intraocular inflammation was low in both the faricimab-treated patients (1.3%) and the aflibercept-treated patients (0.6%). Most AEs were mild to moderate in severity with the exception of 3 in the YOSEMITE trial. Two cases of severe uveitis were reported in the faricimab PTI group and 1 case of severe vitritis in the faricimab every 8 week group, all resulting in treatment withdrawal.^{58,59}

OPT-302

OPT-302 is an emerging decoy receptor targeting VEGF-C/D isoforms, intended for use in combination with standard anti-VEGF-A therapies.⁶⁰ Concurrent phase 3, double-masked, sham-controlled trials, SHORE and COAST, are currently underway in patients with nAMD. They will evaluate the efficacy and safety of OPT-302 intravitreal injections in combination with standard anti-VEGF therapies versus anti-VEGF alone. The SHORE trial uses ranibizumab as a comparator, whereas the COAST trial uses aflibercept. If approved, OPT-302 will represent an expansion of treatment to include VEGF subtypes beyond the VEGF-A isoforms targeted by current therapies.⁶¹ OPT-302 is also being evaluated in patients with DME, having completed a phase 1/2 dose-escalation/expansion trial of OPT-302 in combination with aflibercept, compared with aflibercept alone.⁶² Plans for phase 3 clinical trials in DME have not been announced.

Innovative Delivery Mechanisms

Ranibizumab PDS is an innovative drug delivery mechanism for anti-VEGF therapy designed to decrease the frequency of intravitreal injections, addressing treatment burden. The refillable implant is inserted surgically into the eye in the operating room and then is refilled in the office every 6 months. It has been shown to provide a continuous release of ranibizumab, thus having the potential to drastically reduce the treatment visit burden. The PDS delivers a serum concentration of ranibizumab within the same maximum and minimum range experienced with monthly injections. The concentration within the implant decreases with a half-life of about 25 weeks.⁴⁰

Ranibizumab PDS, approved by the FDA in October 2021, is indicated for the treatment of patients with nAMD who previously responded to at least 2 intravitreal injections of a VEGF inhibitor. The approval was based on the results of the ARCHWAY trial.⁴⁰ This phase 3, open-label, randomized trial compared ranibizumab PDS refilled at 24-week intervals with monthly intravitreal ranibizumab injections. The primary end point was change in BCVA and it demonstrated noninferiority and equivalence of the PDS to monthly injections. Mean change in BCVA was 0.2 letters and 0.5

letters in the ranibizumab PDS every 24 weeks and ranibizumab monthly treatment arms, respectively.⁶³

Common AEs with the PDS included conjunctival hemorrhage or hyperemia, iritis, and eye pain. In the PDS cohort, most AEs occurred within 1 month of implantation. Additionally, 16 patients receiving the PDS experienced conjunctival bleb or conjunctival filtering bleb leak. Events were considered not serious, but 1 case did require surgical resection. The incidence of vitreous hemorrhage was significantly reduced with changes in the operation protocol.^{40,63} There were 4 cases of endophthalmitis in the PDS group, compared with none in the monthly ranibizumab injection group. This aspect, along with long-term effects, such as conjunctival erosion or device explantation, will need to be further studied in the future.

Research on this delivery system in patients with DR and DME is ongoing. Extension of the PDS refill-exchange interval to 36 weeks is being investigated in the phase 3 VELODROME trial, though results are not expected until late 2023.⁶⁴ Additionally, the phase 3 PORTAL extension trial is designed to evaluate long-term safety and tolerability of ranibizumab PDS in patients who completed a previous trial with the implant.⁶⁵

Other Therapies in the Pipeline

Biosimilars

Biosimilars are an area of interest, with FDA-approved biosimilars currently available for aflibercept, ranibizumab, and bevacizumab. Of these products, only the ranibizumab biosimilar is FDA approved currently for use as an intravitreal injection for the treatment of nAMD. The biosimilars for bevacizumab and aflibercept are currently only approved for oncologic indications.^{28,29,34,39} Bevacizumab-vikg is the first ophthalmic formulation of bevacizumab and may soon gain FDA approval for an ophthalmic indication. Recently completed phase 3 NORSE TWO trial for nAMD compared bevacizumab-vikg monthly injections with ranibizumab injections dosed per package labeling. The trial met its primary end point with 41% of patients receiving bevacizumab-vikg demonstrating a minimum of 15-letter increase in BCVA compared with 23% with ranibizumab ($P = .0052$).⁶⁶

Additional biosimilars are in development for each of the 3 major anti-VEGF therapies used in the treatment of nAMD and DME, though biosimilars are not yet widely embraced due to the already low cost of off-label bevacizumab. Compared with the reference product, the expectation of reduced cost with a biosimilar may still drive future treatment selection as more biosimilars come to market.³⁶

Anti-VEGF Therapy

KSI-301 is an investigational anti-VEGF therapy that is unique in structure. It is composed of a humanized immunoglobulin G1 antibody linked to a biopolymer designed to increase intraocular durability. KSI-301 has a strong affinity for VEGF-A and has demonstrated a half-life of 10.5 days in the retina and 12.5 days in the

choroid in animal models or around twice the length of the half-lives of other anti-VEGF targeted therapies. Early phase clinical trials are ongoing.⁶⁷

Gene Therapy

Gene therapy is another promising treatment modality being explored for nAMD and DME. Multiple early-phase trials are ongoing to evaluate the effectiveness of these therapies in which a genetic vector that encodes a monoclonal antibody fragment is injected into the eye, either in the operating room or in the office. These agents would theoretically be a one-time injection for diseases with a historically high treatment burden.⁶⁸ Preliminary information has been presented on the phase 2 ALTITUDE and AAVIATE trials evaluating RGX-314, which encodes a soluble anti-VEGF protein related to ranibizumab. The 2 trials compare a single treatment of RGX-314 with monthly ranibizumab injections in patients with DME and nAMD, respectively. Both trials are still enrolling, but early reports indicate that RGX-314 has generally been well-tolerated.⁶⁸⁻⁷⁰

Another gene therapy, ADVM-022, has had more mixed results. This therapy encodes the monoclonal antibody aflibercept and is intended for use as a single, intravitreal injection in the office. The OPTIC trial is evaluating various doses of ADVM-022 for the treatment of nAMD. Preliminary findings indicate a favorable safety profile with mostly mild, treatable inflammation and over 80% of patients not requiring supplemental anti-VEGF injections at follow-up of up to 92 weeks.⁷¹ The INFINITY trial, evaluating ADVM-022 in patients with DME, was halted after 3 patients developed severe, progressive vision loss from hypotony. While intraocular inflammation was common, it is unclear why these results vary dramatically in DME from those found in patients with nAMD. Underlying mechanisms related to DM may be involved.⁷² Gene therapy is an evolving treatment paradigm that carries the exciting prospect of a one-time treatment for nAMD and DME, though more studies are needed.

Monitoring Innovations

Emerging treatment strategies may reduce injection frequency, but a significant burden is still associated with monitoring these diseases. Frequent office visits are associated with extra cost, travel, and caregiver needs.³ Reexamination and treatment intervals vary by disease stage and patient, but trend toward monthly injections during the loading phase.^{13,20} The ongoing COVID-19 pandemic highlighted the need for telemonitoring options to decrease patient-provider physical contact time and travel.⁷³

Telemonitoring has been studied in patients with AMD and DR, offering an alternative to in-person screening examinations and potentially increasing patient participation.⁷ In 2010, the FDA approved the use of a home monitoring system for early detection of progression from intermediate AMD to nAMD. The ForseeHOME

monitoring system uses preferential hyperacuity perimetry testing that detects changing distortions in patients' relative spatial perception. Real-world analysis of this system demonstrated increased early detection rates, allowing treatment to be initiated before significant VA decline.⁷⁴ It is also cost-effective in patients at high risk of developing nAMD compared with scheduled examination alone, with an incremental cost-effectiveness ratio of \$35,663 per quality-adjusted life-year gained.⁷⁵

Smartphones are now a valuable tool in the home monitoring arsenal, as an application has been developed for patients to download and conduct self-testing under the supervision of their ophthalmologist. The Home Vision Monitor application has been cleared by the FDA and uses shape discrimination hyperacuity to measure changes in visual function. A trial evaluated 417 patients who received the offer to use this application in a single vision center in the United Kingdom. The investigators found that compliance was associated with a diagnosis of nAMD, White British ethnicity, and baseline VA. The uptake of the system decreased as age increased and compliance was higher in patients who expressed higher comfort with the use of modern technologies. The age-related nature of this disease presents an obvious barrier to the use of these systems, but the application did offer increased reassurance for patients who were able to use it properly.⁷⁶

OCT is a noninvasive procedure that can help detect signs of active exudation or disease progression.¹³ Ongoing research in patients with nAMD suggests that OCT combined with an automated, artificial intelligence (AI) screening algorithm could be an efficient method of home monitoring that can automatically analyze patient-generated scans for quantification of retinal fluid. This method also allows for remote review by the clinician. In a small observational study of 15 patients, automated analysis agreed with clinician grading in 94% of cases.⁷⁷ Similar research in patients with DR demonstrates the efficiency of AI image analysis, though obtaining usable images is age dependent, with 81% success in patients aged 18 to 40 years dropping to only 9.4% in patients aged 81 to 90 years.⁷⁸

Monitoring is essential not only for screening and initiation of treatment but for identifying recurrences of fluid for optimal treatment interval and for detecting resistant or progressive disease after first-line therapy. Options are limited in patients who do not respond to anti-VEGF therapy, especially in nAMD, though compliance should always be evaluated when assessing treatment failure. In eyes with refractory DME, identified by persistent retinal fluid on OCT despite various anti-VEGF therapy, clinicians can consider laser photocoagulation, intravitreal corticosteroids, or even pars plana vitrectomy, if there is significant epiretinal membrane.^{20,25} Choices are equally limited in nAMD after failure on anti-VEGF therapy, with laser treatment or PDT as the only alternatives rarely used in current practice.^{11,13} This again highlights the need to develop

new, durable treatments and optimize current treatment options to prevent treatment failure.

Conclusions

Neovascular AMD and DME are 2 of the leading causes of blindness in the developed world. Vision loss severely compromises ADLs and leads to numerous comorbidities that drive the socioeconomic burden of these diseases far beyond the basic cost of treatment. Anti-VEGF therapies with intravitreal injections have been the mainstay of therapy over the past 15 years, but real-world data show poor adherence leading to suboptimal results compared with clinical trials. Emerging therapies aim to improve adherence and clinical outcomes by increasing the durability of response and decreasing the frequency of intraocular injections. These treatments include agents directed at new therapeutic targets, innovative drug delivery systems, single-dose gene therapy, and cost-saving biosimilars. Clinicians and managed care professionals need to understand the benefits and limitations of current and emerging therapies to design treatment strategies that decrease overall disease burden and focus on sight preservation. □

Author affiliation: Judy E. Kim, MD, is professor of Ophthalmology and Visual Sciences, professor of Graduate School of Biomedical Sciences, and the director of Teleophthalmology and Research at Medical College of Wisconsin, Milwaukee, WI.

Funding source: This activity is supported by an educational grant from Genentech, a member of the Roche Group.

Author disclosure: Dr Kim has the following relevant financial relationships with commercial interests to disclose: Consultant: Adverum, Allergan, Alimera Science, Genentech, Novartis, Regeneron

Authorship information: Concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

Address correspondence to: jekim@mcw.edu

Medical writing and editorial support provided by: Brittany Hoffmann-Eubanks, PharmD, MBA

REFERENCES

1. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res.* 2015;49:67-81. doi:10.1016/j.preteyeres.2015.06.002
2. Crews JE, Campbell VA. Vision impairment and hearing loss among community-dwelling older Americans: implications for health and functioning. *Am J Public Health.* 2004;94(5):823-829. doi:10.2105/ajph.94.5.823
3. Köberlein J, Beifus K, Schaffert C, Finger RP. The economic burden of visual impairment and blindness: a systematic review. *BMJ Open.* 2013;3(11):e003471. doi:10.1136/bmjopen-2013-003471
4. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov.* 2016;15(6):385-403. doi:10.1038/nrd.2015.17
5. Holekamp NM, Campbell J, Almony A, et al. Vision outcomes following anti-vascular endothelial growth factor treatment of diabetic macular edema in clinical practice. *Am J Ophthalmol.* 2018;191:83-91. doi:10.1016/j.ajo.2018.04.010
6. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol.* 2015;99(2):220-226. doi:10.1136/bjophthalmol-2014-305327
7. Kawaguchi A, Sharafeldin N, Sundaram A, et al. Tele-ophthalmology for age-related macular degeneration and diabetic retinopathy screening: a systematic review and meta-analysis. *Telemed J E Health.* 2018;24(4):301-308. doi:10.1089/tmj.2017.0100
8. Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond).* 2021;35(5):1305-1316. doi:10.1038/s41433-020-01377-x
9. Saadine JB, Honeycutt AA, Narayan KM, Zhang X, Klein R, Boyle JP. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005-2050. *Arch Ophthalmol.* 2008;126(12):1740-1747. doi:10.1001/archophth.126.12.1740

10. Heier JS, Singh RP, Wyckoff CC, et al. The angiopoietin/Tie pathway in retinal vascular diseases: a review. *Retina*. 2021a;41(1):1-19. doi:10.1097/iae.0000000000003003
11. Schmidt-Erfurth U, Chong V, Loewenstein A, et al; European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014;98(9):1144-1167. doi:10.1136/bjophthalmol-2014-305702
12. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(12):e106-e116. doi:10.1016/s2214-109x(13)70145-1
13. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-Related Macular Degeneration Preferred Practice Pattern®. *Ophthalmology*. 2020;127(1):P1-P65. doi:10.1016/j.ophtha.2019.09.024
14. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med*. 2008;358(24):2606-2617. doi:10.1056/NEJMr0801537
15. De Jong PTVM. Elusive drusen and changing terminology of AMD. *Eye (Lond)*. 2018;32(5):904-914. doi:10.1038/eye.2017.298
16. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. *Neuron*. 2012;75(1):26-39. doi:10.1016/j.neuron.2012.06.018
17. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(3):412-418. doi:10.2337/dc16-2641
18. Wong TY, Klein R, Islam FMA, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141(3):446-455.e441. doi:10.1016/j.ajo.2005.08.063
19. Yau JWY, Rogers SL, Kawasaki R, et al; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556-564. doi:10.2337/dc11-1909
20. ICO. ICO guidelines for diabetic eye care. International Council of Ophthalmology. Accessed November 21, 2021. <https://icoph.org/eye-care-delivery/diabetic-eye-care/>
21. Liu E, Craig JE, Burdon K. Diabetic macular oedema: clinical risk factors and emerging genetic influences. *Clin Exp Optom*. 2017;100(6):569-576. doi:10.1111/cxo.12552
22. Cohen SR, Gardner TW. Diabetic retinopathy and diabetic macular edema. *Dev Ophthalmol*. 2016;55:137-146. doi:10.1159/000439790
23. Mathew C, Yunirakasiwi A, Sanjay S. Updates in the management of diabetic macular edema. *J Diabetes Res*. 2015;2015:794036. doi:10.1155/2015/794036
24. Bakri SJ, Wolfe JD, Regillo CD, Flynn HW Jr, Wyckoff CC. Evidence-based guidelines for management of diabetic macular edema. *J Vitreoretin Dis*. 2019;1-8. doi:10.1177/2474126419834711
25. Figueira J, Henriques J, Carneiro A, et al. Guidelines for the management of center-involving diabetic macular edema: treatment options and patient monitorization. *Clin Ophthalmol*. 2021;15:3221-3230. doi:10.2147/ophth.s318026
26. Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. *Ophthalmology*. 2018;125(10):1608-1622. doi:10.1016/j.ophtha.2018.04.007
27. Eylea. Prescribing information. Regeneron; 2021. Accessed February 8, 2022. www.hcp.eylea.us/download/eylea_fpi.pdf
28. Mvasi. Prescribing information. Amgen; 2021. Accessed February 8, 2022. www.pi.amgen.com/-/media/amgen/repositories/pi-amgen.com/mvasi/mvasi_pi_hcp_english.pdf
29. Zerabev. Prescribing information. Pfizer; 2021. Accessed February 8, 2022. <https://labeling.pfizer.com/ShowLabeling.aspx?id=11860>
30. Avastin. Prescribing information. Genentech; 2021. Accessed February 8, 2022. www.gene.com/download/pdf/avastin_prescribing.pdf
31. Beovu. Prescribing information. Novartis Pharmaceuticals Corp; 2020. Accessed February 8, 2022. www.novartis.us/sites/www.novartis.us/files/beovu.pdf
32. Glassman AR, Wells JA 3rd, Josic K, et al. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (Protocol T extension study). *Ophthalmology*. 2020;127(9):1201-1210. doi:10.1016/j.ophtha.2020.03.021
33. Martin DF, Maguire MG, Fine SL, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398. doi:10.1016/j.ophtha.2012.03.053
34. Byooviz. Prescribing information. Biogen Inc; 2021. Accessed February 8, 2022. www.accessdata.fda.gov/drugsatfda_docs/label/2021/761202s000lbl.pdf
35. Lucentis. Prescribing information. Genentech; 2018. Accessed February 8, 2022. www.gene.com/download/pdf/lucentis_prescribing.pdf
36. Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: "Is there a big change on the horizon?" *Clin Ophthalmol*. 2018;12:2137-2143. doi:10.2147/ophth.s180393
37. Ventrice P, Leporini C, Aloe JF, et al. Anti-vascular endothelial growth factor drugs safety and efficacy in ophthalmic diseases. *J Pharmacol Pharmacother*. 2013;4(suppl 1):S38-S42. doi:10.4103/0976-500x.120947
38. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359. doi:10.1016/j.ophtha.2016.02.022
39. Zaltrap. Prescribing information. sanofi-aventis; 2020. Accessed February 8, 2022. <https://products.sanofi.us/zaltrap/zaltrap.html>
40. Susvimo. Prescribing information. Genentech; 2021. Accessed February 8, 2022. www.gene.com/download/pdf/susvimo_prescribing.pdf
41. Vabysmo. Prescribing information. Genentech; 2022. Accessed February 8, 2022. www.gene.com/download/pdf/vabysmo_prescribing.pdf
42. Rosenfeld PJ, Windsor MA, Feuer WJ, et al. Estimating Medicare and patient savings from the use of bevacizumab for the treatment of exudative age-related macular degeneration. *Am J Ophthalmol*. 2018;191:135-139. doi:10.1016/j.ajo.2018.04.008
43. Khanani AM, Zarbin MA, Barakat MR, et al. Safety outcomes of brolicuzumab in neovascular age-related macular degeneration: results from the IRIS Registry and Komodo Healthcare Map. *JAMA Ophthalmol*. 2022;140(1):20-28. doi:10.1001/jamaophthalmol.2021.4585
44. Tadayoni R, Sararols L, Weissgerber G, Verma R, Clemens A, Holz FG. Brolicuzumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. *Ophthalmologica*. 2021;244(2):93-101. doi:10.1159/000513048
45. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolicuzumab: post hoc review of HAWK and HARRIER. *Ophthalmology*. 2021;128(7):1050-1059. doi:10.1016/j.ophtha.2020.11.011
46. Nurözler Tabakcı B, Ünlü N. Corticosteroid treatment in diabetic macular edema. *Turk J Ophthalmol*. 2017;47(3):156-160. doi:10.4274/tjo.56338
47. Urias EA, Urias GA, Monickaraj F, McGuire P, Das A. Novel therapeutic targets in diabetic macular edema: beyond VEGF. *Vision Res*. 2017;139:221-227. doi:10.1016/j.visres.2017.06.015
48. Rosenfeld S. Dexamethasone implant and anti-VEGF therapy effective for nAMD. HCPLive. July 29, 2020. Accessed February 8, 2022. www.hcplive.com/view/dexamethasone-implant-anti-vegf-effective-namd
49. Storey PP, Tauqueer Z, Yonekawa Y, et al; Post-Injection Endophthalmitis (PIE) Study Group. The impact of prefilled syringes on endophthalmitis following intravitreal injection of ranibizumab. *Am J Ophthalmol*. 2019;199:200-208. doi:10.1016/j.ajo.2018.11.023
50. Greenberg JP, Belin P, Butler J, et al; Aflibercept Sterile Inflammation Research Group. Aflibercept-related sterile intraocular inflammation outcomes. *Ophthalmol Retina*. 2019;3(9):753-759. doi:10.1016/j.oret.2019.04.006
51. Khurana RN, Chang LK, Porco TC. Incidence of presumed silicone oil droplets in the vitreous cavity after intravitreal bevacizumab injection with insulin syringes. *JAMA Ophthalmol*. 2017;135(7):800-803. doi:10.1001/jamaophthalmol.2017.1815
52. Melo GB, Dias Junior CDS, Morais FB, et al. Prevalence of silicone oil droplets in eyes treated with intravitreal injection. *Int J Retina Vitreous*. 2019;5:34. doi:10.1186/s40942-019-0184-9
53. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. *Br J Ophthalmol*. 2021;105(2):216-221. doi:10.1136/bjophthalmol-2020-315933
54. Khanani AM, Skelly A, Bezlyak V, Griner R, Torres LR, Sakkriotis A. SIERRA-AMD: a retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2020;4(2):122-133. doi:10.1016/j.oret.2019.09.009
55. Khan M, Aziz AA, Shafi NA, Abbas T, Khanani AM. Targeting angiopoietin in retinal vascular diseases: a literature review and summary of clinical trials involving faricimab. *Cells*. 2020;9(8):1869. doi:10.3390/cells9081869
56. FDA accepts application for Roche's faricimab for the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). Roche. July 29, 2021. Accessed February 8, 2022. www.roche.com/investors/updates/inv-update-2021-07-29b.htm
57. Heier JS, Khanani AM, Ruiz CO, et al; TENAYA and LUCERNE investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked phase 3, non-inferiority trials. *Lancet*. Published online January 24, 2022. [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(22\)00010-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00010-1/fulltext)
58. Wyckoff CC, Abreu F, Adams AP, et al; YOSEMITE and RHINE investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular edema (YOSEMITE and RHINE): the two randomised, double-masked, phase 3 trials. *Lancet*. Published online January 24, 2022. [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(22\)00018-6/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00018-6/fulltext)
59. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical trials of faricimab for diabetic macular edema: study design and rationale. *Ophthalmol Sci*. Published online December 29, 2021. [www.ophtalmologyscience.org/article/S2666-9145\(21\)00109-3/fulltext](http://www.ophtalmologyscience.org/article/S2666-9145(21)00109-3/fulltext)
60. Opthea. Wet AMD and DME therapies. Accessed February 8, 2022. <https://opthea.com/focus/#opt302>
61. Opthea. DME clinical trials. Accessed February 8, 2022. <https://opthea.com/dme-clinical-trial/>
62. Opthea. Phase 3 wet AMD trial. Accessed February 8, 2022. <https://opthea.com/wet-amd-trials-phase-3/>
63. Holecamp NM, Campochiaro PA, Chang MA, et al; Archway investigators. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration [published online September 29, 2021]. *Ophthalmology*. 2021;S0161-6420(21)00734-X. doi:10.1016/j.ophtha.2021.09.016
64. A study of the efficacy, safety, and pharmacokinetics of a 36-week refill regimen for the port delivery system with ranibizumab in patients with neovascular age-related macular degeneration (velodrome). ClinicalTrials.gov. Updated January 19, 2022. Accessed February 9, 2022. <https://clinicaltrials.gov/ct2/show/NCT04657289>
65. Extension study for the port delivery system with ranibizumab (portal). ClinicalTrials.gov. Updated December 15, 2021. Accessed February 9, 2022. <https://clinicaltrials.gov/ct2/show/NCT03683251>
66. Hutton D. Outlook Therapeutics a step closer to FDA approval of bevacizumab-vikg for treatment of wet AMD. *Ophthalmology Times*. August 3, 2021. Accessed February 9, 2022. www.ophtalmologytimes.com/view/outlook-therapeutics-a-step-closer-to-fda-approval-of-bevacizumab-vikg-for-treatment-of-wet-amd
67. Chandrasekaran PR, Madanagopalan VG. KSI-301: antibody biopolymer conjugate in retinal disorders. *Ther Adv Ophthalmol*. Published July 12, 2021;13:25158414211027708. doi:10.1177/25158414211027708
68. de Guimaraes TAC, Georgiou M, Bainbridge JWB, Michaelides M. Gene therapy for neovascular age-related macular degeneration: rationale, clinical trials and future directions. *Br J Ophthalmol*. 2021;105(2):151-157. doi:10.1136/bjophthalmol-2020-316195
69. Barakat MR. Suprachoroidal delivery of RGX-314 for neovascular AMD: initial results from the phase II AAVIATE study. Abstract presented at American Society of Retina Specialists (ASRS) annual meeting on October 11, 2021; San Antonio, TX.
70. Marcus DM. Suprachoroidal delivery of RGX-314 for diabetic retinopathy without CI-DME: early results from the phase II ALTITUDE study. Abstract presented at American Society of Retina Specialists (ASRS) annual meeting on October 9, 2021; San Antonio, TX. Accessed February 9, 2022. www.regenxbio.com/wp-content/uploads/2022/01/RGX-314-ALTITUDE-ASRS-DennisMarcus_Oct-9-2021.pdf
71. Piaromici DJ, Boyer DS, Khanani AM, et al. Intravitreal gene therapy for neovascular AMD with ADVM-022: results of the phase 1 optic trial. Abstract presented at American Society of Retina Specialists (ASRS) annual meeting on October 11, 2021; San Antonio, TX.

72. Bankhead C. Adverse events halt gene therapy trial for diabetic macular edema. MedPage Today. October 12, 2021. Accessed February 9, 2022. www.medpagetoday.com/meetingcoverage/asrs/94976
73. Corradetti G, Corvi F, Nguyen TV, Sadda SR. Management of neovascular age-related macular degeneration during the COVID-19 pandemic. *Ophthalmol Retina*. 2020;4(8):757-759. doi:10.1016/j.oret.2020.05.015
74. Ho AC, Heier JS, Holekamp NM, et al. Real-world performance of a self-operated home monitoring system for early detection of neovascular age-related macular degeneration. *J Clin Med*. 2021;10(7):1355. doi:10.3390/jcm10071355
75. Wittenborn JS, Clemons T, Regillo C, Rayess N, Liffmann Kruger D, Rein D. Economic evaluation of a home-based age-related macular degeneration monitoring system. *JAMA Ophthalmol*. 2017;135(5):452-459. doi:10.1001/jamaophthalmol.2017.0255
76. Korot E, Pontikos N, Drawnel FM, et al. Enablers and barriers to deployment of smartphone-based home vision monitoring in clinical practice settings. *JAMA Ophthalmol*. Published online December 16, 2021. doi:10.1001/jamaophthalmol.2021.5269
77. Heier JS, Holekamp NM. Prospective longitudinal study: fluid quantification from daily self-imaging with home OCT in neovascular age-related macular degeneration (nv-AMD). Abstract presented at American Society of Retina Specialists (ASRS) annual meeting on October 11, 2021; San Antonio, TX.
78. Barkmeier AJ, Mehra AA. Diabetic retinopathy telemedicine outcomes with artificial intelligence-based image analysis, reflex dilation, and image overread protocol. Abstract presented at American Society of Retina Specialists (ASRS) annual meeting on October 9, 2021; San Antonio, TX.