EURETINA
European Society of Retina Specialists

EURETINA EDUCATION PLATFORM

2019

CLINICAL SURVEY

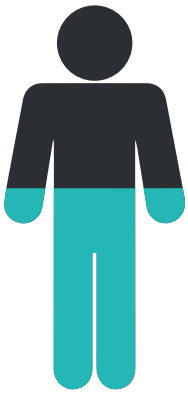
OUTCOMES

Survey Background & Overview

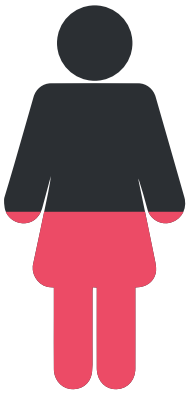
This supplement reports on the results of the 2019 EURETINA Clinical Trends Survey, which was conducted in the fall of 2019 during the 19th EURETINA Annual Congress in Paris, France and online at the EURETINA website. The survey questions explored physician perception, understanding and current practice patterns across several areas of ophthalmology care, ranging from retinal diagnostics, age-related macular degeneration (AMD), diabetic macular edema (DME), retinal detachment and the evolving field of gene therapy.

More than 1,000 doctors responded to 128 questions, which were developed and reviewed with the EURETINA leadership and substantiated by a data scientist. The results of the 2019 EURETINA Clinical Trends Survey aid the EURETINA leadership in identifying the educational needs of its members, and will underpin future exercises to deliver relevant and topical learning assets. The collected data will also enhance learning opportunities featured at the 2020 EURETINA Annual Congress, the 2021 EURETINA Winter Meeting and other educational channels such as journal articles and online forums.

We invite you to study the key findings and be ready to take advantage of EURETINA's educational events. EURETINA encourages all delegates to participate in the upcoming 2020 EURETINA Clinical Trends Survey, taking place online, during the 20th EURETINA Congress and throughout October at ***https://euretina2020survey.questionpro.com.***



53% Male



47% Female

128 Questions on key clinical opinions & practice patterns

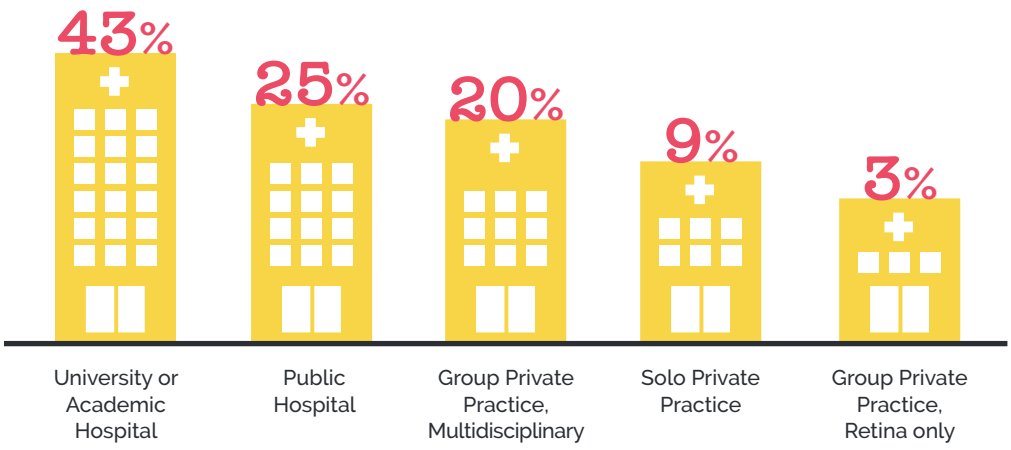
1,043 EURETINA delegates responded to the survey

Q. How many years are you in practice?

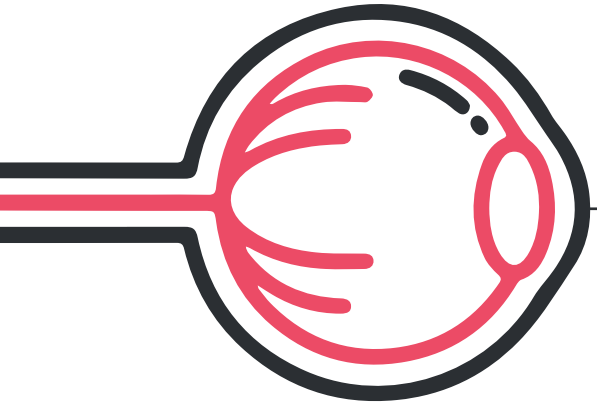
13% currently in medical school or training

42% 10 years+

Q. What is your primary practice setting?



Q. What is your field of expertise?

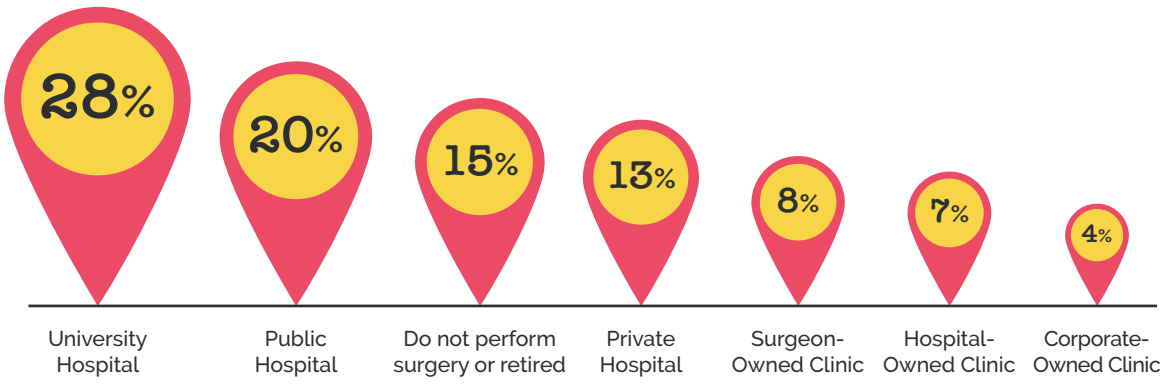


52% Medical & surgical retina specialists

37% Medical retina specialists only

11% Surgical retina specialist or other

Q. What is your primary surgery location?



Diagnostic Approaches for Retinal Disease

Prof. Dr. Dr. Sebastian Wolf

Professor of Ophthalmology, Director and Chair of the Department of Ophthalmology, Inselspital, University of Bern, Switzerland

Imaging techniques are essential to accurate diagnosis in ophthalmology. The 2019 EURETINA Clinical Trends Survey shows that physicians are routinely using optical coherence tomography (OCT), fluorescein angiography (FA), fundus photography and OCT angiography (OCT-A) in the diagnosis of diabetic macular edema (DME) and wet age-related macular degeneration (wAMD). Most respondents are using multimodal imaging in diagnosis, and around half consider OCT-A to be a valuable tool and intend to incorporate it in their practice.

Professor Sebastian Wolf shares his thoughts on imaging technology and describes his experience in selecting optimized tools for accurate diagnosis of retinal diseases.

What is the current status and value of OCT angiography in retinal disease diagnosis?

The use of OCT-A allows physicians to clearly visualize the macular vascular pattern. However, effective use of the technique requires full understanding of vessel segmentation, which may be complicated in pathologic cases. Quantitative use of OCT-A therefore remains relatively challenging, and diagnosis using OCT-A alone would not be optimal for accuracy. At present, the key advantage of OCT-A is in acting as confirmation of OCT findings and providing additional vascular detail.

How can we apply the information visualized from OCT-A into diagnostic assessments?

In diagnosing neovascular disease, the initial step in most cases should be OCT to confirm the presence of fluid. After this, FA or OCT-A can offer vital additional information, such as vascular density or any degree of ischemia. The combination of techniques is important here because visualization of a vascular network without the presence of fluid would not necessarily lead to intervention; in wAMD, treatment is still driven primarily by OCT fluid findings.

The greatest advantage of OCT-A may be in the diagnosis and management of diabetic retinopathy, where microvascular changes and vessel density are predictive of disease severity and potential response to treatment.

In which cases is multimodal imaging more beneficial than relying on a single diagnostic?

If a physician manages a population with a relatively high prevalence of polypoidal choroidal vasculopathy, indocyanine green angiography remains a useful tool in diagnosis and treatment selection because it provides better visualization of the polyp (low blood flow in the polyp limits the effectiveness of FA or OCT-A).

In patients with AMD that have both neovascular and geographic atrophy components, OCT can be supplemented with OCT-A and FA to help with diagnosing and monitoring atrophy. For diabetic patients, colour fundus photographs are important because they enable investigation of DME and retinopathy components.

What is the role of artificial intelligence (AI) in diagnostic assessments using OCT?

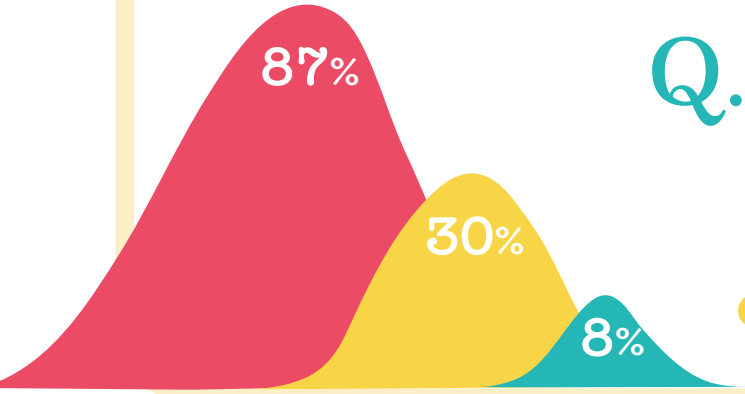
This is a fast-evolving area of technology that has the potential to be very important in all areas of diagnosis. The majority (73%) of respondents to the 2019 EURETINA Clinical Trends Survey believe that AI will have a significant role in the management of retinal diseases in the next 2–3 years.

Today, we are at the stage where AI can assess an OCT and determine whether the patient needs to see an ophthalmologist and how urgent the need is. This represents an important step in optimizing screening.

Because AI using OCT is nearly as good as a physician at detecting the presence or absence of fluid in the retina, the next steps for use of this technology may be in speeding up initiation of treatment. In all cases, diagnosis and treatment decisions should remain with the physician; however, AI has the potential to support and streamline decision making and to perhaps monitor treatment efficacy and response in the future.

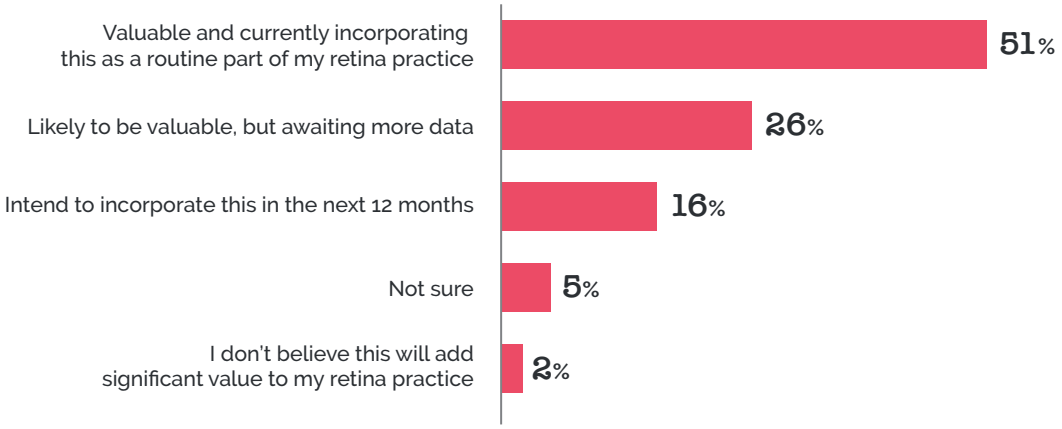
Which OCT do you use?

(Select all that apply)



- Spectral Domain
- Swept Source
- Time Domain

What is your belief in the current value of OCT Angiography?



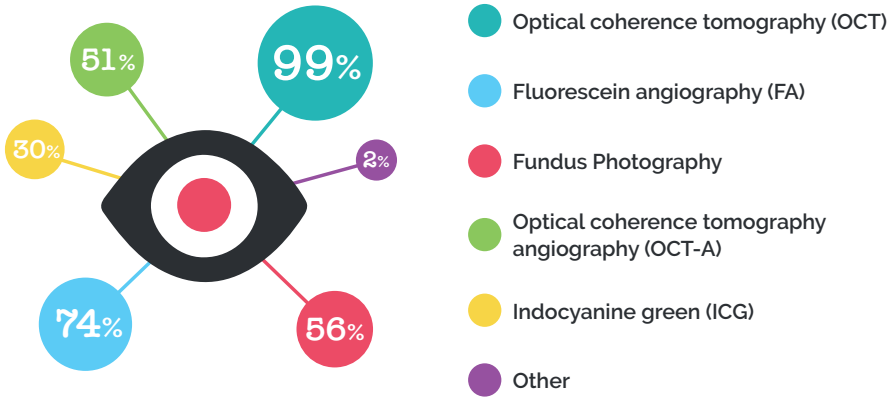
52%

of respondents do not have access to wide-field fluorescein angiography (FA)

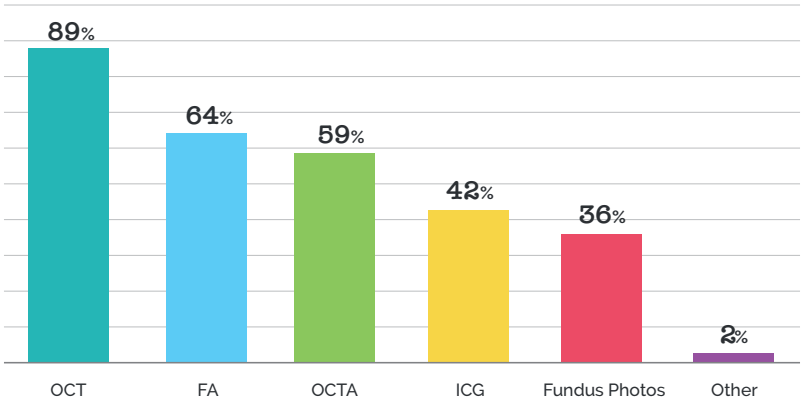
73%

of respondents believe that artificial intelligence will significantly assist their ability to diagnose and monitor retina diseases in the next 2-3 years

Q. What are all the imaging techniques that you use at time of diagnosis for wet AMD patients? *(Select all that apply)*



Q. What are all the imaging techniques that you use for wet AMD at time of follow up, for a patient who is NOT responding well to treatment? *(Select all that apply)*



Q. If you are NOT using multimodal imaging on AMD patients, why not? *(Select all that apply)*

63%	18%	16%	5%	2%
I am using multimodal imaging	No access to this technology in my practice	Not economically viable for me	Too disruptive to integrate into my practice	Other

Age-related Macular Degeneration and Treatment Approaches

Univ.- Prof. Dr. Frank G. Holz, FEBO, FARVO

Chairman and Professor, Department of Ophthalmology, University of Bonn, Germany

The management of age-related macular degeneration (AMD) represents a meaningful proportion of ophthalmologists' responsibilities. The 2019 EURETINA Clinical Trends Survey shows that, on average, respondents see 25 people per week with wet AMD (wAMD), 20 with dry atrophic AMD, and perform 27 anti-VEGF injections per week. Most physicians employ a treat-and-extend approach, with some combining this with 'as-needed' injections.

Professor Holz shares his expert experience on managing patients with AMD and insight into treatment objectives.

Why should treatment always be the goal in patients with wAMD?

There is always variability in treatment response, and it can be difficult to maintain improvements in visual acuity over longer time frames as further degradation including atrophy and fibrosis may occur. However, treatment will nearly always provide major benefits over the untreated natural course of the disease and should be the goal of AMD management once a diagnosis of macular neovascularization is confirmed.

What is your first-line treatment approach and strategy for patients with wAMD?

First-line treatment is typically the use of an anti-VEGF agent. The selection of a specific anti-VEGF product may be driven by various factors including reimbursement considerations or local guidelines; however, the initial approach revolves around this class of therapy. In my routine practice, three loading doses of anti-VEGF are given, one every four weeks, followed by a treat-and-extend approach.

How many lines of best-corrected visual acuity (BCVA) improvements should be targeted with first-line treatment?

The extent of BCVA improvement depends largely on the baseline values and the degree of already existing irreversible damage. The early randomized clinical trials included patients with a degree of vision loss, for example with 20/40 vision at baseline, and from this point large improvements should be possible.

In modern routine practice, if there is evidence of neovascularization with edema, we should aim to initiate anti-VEGF treatment early, even at 20/20 vision. With initiation of treatment in a patient with relatively good vision, there is less scope to see improvement in terms of BCVA, but the morphological improvements will be of great importance in order to maintain vision at a high level.

What percentage of wAMD patients should be expected to be dry on optical coherence tomography (OCT) after treatment?

There is a population of patients who may be non- or poorly responsive to treatment (on average 5–15%) for whom either satisfactory vision improvement or morphological improvement does not develop with treatment. Outside of this population, there is an expectation to see drying of the central retina. 2019 EURETINA Clinical Trends Survey respondents reported that around half of their patients had a dry retina on OCT 6 month after anti-VEGF treatment had been initiated.

How can AMD patient compliance with treatment protocols be improved?

Patients with wAMD are often well motivated to adhere to treatment but, because they are older, may have restricted independence and therefore rely on others to help them attend appointments. Anti-VEGF treatment places a notable burden on patients, and they are most likely to adhere to an appointment schedule if they are noticing improvement in their vision. It is important to reinforce that regular injections are key to maintaining vision improvement.

Are you aiming for a dry retina or do you tolerate small amounts of residual fluid? How does the location of retinal fluid impact treatment outcomes for patients?

While retinal drying is expected in the majority of patients treated with anti-VEGF agents, clinical experience has shown that despite appropriate loading dose and frequent re-treatment, some fluid may remain. Complete dryness is not required for meaningful treatment response, for example small sub-retinal fluid pockets or some degree of sub- retinal pigment epithelium (RPE) fluid would not lead to poor visual acuity outcomes, and therefore can be tolerated.

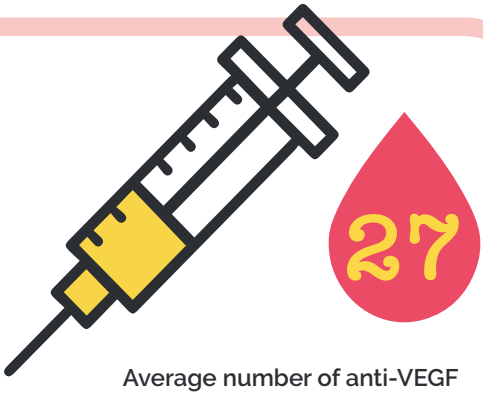
Retinal fluid does not seem to have a uniform effect on the function of neighboring retinal cells. Intraretinal fluid is considered the most toxic. Subretinal fluid does not appear to drive deterioration to the same extent, and fluid in the RPE is not in direct contact with photoreceptors and is thus usually better tolerated in treatment.

Does the amount of retinal fluid at diagnosis influence your treatment approach?

If the amount of retinal fluid does not increase, the treatment approach is not typically affected. If fluid persists during the loading phases, it is advisable to continue with four-week cycles of anti-VEGF injections rather than moving to the 'extend' phase of treatment. Sufficient injection cycles should be allowed to assess treatment response before considering switching or stopping anti-VEGF treatment.

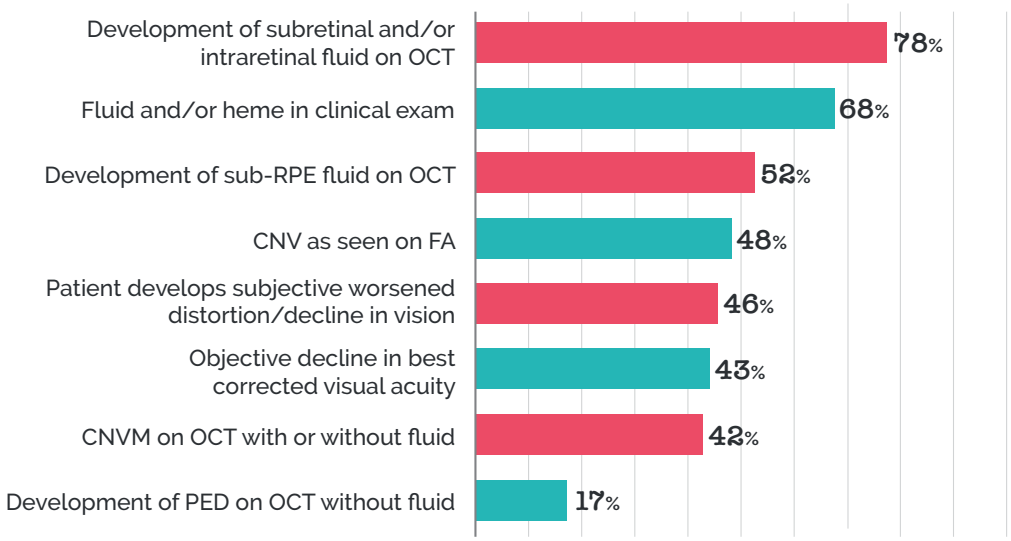
Average number of patients seen weekly that have wet AMD

Average number of patients seen weekly that have dry atrophic AMD

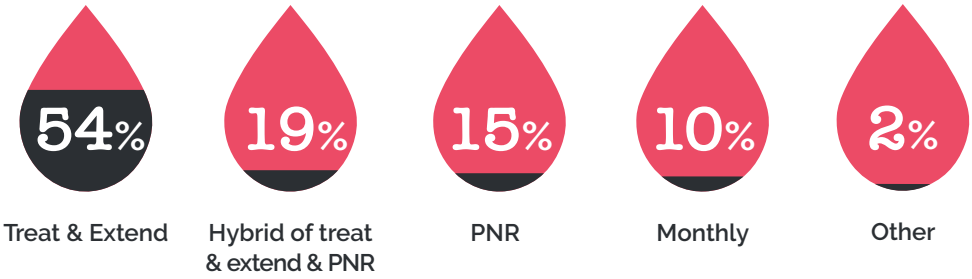


Average number of anti-VEGF injections performed weekly

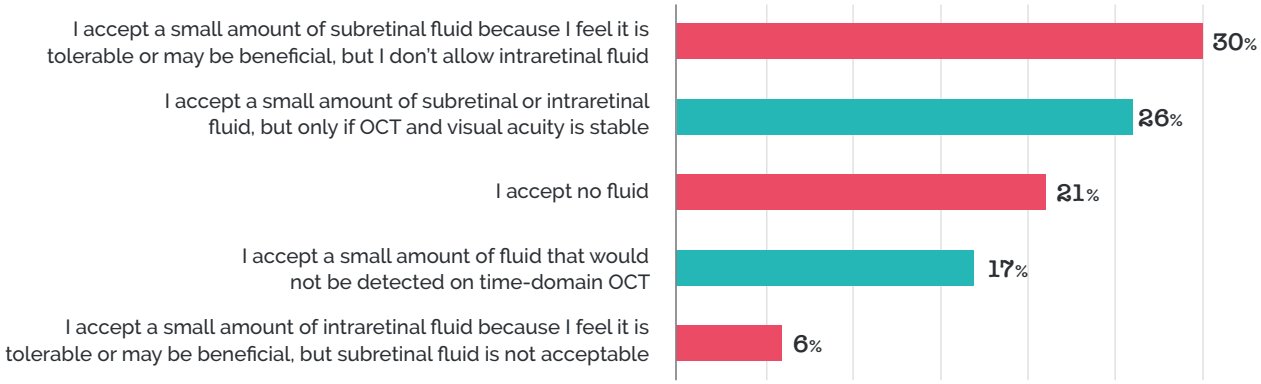
When do you decide to initiate anti-VEGF therapy in a patient with AMD? *(Select all that apply)*



Q. What method/protocol of treatment do you use for the majority of your wet AMD patients?

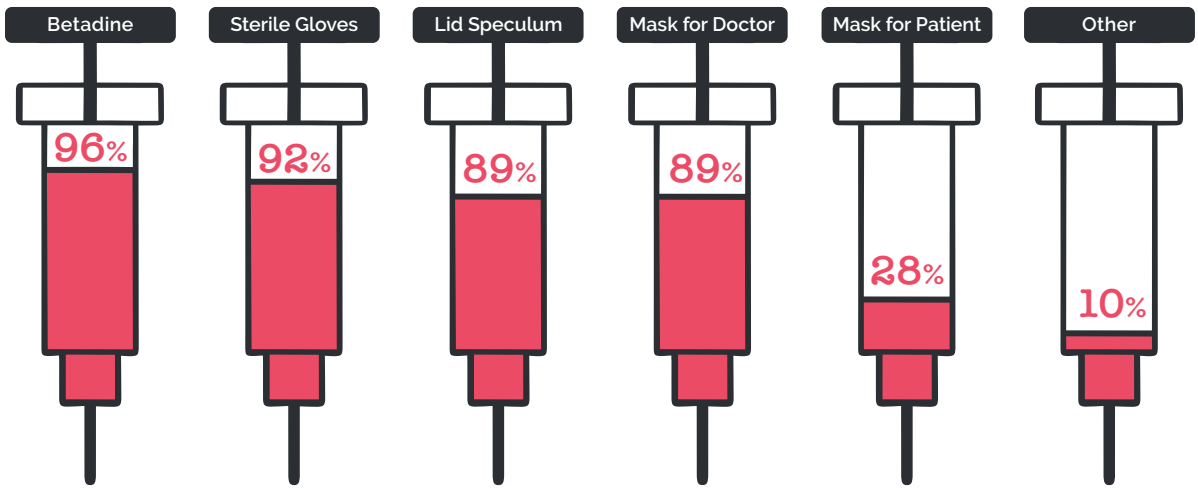


Q. What is your fluid threshold for treatment for patients with wet AMD?



Q. During intravitreal injections, what is your sterile technique?

(Select all that apply)



59%

Average percentage of patients who require regular anti-VEGF injections are adherent with their treatment timeframes

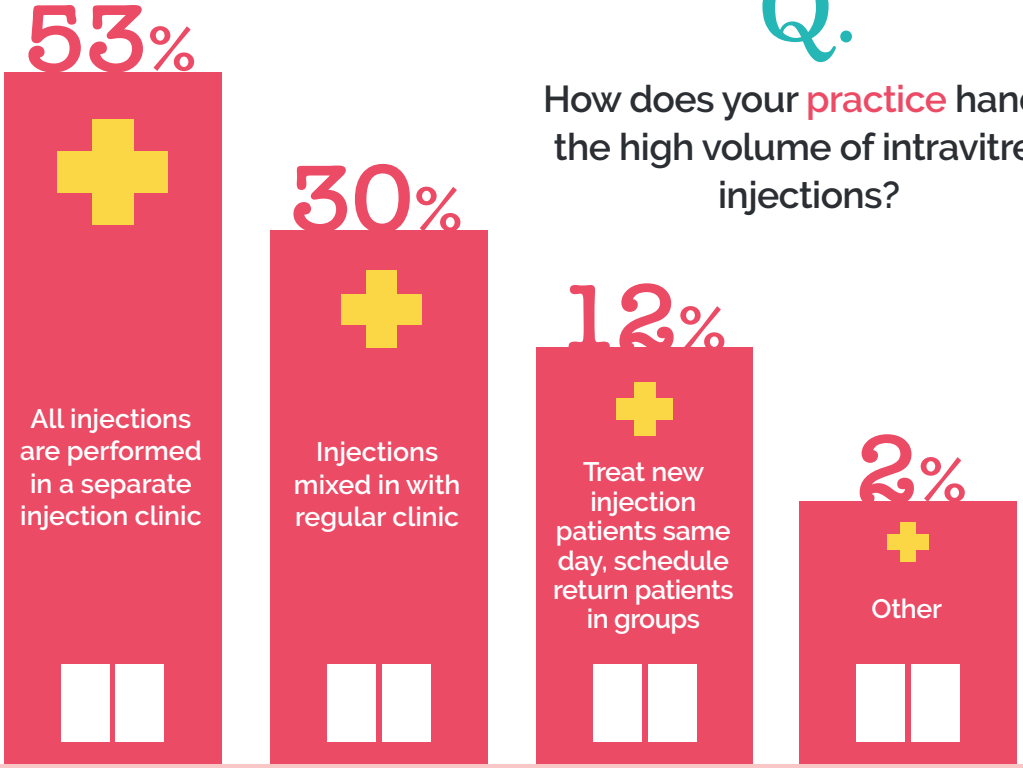
43% of respondents believe that long acting, sustained delivery methods are the greatest unmet need regarding currently available **wet AMD** treatments

3-6 months

67% of respondents would prefer a duration of effect to be 3-6 month for a sustained drug-delivery implant

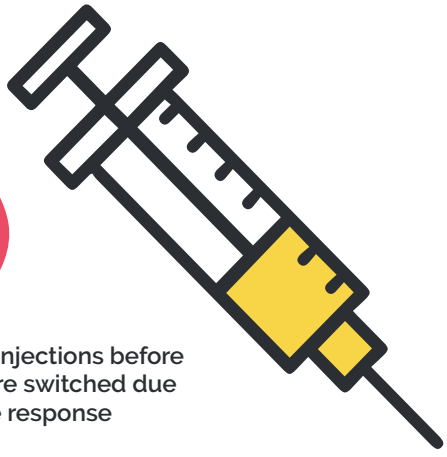
Q.

How does your practice handle the high volume of intravitreal injections?



5

Average number of injections before anti-VEGF agents are switched due to inadequate response



49%

Average percentage of standard wet AMD patients who are dry on OCT 6 months after the initial first-line treatment

Diabetic Macular Edema and Treatment Approaches

Ramin Tadayoni, MD, PhD

Professor of Ophthalmology, Université de Paris; Chairperson, Assistance Publique, Hôpitaux de Paris, France

The 2019 EURETINA Clinical Trends Survey shows that respondents are seeing an average of 40 patients with diabetic macular edema (DME) per month, more than proliferative diabetic retinopathy, central retinal vein occlusion or branch retinal vein occlusion cases. In patients whose disease does not respond to anti-VEGF treatment, therapy is changed after an average of 4 injections, and physicians have a strong understanding of the characteristics of steroids used in treating DME.

Professor Tadayoni examines the management of DME and considerations in treatment switching for non-responding patients.

How do the demographics of patients with DME differ from patients with age-related macular degeneration (AMD)?

In general, DME presents in younger, working age (50–60 years) people, compared with the relatively later average onset of AMD. This can be advantageous in management: people of this age are likely to be autonomous and able to see their doctor unaided, but conflicts with a relatively busy lifestyle. Appropriate diagnosis and treatment are important – DME is the leading cause of blindness in the working-age population.

Awareness of the disease may be lower than is typical in AMD because vision loss may not be dramatic with DME, and patients may not recognize their symptoms easily. Diagnosis and treatment are further challenged by the greater range of diversity of both severity and presentation in DME.

What do you use most commonly as first-line treatment for vision-affecting macular edema and at what stage of disease progression do you make this decision?

First-line treatment in this population is typically an anti-VEGF agent and would be used at a point of significant vision loss. The definition of significant vision loss may differ from one patient to another: certainly at 20/40 or lower but, in many cases, it would be initiated earlier, even at 20/25 vision. If a person presents relatively late and with advanced disease, there should be no delay in initiating anti-VEGF treatment.

In managing patients with disease unresponsive to treatment, it is important to understand the nature of 'unresponsiveness'. This can be hard to define; in some cases, vision may improve but edema doesn't improve. In particularly long-standing DME, protein build-up may be slow to eliminate, but vision can improve without spectacular reduction in thickness because retinal homeostasis is restored. On the contrary, in some cases, the retina is flat with normal or below normal thickness restored, but vision will not increase meaningfully. None of these cases are real 'non-responders'. There are cases, however, when the situation is not as clear and the reduction of thickness is limited, as is vision improvement. At this point, there should be a conversation with the patient to determine how much more invasive treatment is worthwhile.

At what point would you recommend changing agents if a DME patient is unresponsive to anti-VEGF therapy?

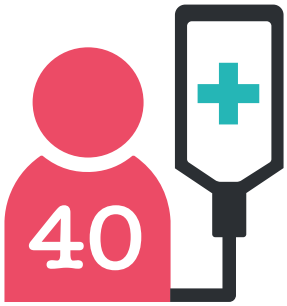
Most frequently, poor response falls in the category of patients gaining limited improved vision with minimal improvement in edema. As a broad rule, continuing treatment for 6 months is appropriate to monitor progress, and cessation before this point may not be ideal.

Steroid therapy can be considered as an alternative to anti-VEGF treatment and may offer a comparatively faster response. In some cases, steroids can be used as first-line intervention, which may be of value in driving a rapid response in a patient with pseudophakic eyes and low intraocular pressure.

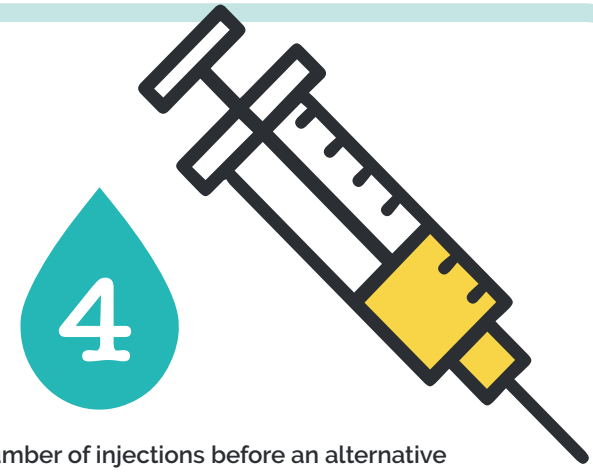
What do you consider to be the promising evolving therapies for DME?

When no injection is working for a patient with DME and the cause relates to vascular abnormalities with leaking capillary aneurysms, using a focal laser on the aneurysm is a promising technique. This approach needs meaningful randomized controlled trial data to verify these encouraging early findings.

Ongoing innovation in reducing the number and frequency of intravitreal injections and consequent burden on both the patient and physician are also of great interest. These areas were also identified by respondents to the 2019 EURETINA Clinical Trends Survey as the key unmet needs with anti-VEGF therapy.



Average number of patients seen on a monthly basis that have DME



Average number of injections before an alternative treatment is considered for DME patients who are not responsive to primary anti-VEGF therapy

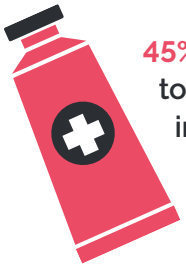
Do you consider systemic safety a critical component of your treatment decisions with anti-VEGF therapies?

44% Yes, always

41% Yes, on a case by case basis

15% No, I believe these therapies are all safe

67%
of respondents have a very strong understanding of the long-term efficacy and safety profile of steroids used for DME

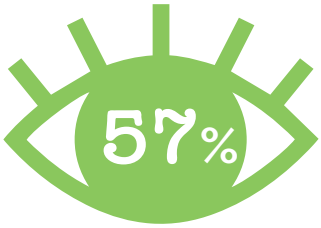


45% respondents do not prescribe topical antibiotics for use with intravitreal injections

6
months

40% is the average percentage of standard DME patients who are achieving 3 or more lines of **BCVA improvements** 6 months after the initial first-line treatment

Q. What is the largest unmet need for current anti-VEGF treatments? *(Top 3 responses)*

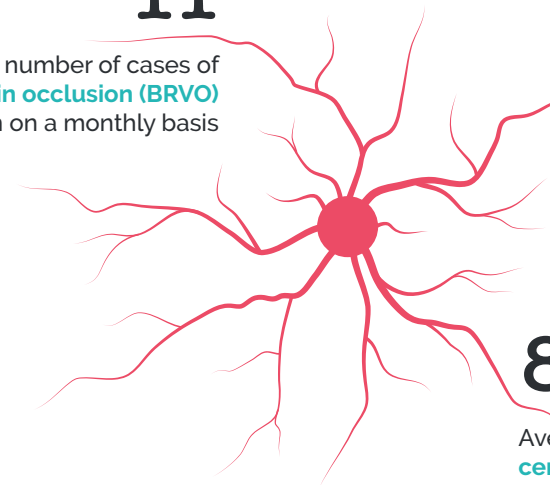


Need extended duration of action

Quantity of injections/ Treatment burden for patient

Need improved functional outcomes/Best-correct visual acuity

11
Average number of cases of **branch retinal vein occlusion (BRVO)** seen on a monthly basis



16
Average number of cases of **proliferative diabetic retinopathy (PDR)** seen on a monthly basis

8
Average number of cases of **central retinal vein occlusion (CRVO)** seen on a monthly basis

45%
Average percentage of standard DME patients who have a CFT of < 250 microns 6 months after the initial first-line treatment

Gene Therapy Approaches in Retinal Disease

Anat Loewenstein, MD, FARVO

Chair of the Department of Ophthalmology, Tel Aviv Sourasky Medical Centre; Professor of Ophthalmology and Vice Dean, Tel Aviv University, Israel

Results from the 2019 EURETINA Clinical Trends Survey suggest that physicians believe relatively strongly that gene therapy will play a significant role in ophthalmology practice in the coming years. However, there is also a need for greater understanding among ophthalmologists of the components and potential disease-specific application of gene therapy, which suggests a position of reticence to adopt this approach until more data are available and efficacy is proven.

Professor Anat Loewenstein provides insight into current understanding and considerations for future application of gene therapy in retinal disease.

Why is gene therapy such a compelling emerging therapeutic area?

Over the past decade there have been many innovations in treatment options for retinal disease. However, the real-world efficacy of these interventions rarely provides the same benefits seen in the patient populations included in randomized controlled trials. The burdens of treatment in routine practice include medicine and clinical costs, physician demands with regular visits, testing and relatively frequent intravitreal injections, and sub-optimal adherence to therapy, especially in patients with wet age-related macular degeneration (wAMD). A key potential benefit of gene therapy is a longer duration of effect, facilitating continuous efficacious treatment with a lower patient and physician burden.

What potential does gene therapy hold as future therapy for inherited and acquired retinal disorders?

For wAMD, the interest in gene therapy revolves around longer delay between injections, rather than significantly greater efficacy. Gene therapy delivered either to the retinal cells or subretinal space by adeno-associated virus (AAV) vectors could allow the continuous production of anti-VEGF, without the need for repeated injections.

This approach may be appropriate for several retinal disease types beyond neovascular macular degeneration, including geographic atrophy. Gene therapy that has neuroprotective or complement inhibition action may prevent the growth of geographic atrophy or non-neovascular disease. This would be especially important for patients with geographic atrophy, for whom a high frequency of anti-VEGF injections would not be appropriate.

In degenerative disease, gene therapy is now becoming available; an intervention has been approved by the US Food and Drug Administration (FDA) for the treatment of retinitis pigmentosa and Leber congenital amaurosis arising inherited retinal dystrophy caused by the loss of both copies the RPE65 gene. Subretinal injection of the AAV vector delivers a working copy of the RPE65 gene and has shown improvement in measures of visual acuity. This represents the first efficacious treatment for these patients and is a key breakthrough in the acceptance of gene therapy and raises hope that treatment will become available for other retinal diseases caused by loss of key genes.

Where are the limitations in the potential applications of gene therapy?

The paucity of evidence means that gene therapy approaches are not robustly supported yet. Current trials with promising data have been conducted in small populations and rare disease types or single mutations. For now, findings cannot be generalized, and existing data may be best interpreted as a successful proof of concept.

Populations that have been studied have had very poor baseline visual acuity, so the feasibility of subretinal injection of gene therapy in patients with relatively good visual acuity is unexplored. The risk of complications with subretinal delivery, which are more dependent on the skills of an individual physician than an intravitreal injection would be, makes it difficult to assess which patients would be most suited to treatment. Finally, the question of cost effectiveness must always be considered with new and expensive treatment options.

How should the practicing retina specialist prepare themselves for new gene therapy treatments in their practice?

Initial patient selection will undoubtedly bias towards patients with very low visual acuity, which may complicate findings. Use in severely impaired patients or those with structural damage may limit the efficacy of treatment as the mechanisms delivered by gene therapy may not overcome the other underlying causes of poor visual acuity.

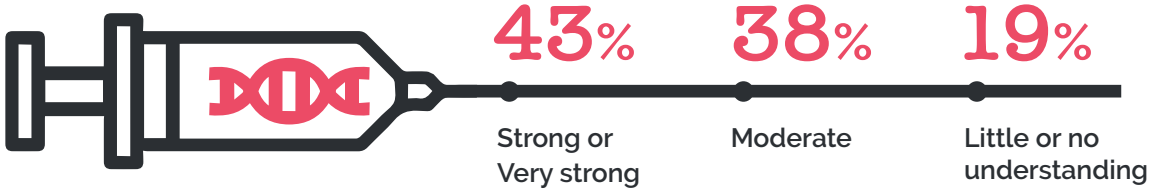
There is a need for greater experience and understanding to help select patients. For example, the natural history of retinal dystrophy is relatively unexploded because of a lack of effective interventions until recently.

What is the estimated timeframe of when gene therapy treatments will become available, and for what specific conditions?

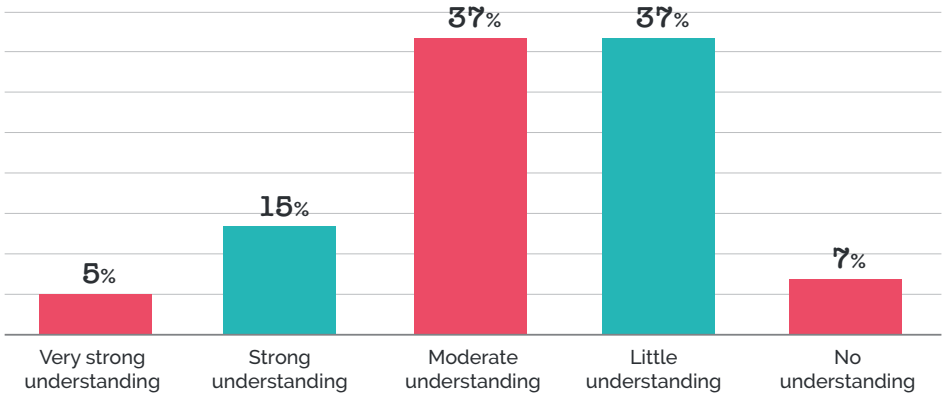
It is likely that several more years of innovation, investigation and experience are required before gene therapy has a significant role to play in clinical practice.

63% of respondent will not genetic test patients for AMD until there is a proven intervention that would be effective for these patients

How strongly do you believe that gene therapies are going to become a significant part of your practice in the coming years?



How strong is your understanding of the components of gene therapy and how gene therapy can be utilised depending on the disease and underlying cause?



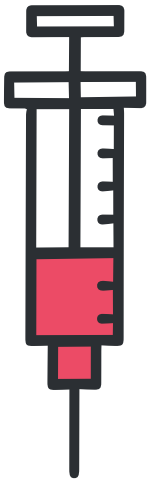
Macular Hole & Detachment Data

4

Average number of **primary** detachment procedures performed per month

2

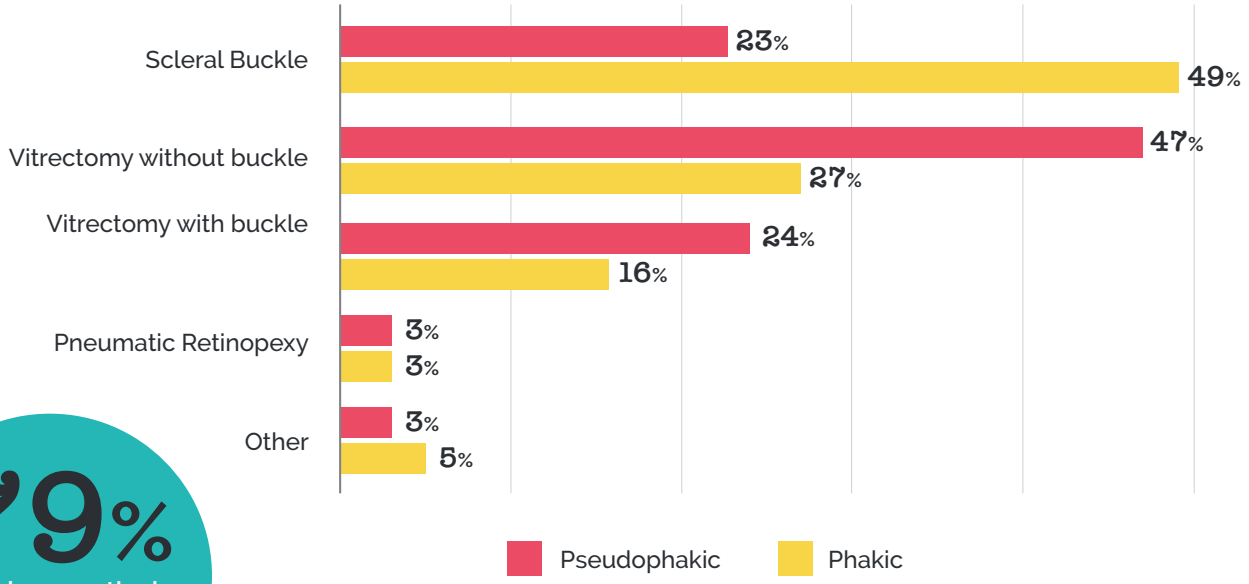
Average number of **secondary** recurrent detachments fixed per month



12%

Average percentage of **RRD (Recurrent Retinal Detachment)** cases in which oral or periorbital steroids are used

Q. How would you treat a phakic vs a pseudophakic patient with an inferior macula-on RD (Retinal Detachment) with a single tear at 8:00?



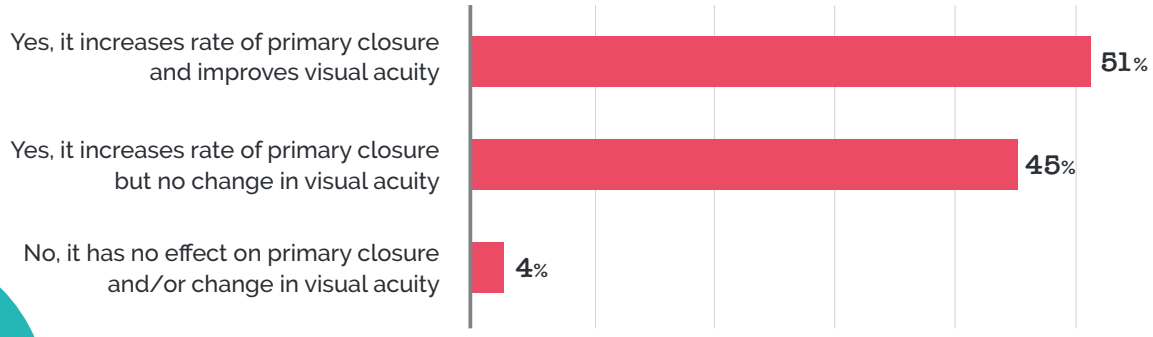
79%
of primary retinal detachments are repaired by primary vitrectomy

66%
of respondents do peel **ILM (Internal Limiting Membrane)**

Average number of **macular hole repairs** per month

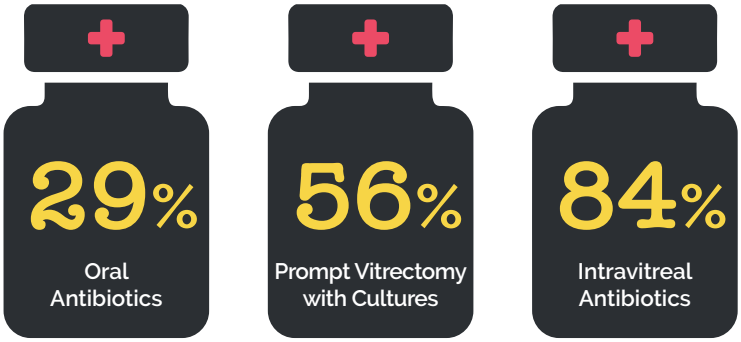
Average number of days recommended for facedown positioning after **macular hole repair**

Q. Does peeling ILM change outcomes of macular hole repair?



53% of primary retinal detachments are repaired by primary scleral buckle

Q. For acute endophthalmitis what medications do you use? *(Select all that apply)*



Average number of endophthalmitis cases related to intravitreal injections observed within the last 2 years

Q. What is your opinion of 3D digital ophthalmic microscopes for retina surgery?