EURETINA
European Society of Retina Specialists

EURETINA EDUCATION PLATFORM

2020

CLINICAL SURVEY

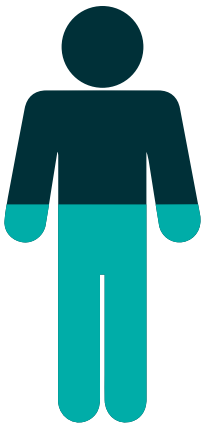
OUTCOMES

Survey Background & Overview

This supplement contains the results of the 2020 EURETINA Clinical Trends Survey, conducted in conjunction with the 20th Virtual Congress of EURETINA. Delegates had the opportunity to complete the survey online between late September and early December 2020. Survey questions examined several areas of clinical practice, including diagnosis of retinal disease, age-related macular degeneration (AMD), diabetic macular edema (DME), and gene therapy.

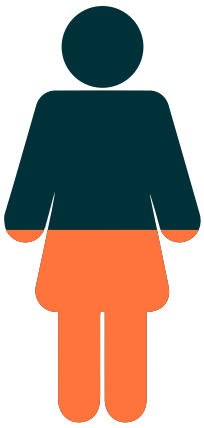
More than 670 physicians responded to the 65 questions, which were developed and reviewed with the EURETINA leadership and substantiated by a data scientist. To better identify the educational needs of its members, EURETINA leadership refers to the results of these surveys and the feedback they elicit. The collected data will also enhance the educational opportunities featured at the 2021 EURETINA Virtual Congress, the EURETINA Winter Meeting and other educational channels such as the EURETINA Online Education Platform and various print and digital supplements.

We invite you to study the Survey's key findings and be ready to take advantage of upcoming educational events. EURETINA encourages all delegates to participate in the upcoming 2021 EURETINA Clinical Trends Survey, launching in September at the 21st Virtual Congress of the EURETINA, and taking place online throughout autumn, at *https://euretina2021.questionpro.com*.



54%

Male



46%

Female

65

Questions on key clinical opinions & practice patterns

675

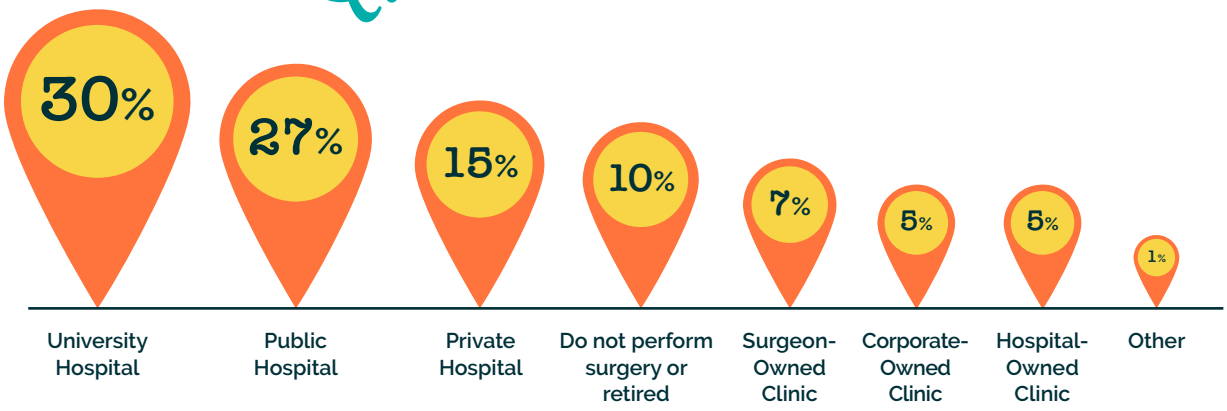
EURETINA delegates responded to the survey

Q. How many years are you in practice?

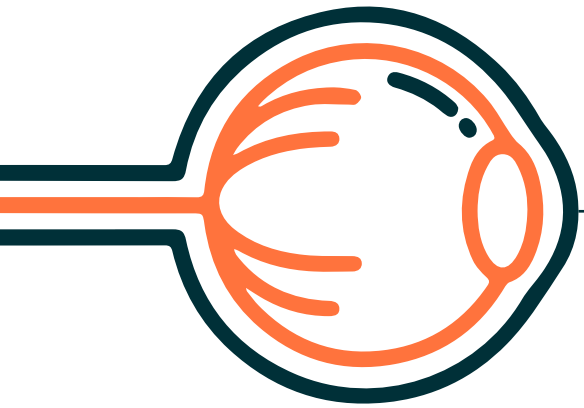
60%
10 years+

8%
currently in medical school or training

Q. What is your primary surgery location?



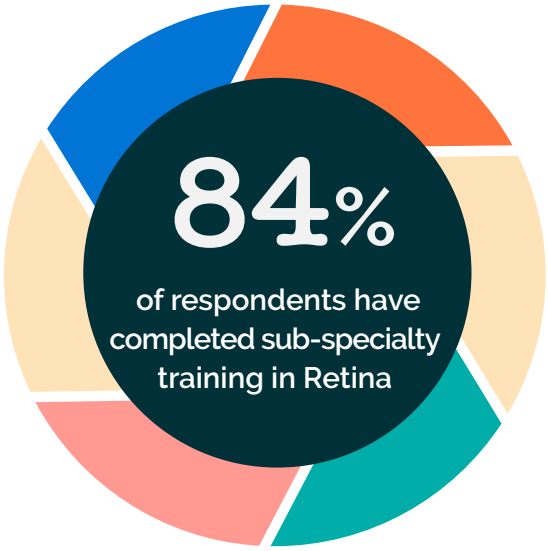
Q. What is your field of expertise?



54% Medical & surgical retina specialists

37% Medical retina specialists only

9% Other or surgical retina specialist



> More than 670 physicians responded to the 65 questions, which were developed and reviewed with the EURETINA leadership and substantiated by a data scientist.

Diagnostic Approaches in Ophthalmology

Anat Loewenstein

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

Financial disclosure and conflict of interest: Consultant to Allergan, Bayer, BeyeOnics, ForSight Labs, NotalVision, Novartis, Roche

Imaging techniques for the diagnosis of diseases of the retina, including diabetic macular edema (DME) and wet age-related macular degeneration (wAMD), continue to evolve. Optical coherence tomography angiography (OCT-A) is the most recent development to enter routine practice.

Professor Anat Loewenstein discusses the relative benefits of imaging techniques and combinations of these techniques – multimodal imaging – in the diagnosis and response to treatment of wAMD and DME.

Where should OCT-A technology be incorporated in a retina practice today and what are some technology improvements we could expect in the coming years?

Most respondents to the Clinical Trends Survey 2020 felt that OCT-A was a valuable asset and that they do, or would, use the technology in their practice. However, around one quarter of respondents were keen to see more data before deciding to use the technique routinely. Professor Loewenstein notes that OCT-A is certainly a valuable tool, but one that needs to be used in the context of its strengths and weaknesses. The visualization of blood flow is a key benefit when combined with structural information attained with OCT. When used alone, OCT-A should be considered a qualitative, rather than a quantitative, tool, and this makes monitoring response to anti-vascular endothelial growth factor (anti-VEGF) therapy challenging without supporting imaging.

Can you comment on the role of artificial intelligence use with OCT diagnostic assessments? How will AI be applied to retina practices in the coming years?

Many survey respondents believe that artificial intelligence (AI) will play a key role in diagnosis and monitoring of retinal diseases in the coming years. Developments in this field are continuing to expand the capabilities of AI, and this recently included the ability to determine the sex of a patient from an image of the fundus alone, representing an observation that most physicians would not be able to make. However, in practice, AI will be best suited to an assistive, not directive, role, where it can help optimize screening and flagging patients for referral to a specialist physician.

What are the key imaging tools you currently utilize to diagnose and monitor a patient with wet AMD and has this approach changed in past years?

In agreement with the Clinical Trends Survey findings, Professor Anat Loewenstein relies on OCT for diagnosis and monitoring of wAMD patients, occasionally supplemented by OCT-A. Use of fluorescein angiograph (FA) appears to be declining; however, this can be a useful tool in assessing patients who are not responding to treatment and may reveal polyps or injury that require modification to management. OCT remains the technique of choice in monitoring treatment response in most patients.

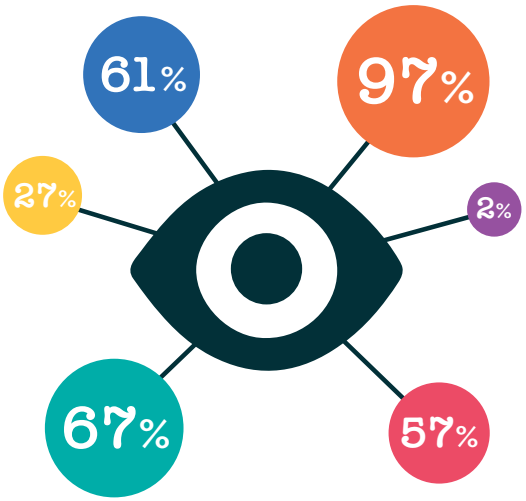
Fundus photography is becoming a very useful tool with current technology allowing for images to be taken by technicians or the patient, allowing useful insight for the physician before they examine the patient further.

Which imaging techniques and screening protocols do you use to diagnose DME? How are these different from your AMD imaging techniques and screening protocols?

OCT is the most important technique for screening and diagnosis. Fundus photography is of benefit when access to the patient is limited. In screening, clinical examination alone remains of value where there is no suspicion of macular edema or retinal thickening, and the patient has good visual acuity. Where there is no diabetic retinopathy, the patient will not have DME, so this examination can save the need for unnecessary multimodal imaging.

FA may be used more routinely in patients with wAMD to confirm diagnosis and only when a patient with DME is non-responsive to treatment.

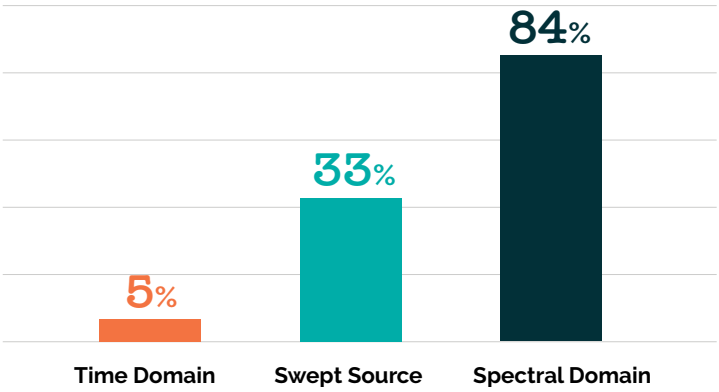
Q. What are all the imaging techniques that you use at time of diagnosis for wet AMD patients? *(Select all that apply)*



- Optical coherence tomography (OCT)
- Fluorescein angiography (FA)
- Fundus Photography
- Optical coherence tomography angiography (OCT-A)
- Indocyanine green (ICG)
- Other

Q. Which OCT do you use?

(Select all that apply)



OCT remained the main modality to diagnose wet AMD since 2016. The use of OCTA and fundus photography have increased by 10% and 13% points, respectively, while FA use has decreased by 14% points.

55%

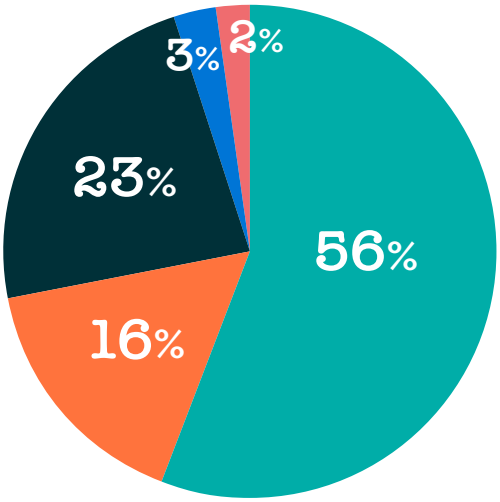
of respondents do not have access to wide-field fluorescein angiography (FA)

75%

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

2020 EURETINA Clinical Survey Outcomes

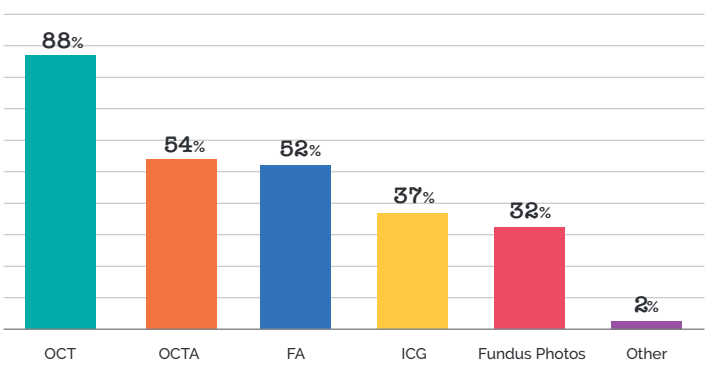
Diagnostic Approaches in Ophthalmology



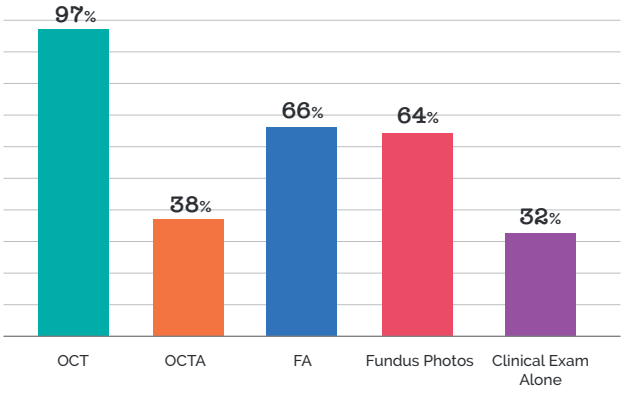
Q. What is your belief in the current value of OCT Angiography?

- Valuable and currently incorporating this as a routine of my retina practice
- Intend to incorporate this in the next 12 months
- Likely to be valuable, but awaiting more data
- Not sure
- I don't believe this will add significant value to my retina practice

Q. What are 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. What are all the imaging techniques that you use for DME patients? *(Select all that apply)*



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

66% I am using multimodal imaging

16% Not economically viable for me

14% No access to this technology in my practice

2% Too disruptive to integrate into my practice

2% Other

Management of Age-related Macular Degeneration

Frank G. Holz

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

Financial disclosure and conflict of interest: Research Grant Support: Acucela, Allergan, Apellis, Bayer, Bioeq/Formycon, CenterVue, Ellex, Roche/Genentech, Geuder, Kanghong, NightStarx, Novartis, Optos, Zeiss
Consultant: Acucela, Allergan, Apellis, Bayer, Boehringer-Ingelheim, Roche/Genentech, Geuder, Grayburg Vision, LinBioscience, Kanghong, Novartis, Pixium Vision, Oxurion, Stealth BioTherapeutics, Zeiss

Neovascular ("wet") and dry age-related macular degeneration (AMD) are common causes of sight deterioration and loss. The EURETINA Clinical Trends Survey 2020 reported that, on average per week, respondents see 22 people with wet AMD (wAMD) and 13 with dry atrophic AMD. Currently, there are no treatments for advanced dry AMD. Wet AMD can be successfully treated with anti-vascular endothelial growth factor (anti-VEGF) therapy, which survey respondents are typically initiating on first detection of fluid and administering with a treat-and-extend regimen. Professor Holz shares his expert experience on managing patients with AMD in routine practice, and on the future of treatment.

When do you start treatment for wet AMD and what is your first line treatment approach?

Treatment for wAMD is most effective when initiated as early as possible. Following a confirmed diagnosis, anti-VEGF agents are the routine first-line treatment.

What regimen of treatment do you use for the majority of your wet AMD patients and why?

In most cases, a short dose-loading period followed by a treat-and-extend regimen is the most appropriate approach. In some cases, treat-and-extend is not the optimal approach, particularly for patients with bilateral active disease, where the dosing interval for one eye may not be appropriate for the other eye. For these patients, a pro re nata (PRN) schedule may be preferred.

How many lines of best corrected visual acuity (BCVA) improvement should we be targeting with our initial first-line treatment?

Improvement in BCVA is largely relative to the baseline value, and therefore there is no specific value that represents 'treatment success'. While there is a ceiling for how much improvement a patient with good visual acuity before treatment initiation might achieve, and a greater scope for improvement in those with poor baseline function, the common theme remains that early and effective treatment is key to maximizing potential gains in BCVA.

What are your treatment outcome goals for a typical wet AMD patient?

The goal of wAMD management is to treat to dryness and to reinstate the normal physiological state of the retina. However, some residual fluid may remain despite intense treatment and may be tolerated. Pockets of sub-retinal fluid that are resistant to anti-VEGF therapy should not be a driver to increase intensity of treatment but can be monitored and tolerated in a treat-and-extend regimen.

How can AMD patient compliance with treatment protocols be improved further?

Education is key; it is important for patients to understand that missed appointments may lead to deterioration in vision, and that these losses may not be recoverable. It is important to support patient adherence by making the appointment system and treatment administration as efficient as possible. In the future, improved telemedicine and home OCT may play a role in optimizing monitoring and further improve patient adherence to wAMD management.

What is currently the greatest unmet clinical need in AMD treatment?

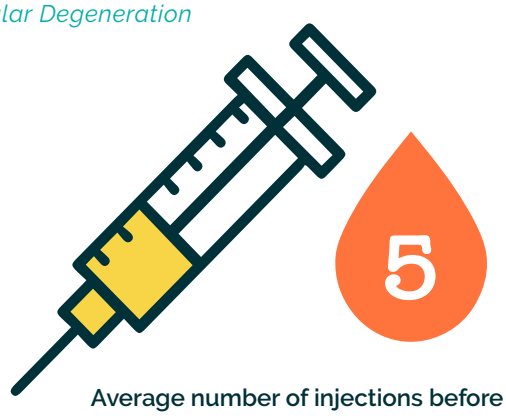
In dry AMD, and geographic atrophy there remains the need for an effective treatment; results from ongoing trials, due in 2021 and 2022, are eagerly awaited. For wAMD, there remains two key unmet needs. For patients who have poor or non-response to anti-VEGF therapy, more efficacious alternatives are needed. Treatments with longer duration of effect are also required, with several developments underway.

2020 EURETINA Clinical Survey Outcomes

Management of Age-related Macular Degeneration

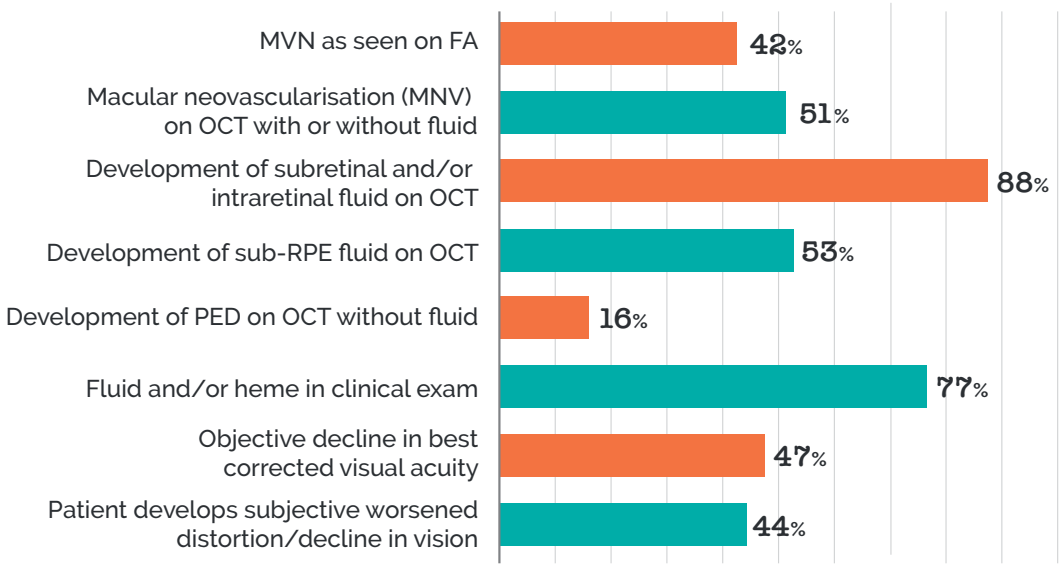
Average number of patients seen weekly that have wet AMD

Average number of patients seen weekly that have dry atrophic AMD

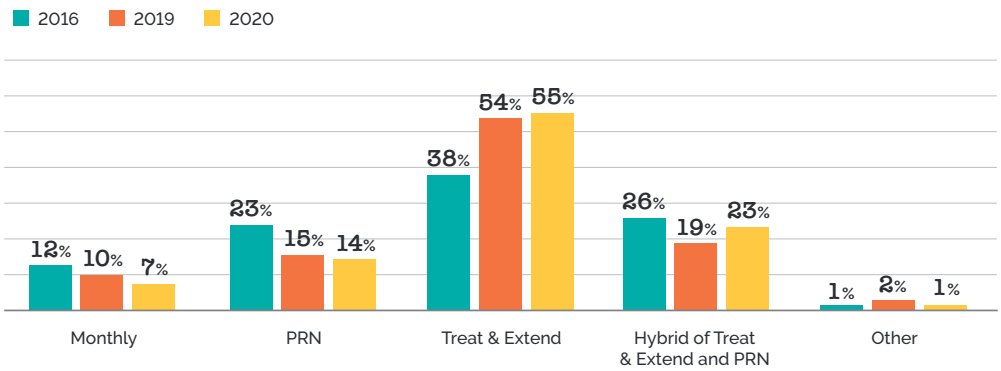


Average number of injections before anti-VEGF agents are switched due to inadequate response.

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



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



The use of monthly and PRN treatment regimens for wet AMD have decreased since 2016, while the use of Treat and Extend has increased by 17% points. ($p \leq 0.001$)

2020 EURETINA Clinical Survey Outcomes

Management of Age-related Macular Degeneration

46% 2016

49% 2019

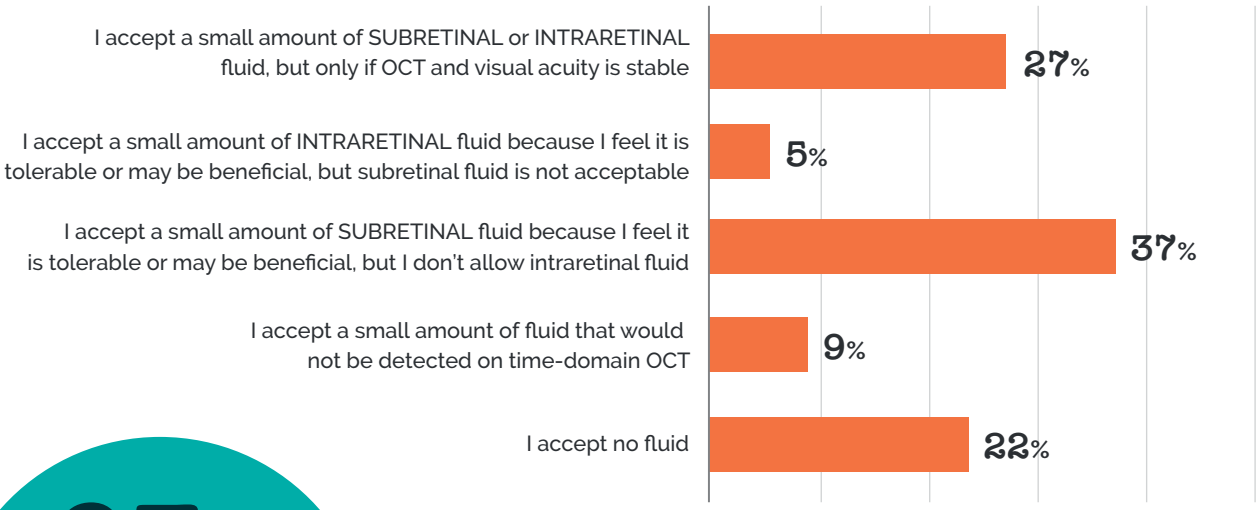
51% 2020

The average percentage of standard wet AMD patients who presented dry on OCT 6 month after first line treatment has increased by 5% points since 2016.

51%

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

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



63%

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

52% 2016

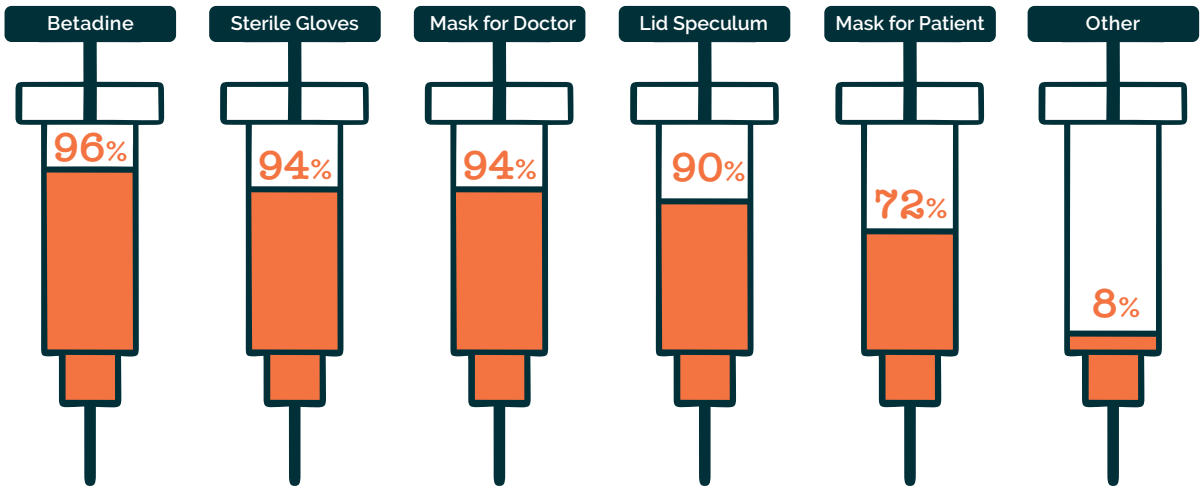
59% 2019

63% 2020

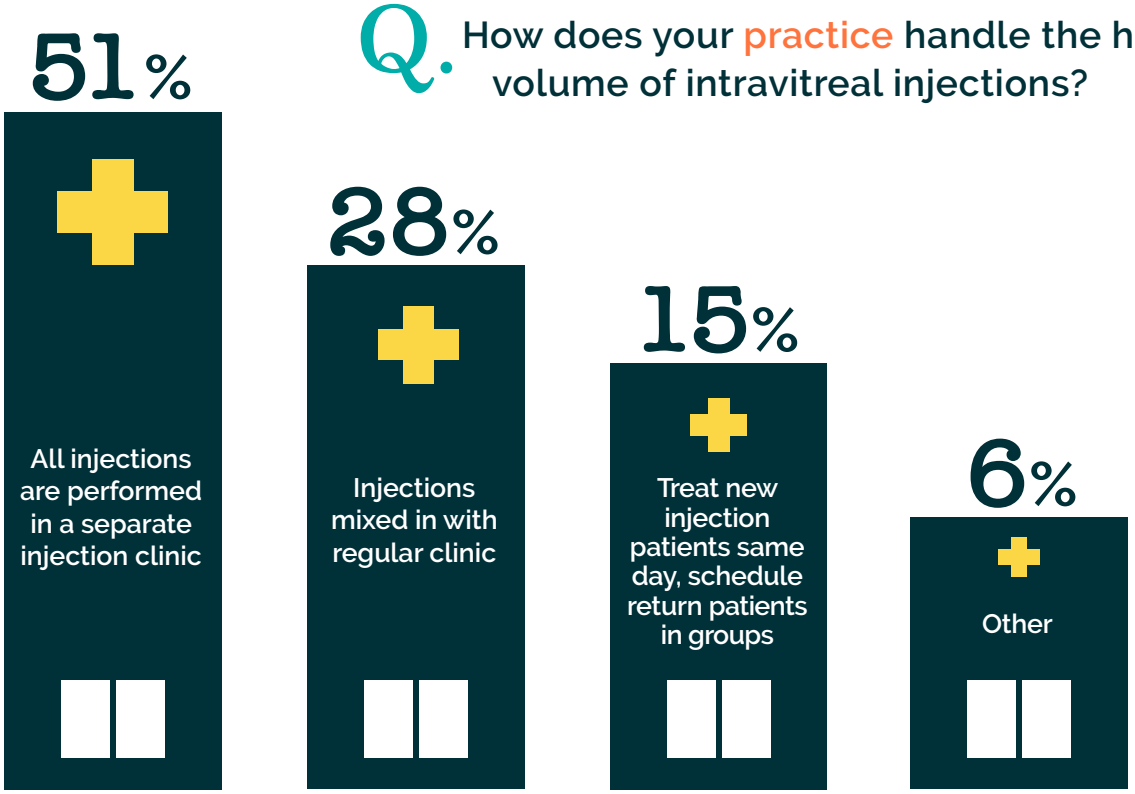
Average patient compliance with anti-VEGF treatment time frames has increased by 9% points since 2016.

Average number of anti-VEGF injections performed weekly

Q. During intravitreal injections, what is your sterile technique? *(Select all that apply)*



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



72% of respondents would prefer a duration of effect to be 6-12 months for a sustained drug-delivery implant

Diabetic Macular Edema (DME) & Treatment

Sebastian Wolf

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

Financial disclosure and conflict of interest: Allegro Ophthalmics, Bayer HealthCare, Boehringer Ingelheim, Chengdu Kanghong Biotechnology, Heidelberg Engineering, Novartis Pharma, RetinAI Medical AG, Roche, Carl Zeiss Meditec

Data from the EURETINA Clinical Trends Survey 2020 show that respondents are seeing an average of 37 patients with diabetic macular edema (DME) each month. Age-related macular degeneration (AMD) and DME both impact central vision and are typically managed using similar drugs; however, the two conditions are pathologically different and require personalized management. Professor Sebastian Wolf explores the key considerations in the effective management of DME in routine practice.

How do the demographics of the typical patient with DME differ from those of patients with AMD?

Patients presenting with DME are generally younger than those diagnosed with AMD (by 15–20 years on average). Many patients who come to their physician with symptoms of DME are of working age, and this is important in understanding the burden of disease that they are likely to experience. In contrast to older patients with AMD, the younger DME demographic are more likely to be able to attend clinics by themselves, and not require as much support from friends and family in their treatment journey.

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? At what point would you recommend changing agents if a patient's DME is unresponsive to therapy?

First-line treatment is always anti-vascular endothelial growth factor (anti-VEGF) therapy, albeit the choice of anti-VEGF may vary from practice to practice. Treatment is initiated as soon as vision-affecting edema is diagnosed, even if the patient currently has good visual acuity (e.g. 20/30) and is given for at least 6–8 injections in order to assess response. Data from the Clinical Trends Survey suggest an average of 4 injections are performed in practice before considering treatment switching. Where patients are non-responsive to anti-VEGF, steroids are prescribed, rather than switching between anti-VEGF agents.

While patient safety is always a priority, Professor Wolf has no notable concerns about the systemic safety profile of anti-VEGF treatment. Interestingly, over half of survey respondents use antibiotics; this practice is becoming less common over the past decade, with no associated increase in endophthalmitis. Where endophthalmitis is suspected, early treatment with an injected antibiotic is essential to improving outcomes, and this can be performed at the intravitreal injection clinic; the patient can then move to a specialist treatment setting.

What are the ideal treatment outcome targets for your DME patients?

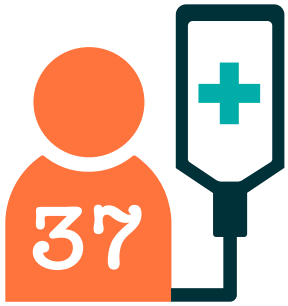
There appears to have been an improvement in clinical outcomes for patients with DME between 2016–2020, and this may be related to earlier and more aggressive treatment. Typical goals of treatment would be to aim for a visual acuity of 20/20. Physicians should be encouraged to treat monthly with an anti-VEGF agent until a dry retina is observed, at which point treatment intervals may be extended as appropriate.

In the coming years, what do you believe are the most promising evolving therapies for DME on the horizon?

Over the past 5 years, an increasing number of survey respondents hold the opinion that extended duration of action, reduced treatment burden for the patient and even further improved visual outcomes are the key unmet needs in optimal anti-VEGF therapy. There is an expectation that greater visual benefit can be provided, but there is little evidence for significant improvement in this area in past years. Emerging therapies may address the need for longer-duration interventions. However, compelling data on visual outcomes are awaited, and there may be safety considerations around intraocular inflammation, particularly in patients with type 2 diabetes mellitus.

2020 EURETINA Clinical Survey Outcomes

Diabetic Macular Edema (DME) & Treatment



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

41%

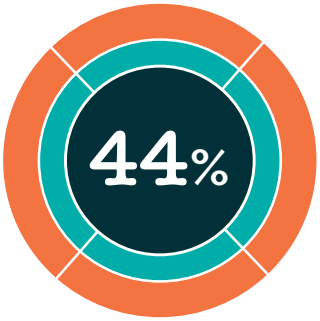
of respondents **do not** prescribe topical antibiotics for use with intravitreal injections

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

51%
Yes, on a case by case basis

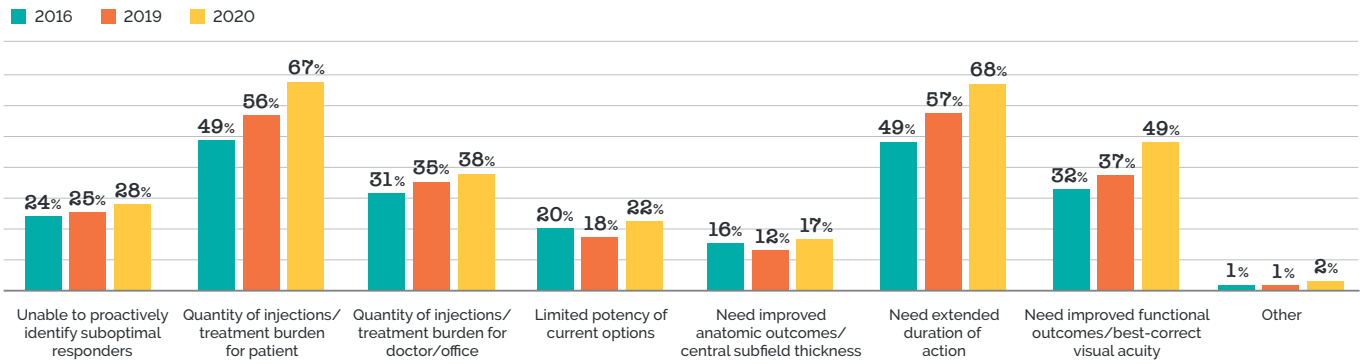
37%
Yes, always

12%
No, I believe these therapies are all safe



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

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



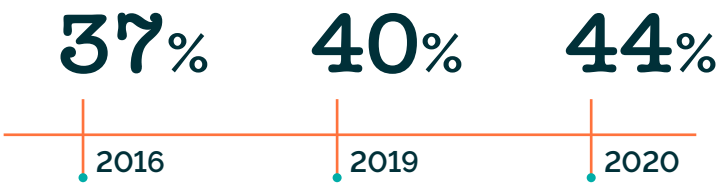
Concerns regarding unmet needs of anti-VEGF treatments have overall increased, but extended duration of action and the treatment burden remain the main issues.

2020 EURETINA Clinical Survey Outcomes

Diabetic Macular Edema (DME) & Treatment

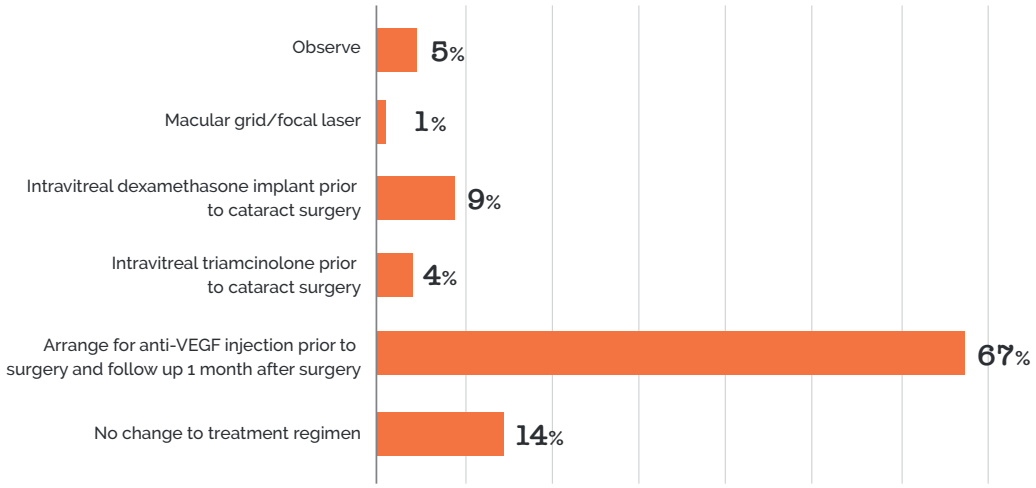
44%

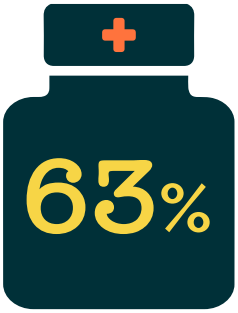
Average percentage of standard DME patients who are achieving 3 or more lines of BCVA improvement 6 months after initial first-line treatment



The average percentage of DME patients who achieve 3 or more lines of BCVA improvement 6 months after first line treatment has increased by 7% points since 2016.

Q. If a patient with DME is going to undergo cataract surgery, what do you do?



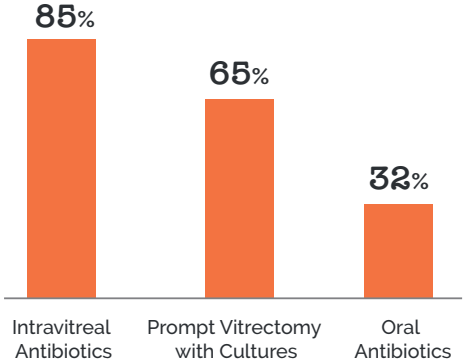


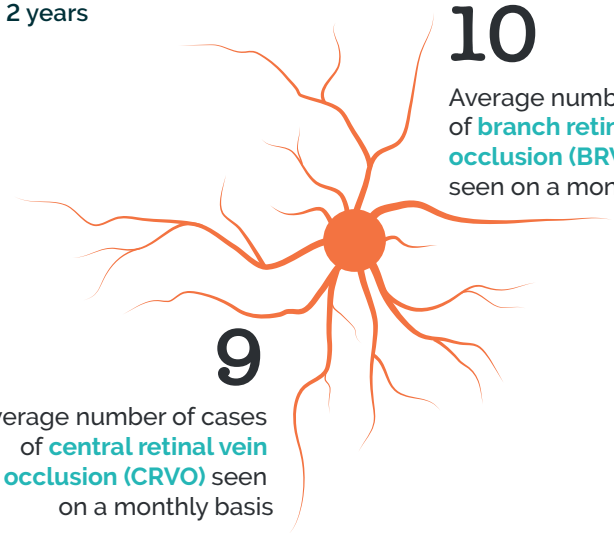
of respondents have a very strong and strong understanding of the long-term efficacy and safety profile of steroids used for DME

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

Q. For acute endophthalmitis what medications do you use?

(Select all that apply.)





10

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

9

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

Gene Therapy & the Future of Retinal Disease Management

Nicole Eter

Department Chair and Medical Director of the Department of Ophthalmology at the University of Münster, Münster, Germany

Financial disclosure and conflict of interest: Advisory, lecture or speaking fees from Apellis Pharmaceuticals, Alcon, Allegan, Bayer, Novartis and Roche: Research funding or study grants from Allergan, Bayer and Novartis

The EURETINA Clinical Trends Survey 2020 reported that most respondents have a strong belief that gene therapies will play an important part in the future of treating both inherited and acquired retinal diseases. However, there was less certainty among physicians about how these therapies work, and how they could be used in practice.

Professor Nicole Eter considers the potential benefits of gene therapy, as well as the practicalities of how this emerging approach could be integrated into practice to help patients with retinal diseases in the coming years.

Why is gene therapy such a promising emerging therapeutic area?

Ultimately, the great promise of gene therapy is to provide a cure for retinal disease at the root of the cause, rather than waiting for disease progression and using a management strategy that aims to minimize symptoms. Furthermore, gene therapy may offer the opportunity to treat a patient just once, with the effect sustained for their lifetime, consequently reducing the burden of not only the disease, but also of treatment regimens.

What potential does it hold as future therapy for inherited and acquired retinal disorders and where are its limitations?

Currently, there is only one gene therapy available, for the treatment of inherited retinal dystrophies caused by variation in the RPE65 gene. As therapies for more variations of retinitis pigmentosa and other inherited retinal diseases enter trials, it is likely that several gene therapy options will be available in the coming years.

For acquired diseases, such as age-related macular degeneration (AMD), the research and application of gene therapy is more complicated. AMD is not caused by just one mutation that leads to one phenotype; it is a multifactorial disease in terms of implicated genes and acquired factors, including the patient's environment and lifestyle. In addition, genetic screening is not routine in patients with AMD, and with around 40 genes that could play a role in disease progression, there is currently insufficient understanding of how to identify, screen for, and target the genes of interest.

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

In terms of hereditary diseases, physicians will be able to accurately screen for specific genes and select the most appropriate treatment. In the clinic, the administration of gene therapy by a sub-retinal injection during vitrectomy will not require any additional education or equipment.

Considering the acquired retinal diseases, physicians will require a greater understanding of patient selection and screening as the treatments are developed. A substantial evidence base of outcomes will be needed in practice, and this was reflected in the findings of the EURETINA Clinical Trends Survey 2020 suggesting that most physicians will not genetically screen their patients with AMD until there is a proven intervention available.

It will be important in practice to use imaging biomarkers that can identify patients with the most rapidly progressing forms of disease, who could then be genetically screened before selection of the most appropriate intervention.

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

The current advances in therapy for retinitis pigmentosa and other retinal diseases will continue, yielding clearer insight into genes of interest and how their variation drives disease progression. For inherited conditions, gene therapy is likely to be the future of effective treatment. It will take several more years, for the understanding of the more complex disease pathways of acquired retinal diseases to develop to a point where gene therapies can be accurately targeted.

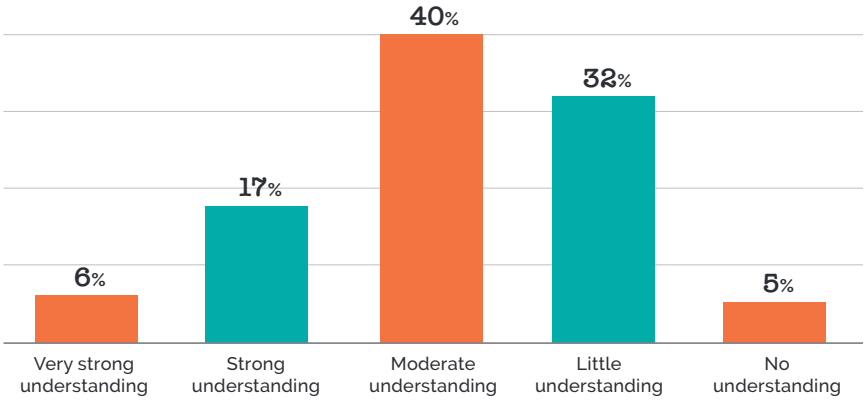
2020 EURETINA Clinical Survey Outcomes

Gene Therapy & the Future of Retinal Disease Management

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

14%	30%	37%	15%	4%
Very strong	Strong	Moderate	Little understanding	No understanding

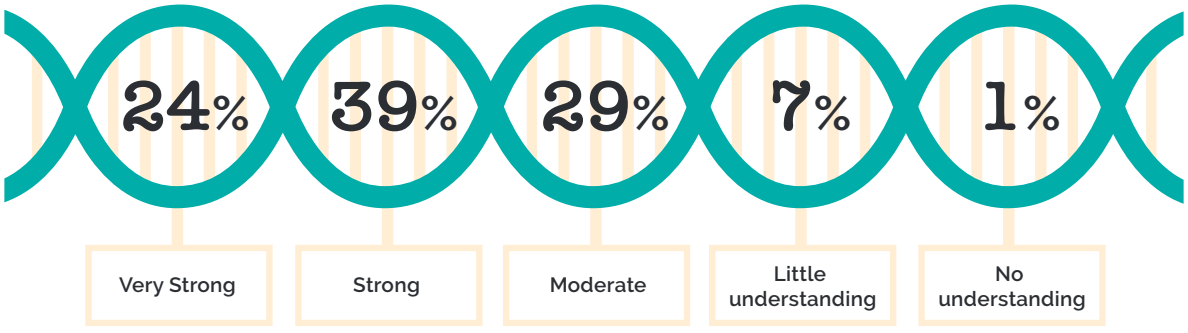
Q. How strong is your understanding of the components of gene therapy and how gene therapy can be utilised depending on the disease and underlying cause?



66%

of respondents **will not genetic test patients for AMD** until there is a proven intervention that would be effective for these patients

Q. How strong is your belief that gene therapies are the future for inherited and acquired retinal disorders?



24%	39%	29%	7%	1%
Very Strong	Strong	Moderate	Little understanding	No understanding