



Patient-Centered Outcomes in Wet Age-Related Macular Degeneration

A Report Based on National Summit Convened in Boston, MA,
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Executive Summary

Age-related macular degeneration (AMD) is a disease that gradually destroys visual function, causing people to lose their ability to read, recognize faces, drive, and do other daily activities. The impact of the disease on patients — and on their caregivers — is profound. Within the past 15 years, the development of anti-angiogenic drugs has dramatically advanced the treatment of AMD. Clinicians are now able to offer patients the opportunity to preserve their vision and, in some cases, even reverse a portion of their vision loss. But not everyone responds to anti-angiogenic drugs, and even patients who do may encounter barriers that make effective treatment less effective. Complicating the issue is that clinicians and patients often have different ways of measuring and defining successful treatment outcomes.

Understanding the concerns, experiences, and perspectives of patients with AMD — and those of their caregivers — is essential to developing true patient-centered care and better long-term vision outcomes. Patients with AMD can experience extreme losses as a result of their decreased vision, including losses of independence, privacy, self-esteem, social interaction, physical safety, and financial security. The treatment outcomes most valued by patients are those that help them avoid or minimize those losses. They want to continue to feel social connection with family and friends, to maintain their identity and independence, to feel safe in their home and other environments, and to maintain their financial security.

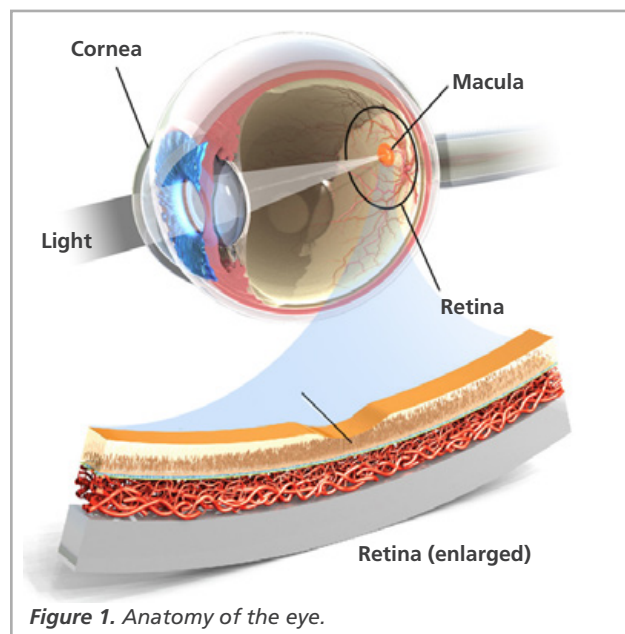
Access to training and support services is also essential for people with vision loss. With the help of such services, patients can continue to lead engaged and enriched lives.

Prevention and early detection of AMD is crucial to successful patient-centered care and outcomes. AMD stakeholders — patients, caregivers, advocates, clinicians, researchers, and policymakers — must work together to raise awareness about AMD; to establish routine screening; to educate caregivers; to encourage the development and use of safe, easy-to-use home screening technologies; and to fund research into all aspects of the disease, from prevention through treatment. They must also work together to reduce barriers that impede patients from getting the most from treatment, including barriers to their participation in self-care, which is fundamental to optimizing long-term outcomes in the management of any progressive disease.

Introduction

What Is AMD?

Age-related macular degeneration (AMD) is a chronic disease that causes the central portion of the retina — the macula — to deteriorate. The macula is critical for seeing fine details, contrast, and color. People with AMD, therefore, experience a gradual blurring of their central vision, leading to a loss of their ability to read, drive, and do other daily activities. They also lose their ability to recognize faces.

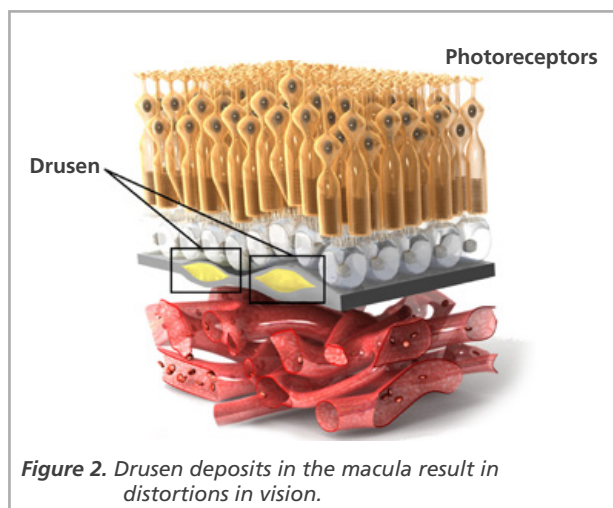


AMD is a leading cause of blindness in the world, particularly among people aged 65 and older. In the United States, an estimated 2.1 million people aged 50 and older have advanced or late-stage AMD (with loss of visual function) and another 9.1 million have early or intermediate AMD (with minimal to significant vision loss).¹ The number of Americans with diagnosed AMD is expected to increase dramatically in the coming years as life expectancies rise and the nation's population ages. For example, it is estimated that U.S. cases of AMD will increase to 5.44 million by 2020, with an additional 17.8 million cases of early AMD.² The global numbers are on a similar trend line. Experts estimate that 196 million people will be affected by AMD by 2020, a number that is projected to climb to 288 million by 2040,³ although recent research has suggested that the risk of developing AMD is significantly lower among people of the Baby Boom (1946-1964) and later generations than for those in earlier generations.⁴ The reasons for this shift in risk are unclear.

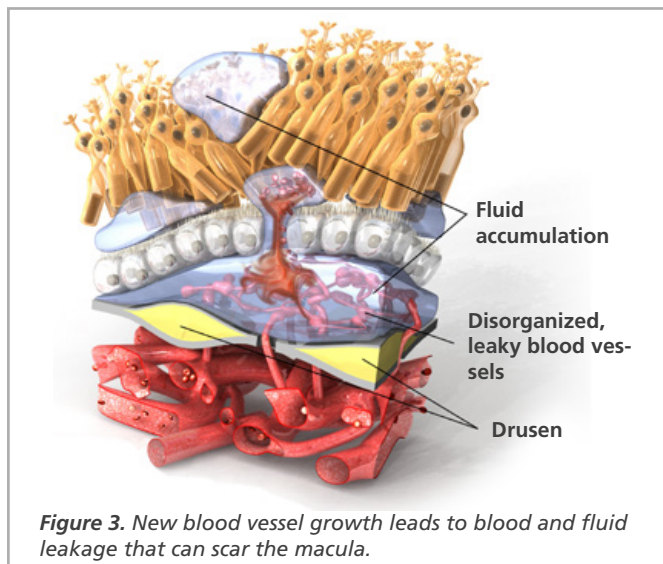
There are multiple categories of AMD: early, intermediate, and advanced or late-stage. Advanced AMD is split into atrophic AMD (known as geographic atrophy) and exudative AMD (also known as wet or neovascular AMD). Both

geographic atrophy and the exudative form of AMD can occur in one or both eyes, although the development of any form of AMD in one eye increases the risk that AMD will develop in the second eye. No form of AMD is painful. As a result, the disease may not be detected by the patient, or diagnosed by a physician (i.e. an optometrist or ophthalmologist) until it produces a marked loss in visual function. When AMD affects vision in one eye, it often goes undetected because the brain uses information from the second eye to self-correct for any loss of vision in the first eye.

Early and intermediate AMD, the most common forms of macular degeneration, are characterized by the accumulation of drusen, which are large yellowish deposits that build up beneath the macula. Cells in the retina may become damaged, producing distortions in vision. Generally, early and intermediate AMD develop slowly, but can progress to exudative AMD or geographic atrophy, which results in significant loss of visual function over time.



The progression from early and intermediate AMD to exudative AMD is typically acute, occurring rapidly, in contrast to the slow progression of geographic atrophy. However, some forms of exudative AMD can be slow and indolent, with gradual vision loss. About 10% to 15% of adults with early and intermediate AMD will progress to exudative AMD and experience abnormal blood vessel growth under the macula. The growth of new blood vessels, known as angiogenesis or neovascularization, leads to fluid, and sometimes blood, leakage within the retina, followed by acute vision loss. Exudative AMD often causes scarring of the macula and retina, producing rapid and permanent loss of central vision in as little as three months.⁵



Barriers Experienced by People with AMD

The World Health Organization (WHO) defines health as “a state of physical, mental, and social well-being, not merely the absence of disease or infirmity.”⁶ Any measurement of a patient’s health must therefore include assessments of the patient’s quality of life. Patients with advanced AMD incur many visual problems that profoundly affect their quality of life. They score significantly lower than same-aged people without the disease across a variety of quality-of-life measurements, including activities of daily living (such as using the telephone, preparing food, and doing laundry), as well as with reading fine print and recognizing people. The more severe the vision impairment, the lower the scores for activities of daily living. People with AMD are also less likely to state that they are as healthy as others.⁷

The decrease in quality of life experienced by people with AMD is similar to that experienced by people with systemic diseases, such as cancer, coronary heart disease, and stroke.⁸ Patients with severe AMD, for example, report a deterioration in their quality of life that is comparable to that reported by patients who have end-stage prostate cancer or who have had a catastrophic stroke that has left them bedridden and requiring constant care.⁹

Another indicator of the impact various levels of visual impairment have on patients’ quality of life emerges from the results of utility-value studies, which ask patients to quantify what they are willing to trade of their remaining lifetime in return for perfect vision in each eye. One such study involving patients with AMD found that those with minor visual impairment would trade 11% of their remaining lifetime to restore their vision, while patients with severe impairment would trade 60%.¹⁰

Despite the impact of vision loss on patients’ quality of life, many clinicians have a poor understanding of this issue. Ophthalmologists, have been found to underestimate the impact of AMD on their patients’ quality of life by 96% to 750%.¹¹

It’s important to point out, however, that a severe drop in quality of life is not inevitable for people who lose their vision. Most of the millions of Americans with vision loss do not live in fear, but have found ways of adjusting their daily routines to have full — and fulfilling — lives. Unfortunately, only about 1 in 10 people experiencing age-related vision loss is ever referred by their physician to services and other support to help them learn to live independently in their communities.

The public fears vision loss, but is generally unaware of AMD. In a 2014 nationwide online poll, Americans cited eye disease as one of their most feared chronic disabilities.¹¹ Indeed, almost half (47.4%) of the respondents rated losing vision as the worst possible health outcome — equal to or worse than losing hearing, memory, speech, or a limb. That same survey, however, found that many Americans are unaware of specific important eye diseases and their risk factors. Only about half of the respondents indicated any awareness of AMD.

In addition to the burden that AMD imposes on the lives of individual patients and their families, the disease also exacts a large economic burden on the broader society. It’s estimated that the annual economic burden of vision loss and eye disorders in the United States is \$66.8 billion in direct costs (e.g., medical costs, medical vision aids, and direct services, including special education and assistance programs) and \$72.2 billion in indirect costs (e.g., productivity losses, long-term care, informal care, and costs of transfer and entitlement programs).¹² Only three chronic diseases — cancer, heart disease, and hypertension — impose higher economic burdens.¹³

Paradigm Change: Anti-Angiogenic Therapies

Angiogenesis research has made dramatic advances since the late 1990s that have led to the development of breakthrough treatments for patients with exudative AMD. Advances in angiogenesis research have led to the identification of anti-angiogenic approaches to treating a variety of diseases, including cancer, skin diseases, and retinal disorders such as exudative AMD. More than 10,000 laboratories around the world are currently involved in angiogenesis research, supported by national research funds, industry, and philanthropy. The ability to intervene in the process of angiogenesis has led to important advances, particularly in the last 15 years, which have had a major impact on people’s lives. Less than two decades ago, patients diagnosed with exudative AMD almost always became functionally blind. Today, exudative

AMD is a highly treatable condition and many people do not lose their vision thanks to these anti-VEGF therapies. In fact, Danish researchers found that the use of anti-angiogenic drugs led to a 50% plunge in the incidence of legal blindness attributable to exudative AMD.¹⁴

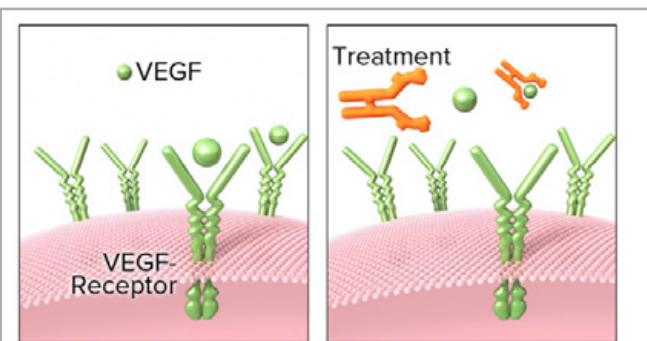


Figure 4. How Anti-VEGF treatment binds to VEG-F receptors in the eye.

In December 2004, the U.S. Food and Drug Administration (FDA) approved pegaptanib, the first angiogenesis inhibitor for exudative AMD. Clinical trials showed that intravitreal injections of pegaptanib slowed the rate of vision loss caused by exudative AMD.¹⁵ This anti-angiogenic therapy became recognized as an entirely new class of disease treatment.

An even more effective drug, ranibizumab, was approved for the treatment of exudative AMD in the United States in late 2006. Ranibizumab, as well as pegaptanib, interferes with a small protein known as vascular endothelial growth factor (VEGF). This growth factor stimulates angiogenesis and promotes vascular permeability (the passage of water and other small molecules through a blood vessel's wall), two processes that play a major role in the development of

on the chart. In addition, up to 40% of those treated with monthly ranibizumab for a year experienced an improvement of 15 or more letters (3 lines) in visual acuity.¹⁶

For the first time, physicians could offer people the opportunity to preserve their vision, and, in some cases, reverse a significant portion of their vision loss. The major drawback to this new therapy, however, was its price tag, costing about \$2,000 per injection per eye. Additionally, the monthly in-office injections require transportation and logistical burdens on patients and their caregivers.

In 2011, the FDA approved a third anti-angiogenic drug, called aflibercept, for the treatment of exudative AMD.¹⁸ It is based on a novel drug technology that fuses binding domains from two proteins (VEGFR1 and VEGFR2) to the Fc fragment of an IgG molecule to neutralize not only VEGF-A (like ranibizumab and bevacizumab), but also proteins such as VEGF-B and placental growth factor (PlGF). Aflibercept can be administered by intravitreal injection every other month, following three initial monthly injections. Clinical trials comparing ranibizumab with aflibercept show both drugs are similarly effective at stopping disease progression and restoring some portion of visual acuity, with fewer total injections for aflibercept.¹⁹

Before ranibizumab was approved, retina specialists began experimenting with another anti-VEGF agent, bevacizumab, which was approved by the FDA for the treatment of colorectal cancer in 2004 (and later for other types of cancer). Bevacizumab is a larger molecule, known as a monoclonal antibody, from which ranibizumab, a monoclonal antibody fragment, is derived.



Figure 5. Leona Trinin shares her perspective on living with AMD.

exudative AMD. Clinical trials demonstrated that 95% of patients treated with a once-monthly intravitreal injection of ranibizumab maintained their vision as long as the injections continued over the course of the trial.^{16,17} "Maintaining vision" meant that their ability to read a vision chart declined by no more than 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, or three lines

Bevacizumab is not indicated for eye diseases, and has not been FDA-approved for use in the eye. Nonetheless, it has been shown to be clinically effective for the treatment of exudative AMD in a large randomized clinical trial funded by the National Eye Institute,²⁰ and is used "off label" for this purpose at a cost of about \$50 to \$75 per intravitreal injection. (A drug is used "off-label" when it is prescribed for a use not approved by a country's regulatory agency.) When treatments are used off-label, patients should be properly informed of safety risks. Because it is produced in large vials for cancer treatments, bevacizumab must be divided by a compounding pharmacy into much smaller quantities for treating the eye. There have been numerous documented cases of infection from bevacizumab's use in the eye, likely due to the preparation of the solution and not to the molecule itself.²¹ In addition, research has found significant variations in the concentration of proteins in bevacizumab samples taken from various pharmacies.²² Clinical trials comparing ranibizumab with bevacizumab have suggested that both drugs are similarly effective at stopping disease progression and restoring visual acuity, at least when dosed monthly during the first two years of treatment.

Session 1: Patient-Centered Outcomes in Wet AMD

Identifying and Meeting a Need

By 2009, anti-VEGF therapies had revolutionized the treatment of exudative AMD — and the fields of optometry and ophthalmology. Given these remarkable treatment advances, the Angiogenesis Foundation believed it was important to bring the AMD stakeholder community together to review the progress made, the challenges faced, and the questions that still needed to be answered to best meet the needs of people living with exudative AMD. The Foundation convened a series of expert summits around the world on exudative AMD. (See Table 1.) The latest of these summits — the National Summit on Patient-Centered Outcomes in Exudative Age-Related Macular Degeneration — was convened in Boston on October 27, 2017. Its participants consisted of patients, caregivers, researchers, national leaders in vision advocacy, and clinicians. As with the earlier summits, this event was not a traditional scientific meeting, rather, it was an interactive, professionally moderated series of presentations and roundtable discussions aimed to establish a dialogue and consensus among the participants. This white paper report provides an overview of the key points raised and discussed during the summit.

AMD Summits Convened by the Angiogenesis Foundation

November 2011	International Expert Summit for Age-Related Macular Degeneration, Berlin, Germany
March 2012	Latin American Exudative AMD Coalition Expert Summit in Bogota, Colombia (in partnership with the Pan-American Retina & Vitreous Society)
July 2012	Australian Exudative Age-Related Macular Degeneration Coalition Expert Summit, Sydney, Australia (in partnership with the Macular Disease Foundation Australia)
February 2013	Asia-Pacific Exudative AMD Coalition Expert Summit, Hong Kong
June 2013	Advocating for the Improved Treatment and Outcomes for Exudative Age-Related Macular Degeneration, Berlin, Germany
August 2017	National Expert Summit on Improving Long-Term Patient Outcomes for Exudative Age-Related Macular Degeneration, Cambridge, United States
October 2017	National Summit on Patient-Centered Outcomes in Exudative Age-Related Macular Degeneration

Table 1. AMD Summits Convened by the Angiogenesis Foundation

The Angiogenesis Foundation

Founded in 1994 and headquartered in Cambridge, Massachusetts, the Angiogenesis Foundation is focused on advancing the clinical benefits of angiogenesis and anti-angiogenesis therapy. The Foundation is the premier nonprofit organization dedicated to helping people lead healthier, longer lives through angiogenesis-based treatment and prevention. As a nonprofit, third-party scientific organization, the Angiogenesis Foundation is independent of any individual, institution, or commercial entity.

The Angiogenesis Foundation has been supporting innovation in angiogenesis-based medical therapies for nearly a quarter century. Thanks in part to its programs aimed at advancing research, advocacy, and education, there are now more than 32 FDA-approved drugs and medical devices used to control angiogenesis. Angiogenesis-related research continues across a variety of fields in which the control of the vasculature is critical, including cancer, chronic wounds, ophthalmology, and cardiovascular disease.



Figure 6. Participants of the National Summit on Patient-Centered Outcomes in Exudative Age-Related Macular Degeneration

The National Summit on Patient-Centered Outcomes in Exudative Age-Related Macular Degeneration opened with patients discussing how their life had changed as a result of their diagnosis of exudative AMD, their treatment protocol, and the disease's progression.

Patient Stories

Leona Trinin: The patient said that having exudative AMD has “drastically” altered her life, forcing her to move out of her former house so that she can live near one of her children. She remains able to live independently, but daily tasks are becoming increasingly difficult, including doing

such simple things as putting a plug into a wall socket and bringing food from a plate to her mouth. Her inability to use the computer has left her feeling “that I’m not in this century at all,” she said. Vision loss has also forced her to curtail her creative writing pursuits, a factor that has greatly diminished her self-identity. Her social life has been negatively impacted as well, for she has had to give up driving and must now rely on family, friends, taxis, and busses for her transportation. “I have less autonomy, less freedom to move through the world,” she said. Yet, although the loss of her vision has led to moments of depression, the patient has also managed to keep her sense of humor. “I’m a macular degenerate,” she quipped.

“I have less autonomy, less freedom to move through the world. ... Sometimes I feel that I’m not in this century at all.” — Leona Trinin

The patient was still teaching 20 years ago when she was first diagnosed. At a regular ophthalmology exam, she was diagnosed with dry AMD. The ophthalmologist didn’t tell her much about the condition, other than she wouldn’t notice the effects of it for a while. The patient eventually switched to an ophthalmologist who specialized in AMD. When, during a routine exam, he saw that her condition had transitioned to exudative AMD in one of her eyes, he sent her to a retina specialist. She then had laser treatment, which took away the central vision in the affected eye. Later, she had anti-VEGF injections, although she at first had to travel to another city by train to receive them. She said that she was fortunate that the cost of the injections was not an issue, as she was old enough to qualify for Medicare by then.

The patient said she missed the symptoms of a bleeding episode in her affected eye — one that led to scarring — because she mistakenly thought the symptoms were the result of a cataract. She had not been adequately informed, she said, about how to identify such an episode and that it required emergency treatment. When she experienced a second bleeding episode, she sought immediate treatment, with more successful results. Getting to treatments remains a major logistical burden, but the patient pointed out that she is more fortunate than many patients because she has family, friends, and a hired assistant who can drive her to and from the appointments. The patient expressed her amusement (and a bit of annoyance) at the observation that her ophthalmologist’s waiting room contains piles of magazines, none of which she (and, presumably, the other patients with exudative AMD) can read.

The patient ended by underscoring that exudative AMD has not only affected her own life profoundly, but also the lives of her family members. It has changed her family’s dynamics, priorities, and budget, she said. She strongly recommends that clinicians add to their staffs a social worker and/or psychologist who could help the patient’s family or satellite group of close friends better cope with the changes to their lives that come with caring for a loved one with

exudative AMD.

Eloine Vieira: The patient has lived with dry AMD for more than five years, and was diagnosed with exudative AMD within the past four months. The exudative AMD diagnosis was particularly upsetting, she said, as she has significant hearing loss and relies on lip reading. She worries about the isolation that will come if she loses both her vision and her hearing.

The patient considers herself extremely fortunate, however, to have had her exudative AMD diagnosed very early. More than five years ago, through her retina specialist (an ophthalmologist with a sub-specialty in diseases and surgery of the vitreous body of the eye and the retina), she was enrolled in a clinical trial that was testing the effectiveness of a home monitoring device (ForeseeHome AMD Monitoring Device) designed to catch the progression from early and intermediate AMD to exudative AMD at its earliest stage, when the chances of preserving vision are greatest. After the study ended, the patient was permitted to keep her device. She continued to use it as instructed, taking a quick test every day; to check for tiny changes in her vision. Fortunately, the ForeseeHome device detected changes that indicated a transition to exudative AMD. The information was automatically forwarded to the patient’s retina specialist, who immediately scheduled her for anti-VEGF injections to preserve her vision. The doctor told the patient that if the diagnosis had been delayed another four or five months, she would have lost some vision. “To me, it was a miracle,” said the patient.

When asked about how much she has understood about her treatment regimen through the years, the patient said that she now has a general idea of her treatment and how it protects her vision. When she was originally diagnosed with dry AMD, however, her ophthalmologist at the time didn’t pass on to her the seriousness of the condition, and she was not referred to a retina specialist for some time.

Peter Jenney, M.D.: The patient was first diagnosed with exudative AMD in 1996. He had noticed that straight horizontal lines suddenly appeared wavy, so he went to see an ophthalmologist. At that time, the only treatment for exudative AMD was laser photocoagulation. Unfortunately, the treatment caused the patient to lose his central vision in that eye. Sixteen years later, the patient noticed that straight lines were appearing wavy in his untreated eye. He went to see his doctor, and was sent to a retina specialist that very day. The patient was relieved that a new treatment — an anti-VEGF injection — was available, and he has been receiving injections ever since, first at monthly and later at 6-week intervals. Because the patient has only one “good” eye, his retina specialist is strict about not extending the treatment interval to longer than 6 weeks. The patient said the vision in the eye currently being treated is 20/40 and stable, so he feels fortunate. He can still drive, although his wife drives him to his retina specialist’s office on treatment days.

The patient is a medical professional; therefore, exudative AMD and its treatment is a bit less mysterious to him than it is to many other patients with the condition. He also said his own medical training makes it easier for him to communicate successfully with his retina specialist. He believes strongly that patients must take responsibility for telling their healthcare team what treatment works best for them.

Additional patient perspectives: Other patient participants in the summit also shared their experiences with exudative AMD and its treatment. The patients described how “everything has changed” in their lives, including being able to do what were once ordinary acts, such as putting toothpaste on a toothbrush. One patient, a 91-year-old who has had exudative AMD for five years, said she can no longer see and now relies on her daughter for help with all her daily activities, starting with making coffee in the morning. Many activities that previously gave her pleasure — such as watching her favorite TV soap operas and participating in the cooking for her large, extended family at holidays — are no longer possible, she added.

The woman’s daughter spoke about how her mother’s vision loss had brought dramatic changes to her own life. Because her mother can no longer be left on her own, the daughter had to give up her job. The daughter also underscored the importance of not missing appointments with the retina specialist. She had not realized that her mother’s vision could worsen — permanently — by missing three months of treatment, which is what happened when the mother travelled out of the country to visit relatives. “Educate yourself on what AMD is so you can understand the treatment,” the daughter advised other caregivers.

Several of the patients spoke about the psychological effect the disease has had on them. “I went through a period when I was depressed about it,” said one. “But then I realized you just have to live with this thing and do the best that you can.” All said that the problems associated with anti-VEGF treatment — such as getting someone to take them to the retina specialist’s office and the discomfort of the injections — can be burdensome, but that such difficulties are far outweighed by the treatment’s benefits. As one patient put it: “It’s uncomfortable for a day, but I try not to let it be the focus of my life.” “I’d rather get the shots than not be able to see,” said another.

“I went through a period when I was depressed about it. But then I realized you just have to live with this thing and do the best that you can.”
— Nita Goldstein

General Discussion about Treatment Response

Between 5 percent and 10 percent of patients who receive anti-angiogenic drugs do not respond to the treatment,²³ and this non-response is particularly prevalent among patients with other chronic diseases. Over time, various forms of incomplete response, in some cases due to inadequate treatment, can affect between 19 and 67 percent of exudative AMD patients. Not responding to treatment can be incredibly discouraging for patients and these statistics underscore the need to integrate behavioral mental health services into each patient’s exudative AMD treatment plan early on, so that patients will be prepared if they do not respond to the anti-VEGF drugs. Patients also need to be told that if they don’t respond to the first anti-VEGF drug they are given, they might respond to another and that it can take several months for some patients to respond to treatment. Response to treatment can vary from cessation of neovascularization and preservation of existing visual acuity to an improvement in visual acuity. Expectations about treatment, therefore, need to be clearly communicated to patients from the start. Clinicians also need to do a better job of emphasizing to patients that every scheduled anti-VEGF injection is important to maintaining their vision, and that the earlier they receive treatment, the more vision they are likely to retain.

Patients with exudative AMD would also greatly benefit from having a social support network, including someone who can go to every appointment with them and take notes on the advice and directions provided by healthcare professionals. This support is of particular importance during the initial diagnosis meeting, where the patient must take in a lot of information and emotions can run high. Many patients lack such social support, however, and even when they do have it, family members cannot always attend every appointment. Clinicians could help families provide support to loved ones by encouraging them to “sit in” on medical visits via telephone.



Figure 7. Eloi Vieira shares her experience of AMD.

Session 2: Patient-Centered Outcomes Research (PCOR) in Wet AMD

Impact of Low Vision on Daily Life and Independent Living for Patients with Exudative AMD

“Patients are the gold standard for measuring quality of life.” — Gary Brown, MD

People with exudative AMD have reported experiencing several profound types of losses as a result of their decreased vision:

- Loss of independence. They often can’t drive, shop, make meals, or take medications.
- Loss of privacy. They often can’t read mail or pay bills and need help with bathing.
- Loss of self-esteem. They often can’t see faces or dirt in their homes or on their clothes, which can cause embarrassment.
- Loss of financial independence. They incur added costs for caregivers, travel, and housing, and many are also forced to quit their jobs, resulting in years of lost wages.

No wonder, then, that 30 percent of people with exudative AMD have clinical depression — about twice as high as in an age-matched population. Clinicians can make a huge difference in the lives of their patients with exudative AMD by catching and treating that depression. Depression can often be avoided or reduced by connecting patients to community services, including low-vision therapy, orientation and mobility training, and independent living supports. Isolation is a key predictor of depression; thus, helping patients join a support group and/or re-engage with their community plays a significant role in preventing and relieving depression.

Good quality-of-life tools are essential for assessing patient-centered treatment outcomes. They enable clinicians and patients to identify the most effective treatments, in terms of what matters most to patients. Quality of life in relation to vision has been measured by asking people first how long they expect to live and then how much of the theoretical remaining time in their life they would hypothetically trade in return for a treatment that would guarantee normal vision in each eye permanently. Research using such measurements shows just how crucial vision is to quality of life. Yet clinicians often fail to appreciate the significant effect that their patients’ vision loss is having on their quality of life.⁹ Surveys have also shown that the general public does not grasp the devastating effects that exudative AMD has on

people’s lives, attributing total blindness with only an 18% reduction in quality of life — one-fourth of the 74% reduction cited by patients who have gone blind as a result of exudative AMD.

A cost-utility analysis of large clinical trials showed that the use of anti-VEGF therapy provided a quality-of-life gain of 16.3% for patients being treated for exudative AMD in both eyes.²⁴ Early treatment is essential for reducing both the human and economic costs associated with exudative AMD. Research has shown that quality-of-life gains are higher with anti-VEGF therapy when the treatment is started early.

Cost-effectiveness analysis is another helpful tool in measuring the benefits of available medical interventions in ophthalmology, with a focus on the financial burdens of vision loss and the cost savings involved in preserving vision. The clinical inputs that go into cost-effectiveness analyses in ophthalmology, however, need to be standardized, since most current analyses are not comparable. Costs associated with AMD-related vision loss are huge, up to \$83,000 a year for patients with total blindness. Those costs include direct medical costs, both ophthalmologic and non-ophthalmologic, but the greatest costs associated with exudative AMD (67%) are non-medical, such as for caregivers, transportation, and residence changes.²⁵ A recent study conducted by the Association for Research in Vision and Ophthalmology (ARVO) showed that from 2008 to 2015, the U.S. government saved an estimated \$9.0 billion and exudative AMD patients saved approximately \$2.2 billion from the use of optical coherence tomography (OCT) to guide optometrists and ophthalmologists in recommending personalized anti-VEGF treatment. This information helps government agencies to assess their return on investment for research grants; in this case, grants awarded toward OCT research yielded a 21-fold return in government cost savings.²⁶ This type of analysis shows that technologies that help doctors personalize the frequency of treatments, such as OCT, can help guide decision-making and improve outcomes while minimizing unnecessary drug spending. However, this information must be considered in concert with patient-centered outcomes, including long-term vision outcomes, as the medical and societal costs of vision loss outweigh the costs of vision-preserving treatments.

With the knowledge that quality-of-life is how patients with exudative AMD measure and value treatment outcomes, what can the disease’s stakeholders — patients, patient-advocates, caregivers, clinicians, researchers, and policymakers — do to help inform patient-centered outcomes research?

***“If the care isn’t for the patient, who is it for?”
— Alan R. Morse, JD, PhD***

Patient-Centered Outcomes Research in Vision

Patient-centered care establishes a partnership between patients and practitioners to ensure that decisions respect patients’ wants, needs and preferences for their own care. It also ensures that patients have the education, support, and information they need to make effective decisions and that patients are recognized as the only valid source of information about many aspects of quality of care. This concept — that decisions about care should be made by patients rather than doctors — is often considered radical. Physicians commonly interrupt their patients after 18 seconds — that is, before the patient finishes explaining their problem.²⁷

Researchers are measuring patient-reported outcomes for exudative AMD with the same instruments today as they used three decades ago. Best corrected visual acuity (BCVA) is the most commonly used outcome measure in vision research, but it is essential to include other outcomes that are relevant to patients, including measures of visual function (such as contrast sensitivity and reading speed) and patient-reported outcomes (such as the National Eye Institute Visual Function Questionnaire-25 and the Activities of Daily Vision Scale). (See Table 2.)

The Patient-Centered Outcomes Research Institute (PCORI), which was authorized by Congress in 2010 as part of the Patient Protection and Affordable Care Act, is currently tasked with funding patient-centered research. The focus of that research is on what informed patients value, while recognizing that segments of the population may look at treatment choices very differently. All treatment comparisons and outcomes are viewed through the lens of their relevance and importance to patients. Patients with exudative AMD deem visual function (how well a person is able to use their vision to accomplish everyday tasks) to be most relevant. They don’t care if there is a little bit of fluid in their eye.

What patients want to know is what that fluid means in terms of their functional vision. Will they be able to continue with their everyday activities? PCORI represents an excellent untapped funding resource for vision-related research projects.

Examples of Quality-of-Life Survey Instruments Used in Ophthalmology

National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25)	This questionnaire “measures the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases.”
Rand Medical Outcomes Study (MOS) Short Form 36 Item Survey	Commonly known as the SF-36, this “set of generic, coherent, and easily administered quality-of-life measures” is useful for evaluating the functional status of individuals with vision loss.
Instrumental Activities of Daily Living Scale (IADL)	IADLs have been used for several decades to assess a person’s ability to perform daily living tasks that enable an individual to remain independent, such as using a telephone, doing laundry, preparing food, and handling finances.
Functional Reading Independence (FRI) Index	This patient-reported outcome measure assesses the reading function of individuals with geographic atrophy due to age-related macular degeneration.

Table 2. *Examples of Quality-of-Life Survey Instruments in Ophthalmology.*

General Discussion

What treatment outcomes are most important to patients with exudative AMD? And what tools are needed to measure functional vision and the quality-of-life factors that are important to patients?

Treatment Outcomes Most Valued by Patients

Interpersonal relationships.

Loss of vision often compromises and alters a patient’s relationships with family and friends. The family reorganizes around taking care of the patient, a change that can place an enormous psychological and emotional burden on everyone involved. Friends, too, may reorganize their contacts with the patient — often by not including the patient in activities and events as frequently as before. Even programs specifically designed for older people, such as at churches and community centers, frequently fail to accommodate people with vision loss. As a result, patients with exudative AMD find they can no longer participate in activities and communities that were once at the center of their social life. In addition, family and friends sometimes fail to realize — or empathize — with the extent of the patient’s vision loss. (One patient at the summit spoke about how her bridge club became annoyed when she brought a bright light to the table.) The loss of central vision, which takes away the ability of the patient to see the faces of grandchildren and others, deepens this sense of social isolation.

Patients with exudative AMD value treatment outcomes that enable them to feel socially connected with family and friends.

Identity and independence. Patients with exudative AMD often say that the disease has caused them to lose their identity and sense of purpose. Due to their vision loss, some patients are forced to give up their jobs at an earlier age than planned, for example. They may also lose their ability to volunteer and contribute to their community. (“I went from being a giver to being a taker,” said one patient at the summit.) Patients with exudative AMD also say they greatly miss their sense of independence. Mobility, both inside and out of the home, is significantly reduced. Patients find it difficult to both

cook and exercise — hurdles that are particularly frustrating for them, given that research suggests that a healthful diet and regular exercise may be protective against developing AMD or slowing its progress.^{28,29,30} Vision loss further limits people’s independence because it affects their ability to interact with technology and “feel part of this century,” as one patient put it.

“I went from being a giver to being a taker.”
— Leona Trinin

Patients with exudative AMD value treatment outcomes that enable them to maintain their identity and their independence.

Dietary Interventions for AMD

The Angiogenesis Foundation encourages research and education on the preventative potential of diet for AMD patients and those at risk for developing AMD. Below is a list of recent research findings on AMD and dietary factors:

1) Fish Consumption:

- a. Higher intakes of fatty fish (source of both EPA/DHA) may prevent or delay the occurrence of visually significant intermediate AMD.³¹
- b. In women, regular consumption of fish high in EPA/DHA was associated with a significantly decreased risk of AMD incidence and may be beneficial as a means of primary prevention. Women who consumed one or more servings of fish per week had a relative risk reduction of 42% compared to women who consumed less than one serving of fish per month.³²

2) Vitamin Supplements:

- a. Omega-3 Supplementation: Patients with exudative AMD being treated with anti-VEGF injections who took omega-3 supplements had significantly lower levels of vitreal VEGF-A when compared to non-supplementing patients receiving the same treatments.³³
- b. Lutein and DHA Supplementation: Patients with early AMD who took lutein and DHA supplements had significantly increased macular pigment ocular density (MPOD) compared to patients with early AMD given placebo over the course of one year. This increase in MPOD may aid in prevention of advanced stage AMD.³⁴
- c. Lutein and Zeaxanthin Supplementation: Patients with early AMD who take lutein and/or zeaxanthin have increased MPOD, and supplemental lutein enhances retinal sensitivity.³⁵

3) Mediterranean Diet:

High adherence to a Mediterranean diet has been associated with a lower prevalence of early AMD and a 26% reduction in the risk of progression to exudative AMD.³⁶ The traditional Mediterranean diet is characterized by high consumption of plant foods, moderate consumption of fish, olive oil as the primary source of fat, a low to moderate consumption of dairy products, and low meat intake.

Safety. As vision diminishes, a patient's personal safety becomes increasingly problematic. The dangers are ubiquitous, from being unaware that a stove is turned on to not being able to read the instructions on a medication bottle. Fears regarding personal safety lead patients with exudative AMD to become even less mobile, and that, in turn, increases their sense of isolation. Many types of magnifiers and other daily living aids are available to people with low vision, but Medicare and other insurers do not always cover their costs. Some healthcare systems send occupational therapists, physical therapists, and workmen (to install safety equipment) into homes to help ensure better patient safety. Nonprofits also receive some government money to help people with vision loss safety-proof their homes, but the funding is too small to meet the growing need for such services. Emerging technologies offer vision enhancements or "live" help to low-vision patients, but these technologies require training and often come with a steep cost.

Patients with exudative AMD value treatment outcomes that enable them to feel safe in their home and other environments.

Financial stability. Diminished vision can lead to a significant decline in a patient's economic resources. Patients with exudative AMD who have to take an earlier-than-planned retirement lose not only the income they would have earned, but also, in many cases, contributions to their pension. In addition, as the disease progresses, a family member or other loved one may have to quit his or her outside job to help the patient with basic daily living tasks, such as cooking and bathing. The disease's economic burden thus gets extended to others in the family. Patients also have added medical expenses, as well as extra daily living costs related to transportation, caregiving, and moving to a different residence.

Patients with exudative AMD value treatment outcomes that help them maintain their financial security.

Measuring Functional Vision in Terms of Quality of Life

Some functional vision tools currently exist, but they aren't widely used — in part, because patients are unaware of these measures. One such measure is contrast sensitivity, which is especially important in situations of low light or glare, when the contrast between objects and their background is often reduced. Another is dark adaptation, which is important for any situation in which an AMD patient with impaired dark adaptation goes from a well lit environment to dimly lit surroundings. Retaining contrast sensitivity and dark adaptation is imperative for patients who want to keep driving because it impacts their ability to drive at night. Patients seldom raise functional questions or concerns with their ophthalmologists,

however. Nor are ophthalmologists inclined to test for anything other than visual acuity, particularly given the time pressures of the office visit.

There are three main vision-related functions that patients with exudative AMD want to maintain: reading comprehension, depth perception, and facial recognition. Tools that would help measure and assess these functions — and the effect that various treatments have on them — are urgently needed. The measures must also reflect real-world experiences, and must always focus on improving the patient's quality of life.

"There is much that can be done. There is much that should be done." — Alan R. Morse, JD, PhD

Action Agenda for Future Research

- Conduct and fund comparative effectiveness research on available exudative AMD therapies that takes the following patient values into account:
 - o *Quality of life in terms of:*
 - Interpersonal relationships
 - Identity and independence
 - A sense of personal safety
 - Financial stability
 - o *Functional vision in terms of:*
 - Contrast sensitivity
 - Dark adaptation
 - Night vision
 - Reading speed and comprehension
 - Depth perception
 - Facial recognition
- Work to standardize clinical inputs and quality of life measures that go into cost-effectiveness and comparative effectiveness analyses for AMD-related research.
- Conduct and fund AMD-related research that investigates outcomes success of patient-centric, prevention/early detection/treatment approaches.
- All points in the disease's progress, from prevention through treatment.
- Conduct and fund AMD-related research on improved drug delivery systems.
- Conduct and fund research on the development of AMD-related biomarkers.
- Advocate for a vision module in the National Health and Nutrition Examination Survey (NHANES) and in other national health surveys.

Session 3: Achieving Prevention and Early Detection

Several factors could help with the prevention and early detection of AMD.

Raising awareness. Public awareness of AMD remains low. The disease needs a major, coordinated, ongoing public awareness campaign. It should emphasize both prevention and the importance of screening. It also needs to reflect language and cultural differences throughout the country. Such a campaign would benefit from having one or more “celebrity” spokespeople to “put a face on the disease.” The Entertainment Industries Council could be approached to help promote accurate information about AMD in scripts for television and film. Such a campaign has been remarkably successful in Australia, and that effort could be a model for developing one for the United States.

Emphasizing routine comprehensive eye examinations by an eye doctor (optometrist or ophthalmologist). By the time individuals recognize a problem with their vision (such as by using an Amsler grid at home) and get seen by a retina specialist for treatment, they may have already experienced some permanent vision loss. Seniors and those with a family history of AMD need to have access to regular well eye exams, and Medicare and other insurers need to fully cover these exams. The public must also be educated about why such exams are important and when (at what age) they should begin on a regular basis.

Educating caregivers. Caregivers are all too often forgotten when treatment plans are devised for patients with exudative AMD. Caregivers as well as patients need to be educated about AMD and its treatment. With the patient’s permission, they also need to be included in descriptions and explanations of what the progression of the disease might be and how it will impact not only the patient’s life, but theirs as well.



Figure 8. Peter Jenney, M.D. listens to presentations.

Encouraging the development — and use — of home screening technologies. Clinicians and the public alike need to be educated about clinically proven, FDA-cleared machines (such as the ForeseeHome device) that are providing early detection of the progression from dry to exudative AMD. Smartphone apps that test and monitor vision changes also need to be more widely promoted. Local drugstores could also offer vision tests, as they do with blood pressure tests.

Identifying biomarkers. A major advance in the early detection of exudative AMD would be the identification of blood biomarkers. Researchers have already identified several potential genetic markers, which may help to identify individuals who are at high risk of developing the disease, but more research is needed.

Populating and utilizing research databases. Little is understood about the causes of AMD. Nor is it clear why some treatments work for some patients but not for others. A large patient database is needed to increase knowledge about both issues. Two large, vision-related electronic health registries are currently available for data mining in the United States — the Vestrum Health Retina Research Dataset, which is an independent registry, and the IRIS (Intelligent Research in Sight) Registry, which is administered by the American Academy of Ophthalmology — but their data are separate and have been underused. A new database is in development and may be available in another three years. Such projects, however, are challenged by a lack of sufficient funding.

Including vision in national health surveys. Research into the causes of AMD must include surveys of people before they are diagnosed with the disease. If not, factors that cause the disease may be missed. Currently, the National Health and Nutrition Examination Survey (NHANES), which is administered by the Centers for Disease Control and Prevention, does not include a vision module. That omission needs to be corrected.

National Exudative AMD Patient and Caregiver Survey: Quantifying Experiences of Exudative AMD

In partnership with the American Macular Degeneration Foundation, the Angiogenesis Foundation is leading a groundbreaking initiative to survey patients receiving injections for exudative AMD and their caregivers. The Foundation analyzed 345 surveys and received 252 responses from patients with exudative AMD and 93 responses from caregivers. The respondents spanned 39 states across the U.S.*

Treatment Outcomes

With injections, most patients have stable or improved vision. 80% said their vision stabilized or improved. 20% said their vision worsened.

Treatment Schedules

Long term studies suggest that regular treatments, either once a month or every other month, will lead to the best vision outcomes. However, more than 20% of survey respondents are getting injections less than 6 times per year.

Missing Injections

64% of patients said that vision was their top health priority and 89% of respondents said making it to every injection appointment is important. While 66% have never missed an injection, 34% have missed an injection at some point and of those who missed an injection, 23% lost vision as a result. Most people who missed injections did so because of health reason.

Reliable Information

While 87% of patients are relying primarily on their doctor information, 40% of patients are also looking online for more information about AMD.

Early Detection

More than 95% of survey respondents agreed that you should have your eyes checked as soon as possible if you notice vision problems. 96% said If you’re getting injections, you have to stick to the recommended schedule - it’s critical for preserving your vision.

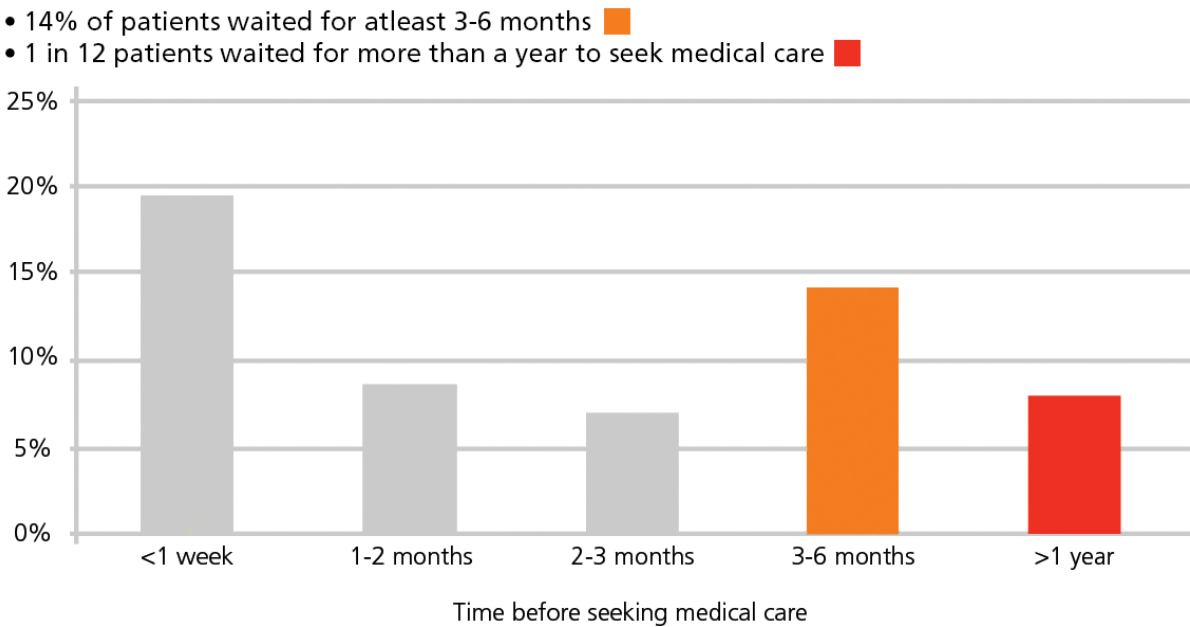


Figure 7. How long did patients wait to see their doctor about vision loss?

*This is an ongoing survey which began in January 2018; results published for this white paper analyzed surveys completed through February 28, 2018. Survey limitations: survey patients and caregivers were not randomized.

Session 4: Getting the Most from Treatment

What key barriers keep patients from getting the most from their treatments, and what actions are needed to improve the treatment experience — and treatment outcomes — for patients?

“Today, people living with wet AMD are able to maintain their vision thanks to groundbreaking anti-VEGF medicines. But we must raise awareness of the importance of early detection and intervention, receiving these medicines on a regular schedule, and the very real danger of undertreatment.” William Li, MD

Barriers to Getting the Most from Treatment

The chronic nature of the disease. Because exudative AMD is a chronic disease, both patients and clinicians may develop “treatment fatigue.” They may then be less inclined to demand strict adherence to the planned treatment protocol.

A lack of early detection. Functional vision is defined as how well an individual uses their vision to accomplish everyday tasks, such as driving, reading, or recognizing faces. It is generally accepted that visual acuity of 20/40 or better is the limit of functional vision. Yet, in the United States, the mean visual acuity at diagnosis of exudative AMD is 20/80, and recovery of functional vision is unlikely, despite administration of anti-VEGF agents.³⁷ There is further evidence of the lack of early detection in large, pivotal anti-VEGF trials. The proportion of patients who had better than 20/40 vision at the time of exudative AMD diagnosis was a mere 36% in one major clinical trial²² and 41% in another.³⁸ Clearly, a significant effort must be made to identify these patients earlier with the help of instruments like the ForeseeHome device.

A false sense of security. If patients are responding well to an anti-VEGF drug, they may mistakenly believe it would be okay to take a break from treatment. Other patients mistakenly believe that losing a small amount of vision is nothing to be concerned about, as future treatment will help them regain it.

Mismatched patient/clinician expectations. Even when the communication channels between patient and clinician are good, some patients may become discouraged if their anti-VEGF treatment doesn’t work right away, making them less likely to adhere to the treatment schedule prescribed to them by their clinician. It’s important that clinicians emphasize four points with their patients: 1) stabilizing vision with anti-VEGF treatments can take time and multiple injections; 2) the treatments are working when vision is stable, meaning it is not worsening over time; 3) if one

treatment is not effective, switching to another treatment option may be a valid option to stabilize vision; and 4) every scheduled injection is important for maintaining vision over the long term.

Geographic disparities. Most retina specialists practice in urban areas. As a result, people with exudative AMD who live in rural areas have difficulty accessing timely and consistent treatment. Lack of transportation in rural areas can make visiting a doctor even a few miles away impossible for some patients. Deliberate incentives should be developed to encourage retina specialists and other eye care professionals to practice in rural communities.

Isolation and depression. Whether people live in urban or rural areas, they may not have a network of family and/or friends to provide emotional and physical support as they grapple with the lifestyle and other changes associated with exudative AMD. When depression, which frequently accompanies vision loss, is added on, the sense of isolation can deepen. Both isolation and depression can keep patients from adhering to their treatment protocol, thus hindering its effectiveness at helping them maintain their vision. Helping patients with visual impairments gain access to specialized training and services is essential for both their physical and psychological health.

Additional health concerns. Patients with exudative AMD often have an additional health issue that requires their immediate attention (such as getting chemotherapy for cancer). Or a spouse or other family member may have a serious health issue. As a result, patients with exudative AMD may decide to put concerns about their vision “on the back burner” while they take care of the other health issue.

Non-evidence-based treatments. Some patients seek alternative interventions for their vision loss that have not been FDA-approved or supported with evidence from large randomized controlled trials, such as sub-threshold laser therapy, stem-cell therapies, microcurrent stimulation, acupuncture, and multi-vitamins (promoted as a cure, not just as a possible preventive measure). These interventions can lead to harm by delaying scientifically validated treatments and, in some cases, by causing direct physical injuries to the patient.

Miscommunication regarding clinician’s instructions. Patients with exudative AMD may receive written instructions in a form they cannot read, either because of their vision loss or because of cognitive disabilities or language barriers. Verbal instructions may also be difficult for patients to understand, due to hearing loss. In addition, patients may have physical conditions that interfere with their ability to follow their clinician’s instructions for home self care.

Weak partnerships between ophthalmology and rehabilitation communities. Patients would be more

compliant with their treatment for exudative AMD if they had easy and affordable access to transportation and vision aids. Rehabilitation should go hand in hand with treatment. It should not be an afterthought. When people undergo knee-replacement surgery, they are given comprehensive information about how to make their home safe during rehabilitation. Similar efforts need to be made for people being treated for exudative AMD.

Action Agenda

- Institute a massive, coordinated national awareness campaign about AMD, ideally with celebrity spokespeople, that differentiates vision loss associated with wet AMD from that associated with cataracts and other eye diseases.
- Encourage patients with AMD to take a lead in educating their children and grandchildren about the importance of prevention and early screening.
- Inform patients at start of treatment that if one anti-VEGF drug is ineffective, they can switch to a different one.
- Carefully set and re-set patient expectations to understand that vision stabilization means the treatment is working, and that vision may take time to stabilize.
- Encourage hospitals, clinics, community centers, and others to organize and facilitate low-vision support groups.
- With patients' permission, make it possible for caregivers to attend office visits to the retina specialist, including by phone, if necessary.
- Start educating about vision health in primary school. Include a unit on vision health (including a "hands-on" demonstration of the Amsler grid) in health education classes at both the primary and high school levels. The unit should include a discussion of foods that help promote healthy vision.
- Fund AMD-related research that investigates all points in the disease's progress, from prevention through treatment.
- Fund AMD-related research on improved drug delivery systems.
- Fund research on the development of AMD-related biomarkers.
- Fund AMD-related research on the cumulative effect of implementing progression-risk-reducing lifestyle changes.
- Empower and reimburse nurse practitioners to deliver more AMD-related information and services to patients.
- Fill time spent by patients in ophthalmologists' waiting rooms to deliver educational material on exudative AMD, with an emphasis on the importance of treatment adherence. Make sure the information is offered in an audio format.
- Develop ways of describing exudative AMD so that it sounds less ominous (perhaps by deemphasizing "degeneration") but without downplaying the importance of prevention, early detection and treatment adherence.
- Devise a "vision-health" program that could be administered by community health workers.
- Educate primary care physicians about the need to educate their older patients about exudative AMD. Have them pass out Amsler grids at annual checkups.
- Educate the public about the potential harms from using non-evidence-based interventions for vision loss.
- Develop strong partnerships between the optometry, ophthalmology, occupational therapy, and rehabilitation communities so that patients with AMD can get timely access to transportation, vision aids and other vision-related services.
- Prescribe rehabilitation therapy as a standard of care, and work with insurers to make such therapy reimbursable.
- Develop clinical-practice systems that refer each patient to a low-vision specialist to teach the appropriate use of low-vision devices; make sure these costs are covered by insurers.
- Encourage ophthalmologists and optometrists to use newly developed Web-based apps that help refer patients to vision rehabilitation services in their communities.
- Create educational tools with clear, simple messages for patients undergoing treatment to be distributed in retina clinics.
- Spread the word about the dangers of undertreatment and promote a positive attitude among patients to get the most out of their treatment.
- Promote early detection of exudative AMD by increasing the use of at-home monitoring devices, such as the ForeseeHome device.
- Increase access to regular well-eye exams, and support the full coverage of these exams by Medicare and other insurers. Also, educate the public about why such exams are important.
- Advocate for a vision module in the National Health and Nutrition Examination Survey (NHANES) — and in other national health surveys.
- Support incentives to encourage retina specialists and other eye care professionals to practice in rural communities.
- Build coalitions with stakeholders working to improve the lives of patients with other eye diseases. There is an urgent need to coordinate the educational efforts currently underway for all eye diseases and to increase access to resources that will assist patients and their families. The Angiogenesis Foundation can help facilitate this effort.

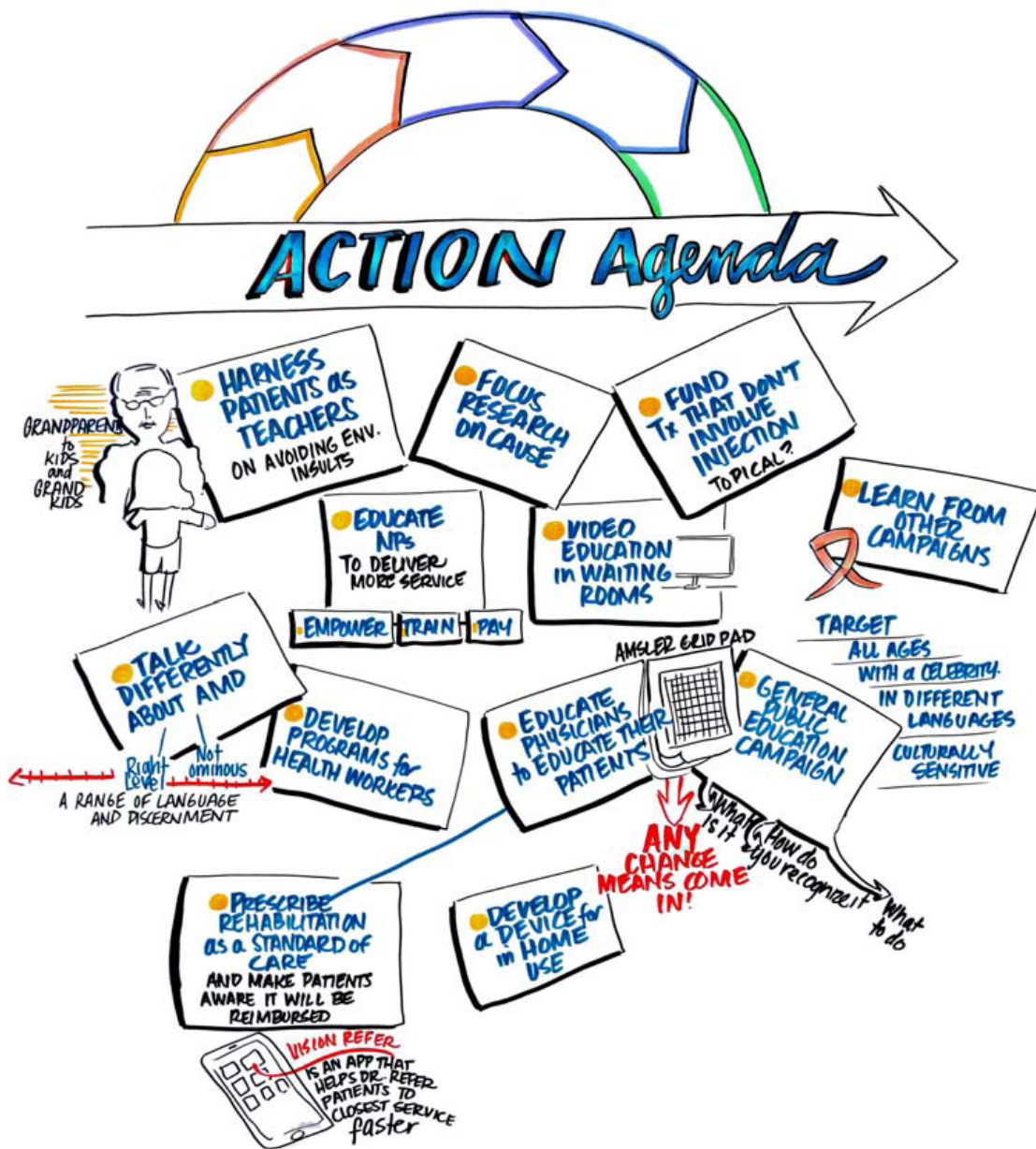


Figure 10. Graphical representation of the action plan developed by summit participants.

"Macular Degeneration" (a poem)

By Leona Trinin (AMD Patient)

It is not a curtain being pulled
Over windows closing out the light
Nor is it smoke filling the air
Until it's too foggy to see
It's far more insidious
Than that and tricky

*Bending and refracting
Blurring and bending*

In a room of table edges and venetian blinds
Door frames wiggle
Straight lines bend
Reminders that not all is well
The carpet of my retina is lumpy
And bumpy with drusen

*Slurring my sight
Slopping the lines*

An evil elf has spattered
Raindrop distortions on my window
My line of sight is not a line
At all but a snake
Insinuating his way
Between me and my goal

*Wobbling my directions
Shifting my fate*

Well-wishers praise longevity
What do they know of its cost?
A river running too far and too thin
Becomes muddied and sullied
As I wait for disaster
I wander in my garden
Where starburst blossoms
Explode on my retina

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