Advocating for the Improved Treatment and Outcomes for Wet Age-Related Macular Degeneration

A Report Based on an International Expert Summit
Convened in Berlin, June 2013

The Angiogenesis Foundation

KEY POINTS

1. Age-related macular degeneration (AMD), which primarily strikes people over the age of 50, is a leading cause of irreversible blindness in the world.

2. During the past decade, new diagnostic techniques and therapies, primarily in the form of VEGF-targeted antiangiogenesis drugs, have produced a true paradigm shift in the diagnosis and treatment of wet AMD—the most serious form of the disease. Patients now have effective treatment options that can help prevent vision loss, and in some cases, even restore vision.

3. With the rapid development of advances in the treatment of AMD, however, questions have risen about the best timing, dosing, and sequencing of treatments, as well as about other matters regarding the diagnosis and long-term management of the disease.

4. There is a persistent concern that the majority of patients with wet AMD are not receiving the optimal evidence-based care that they need to maintain vision and prevent progressive vision loss.

5. Clinicians, patient-advocates, academic researchers, the drug industry, payers, and policymakers need to work together to overcome the often formidable financial and social barriers to optimal AMD care, and to develop a continuum of care that is efficient, effective, and compassionate.

6. Looking to the future, a new generation of multi-skilled and independent AMD opinion leaders need to be identified and mentored, as almost all aspects of AMD prevention, diagnosis, and treatment are undergoing rapid evolution.

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Introduction

What Is AMD?

Age-related macular degeneration (AMD) is a disease associated with aging that gradually destroys sharp, central vision, thus causing people to lose their ability to read, recognize faces, drive, and do other daily activities. As its name implies, AMD affects the macula, which is located in the center of the retina, the light-sensitive tissue at the back of the eye. The macula is the part of the eye critical for seeing fine details.

There are two main types of AMD: early (with no or minimal vision loss) and late (with vision loss). Late can be further split into dry, or atrophic, AMD (also known as geographic atrophy) and wet AMD. Both the dry and wet forms can occur in one or both eyes, although the development of AMD in one eye increases the risk that AMD will develop in the second eye. Neither form of AMD is painful. As a result, the disease may not be diagnosed until it produces a marked loss in vision. When AMD affects one eye, it often goes undetected because the brain uses visual information from the second eye to compensate for any loss of vision in the first eye.

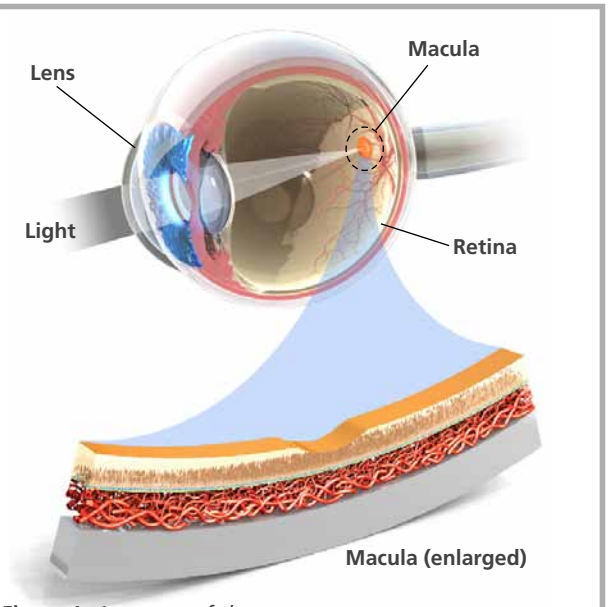

Figure 1. *Anatomy of the eye*

Early AMD, the more common form of macular degeneration, is characterized by the accumulation of drusen, small yellowish deposits that build up beneath the macula. Cells in the retina may become damaged, producing distortions in vision. Early AMD generally develops slowly, but can progress to late-stage dry AMD, which can impose significant vision loss.

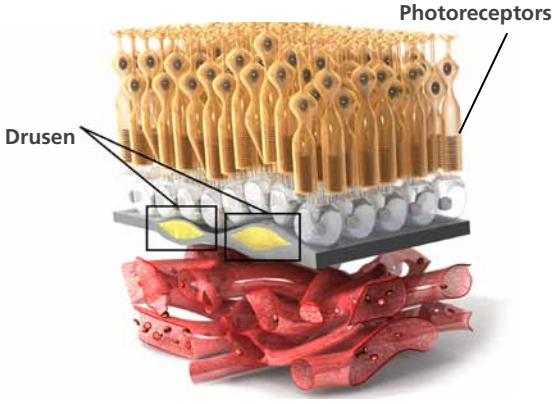

Figure 2. *Drusen deposits in the macula result in distortions in vision*

Wet AMD is the more serious form of the disease. For reasons that are currently unclear, 10% to 15% of adults with early AMD will progress to wet 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 blood leakage, which, in turn, can cause scarring of the macula and retina, producing rapid and permanent loss of central vision in as little as three months.[1]

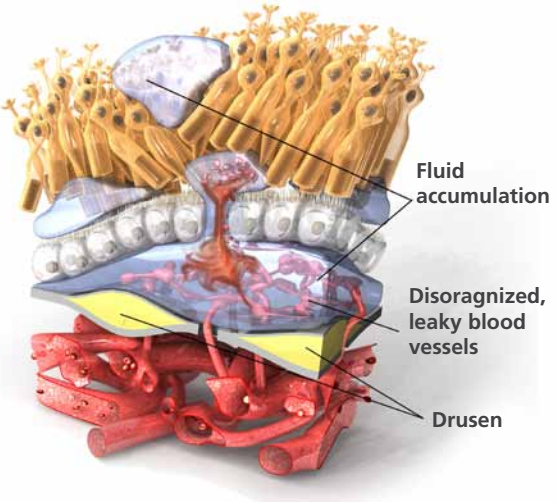

Figure 3. *New blood vessel growth leads to blood and fluid leakage that can scar the macula*

AMD is a leading cause of irreversible blindness in the world and the leading cause of blindness among people aged 65 and older in many industrialized countries.[2] Yet AMD is a relatively unappreciated disease. In 2007, the World Health Organization (WHO) estimated that wet AMD affects 3 million people globally and accounts for 8.7% of all blindness and 50% of blindness in industrialized nations.[3] WHO projects that these numbers will double by 2020 as populations age in many countries. This has driven the WHO, in partnership with the International Agency for the Prevention of Blindness (IAPB) to create the program VISION 2020: The Right to Sight, with the aim to eliminate avoidable blindness worlwide by 2020. (Learn more at http://www.iapb.org/vision-2020.)

Paradigm Change: Antiangiogenesis Therapies

Antiangiogenesis-focused research, which began in the early 1970s, made dramatic advances in the late 1990s.[4] Those advances culminated in the identification of specific antiangiogenic-related approaches to treating a variety of diseases, including cancer, skin diseases, and blinding disorders such as wet AMD. More than 10,000 laboratories around the world are currently involved in angiogenesis research and more than USD$5 billion has been invested globally in treatment-oriented research and development. This rapidly developing field has witnessed important advances, particularly in the last decade, that have had a major impact on the lives of patients. At the start of the 21st century, patients diagnosed with wet AMD almost always became functionally blind within two years. Today, vision loss and blindness from wet AMD is largely treatable with early, appropriate care. Indeed, since the advent of antiangiogenic drugs, the incidence of legal blindness attributable to wet AMD has plummeted by 50% in some countries.[5]

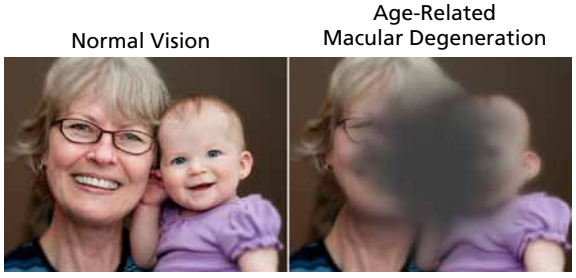

Figure 4. *Example of central vision distortion caused by wet AMD*

In December 2004, the U.S. Food and Drug Administration (FDA) approved pegaptanib, the first inhibitor of angiogenesis to be successfully developed for wet AMD. Clinical trials showed that intravitreal injections of pegaptanib slowed the rate of vision loss caused from wet AMD.[6] This antiangiogenic therapy, aimed at halting abnormal blood vessel growth, became recognized as an entirely new class of disease treatment.

An even more effective drug, ranibizumab, was approved for the treatment of wet 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 wet 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.[7,8] "Maintaining vision" meant that their ability to read a vision chart declined by no more than 15 letters, or three lines. 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.

For the first time, physicians could offer their patients the opportunity to save vision, and, in some cases, to reverse vision loss. The major drawbacks to this new therapy, however, were its price, about USD$2,000 per injection, and the burden that receiving a monthly injection places on the patient and caregivers.

Before ranibizumab was approved, retinal specialists began experimenting with another anti-VEGF agent, bevacizumab, which had begun to be used 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.

Bevacizumab is not indicated for eye diseases, and has not been approved by any regulatory authority for use in the eye. It has been shown, nonetheless, to be clinically effective for the treatment of wet AMD,[8] and is used off-label for this purpose at a cost of about USD$50 per intravitreal injection. (Off-label drugs are ones that are prescribed for a use not approved by a country's regulatory agency.) Because it is produced in large vials for cancer treatments, bevacizumab must be divided by a pharmacy into the much smaller quantities needed for treating the eye. Numerous documented cases of infection from bevacizumab's use in the eye have been reported, likely due to the preparation of the solution

and not to the molecule itself. 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.[8,9] Patients should be able to receive licensed therapies, but when other treatments are used off-label as an alternative, patients should be properly informed of safety risks.

On November 18, 2011, a third antiangiogenic drug, aflibercept, received its first global approval for the treatment of wet AMD from the U.S. FDA.[10] It is based on a novel drug technology that fuses binding domains from the proteins (VEGFR1 and VEGFR2) together to neutralize not only VEGF-A (like ranibizumab and bevacizumab) but also VEGF-B and PlGF. Aflibercept is designed to be administered by intravitreal injection every other month, following three initial monthly injections. Clinical trials comparing ranibizumab with aflibercept show that both drugs are similarly effective at stopping disease progression and restoring visual acuity, with fewer injections for aflibercept.[11] In 2012, aflibercept was approved for the treatment of wet AMD in many European, North American, South American, and Southeast Asian countries.

Past Summits: Identifying and Meeting a Need

By 2009, it had become clear that the advent of anti-VEGF therapies was revolutionizing the treatment of wet AMD—and the field of ophthalmology. Given these remarkable treatment advances, the Angiogenesis Foundation recognized that it was an opportune time for the AMD stakeholder community to take a step back and review the progress it had made, the challenges faced, and the questions that needed to be answered to best meet the needs of those with wet AMD.

As a scientific nonprofit organization whose mission is to conquer disease through the control of neovascularization, the Angiogenesis Foundation recognized that it was well positioned to play the role of the neutral facilitator of such a review. As its first major global step, it decided to assemble an interdisciplinary group of international leaders in AMD treatment and translational science. The International Expert Summit for Age-Related Macular Degeneration was convened in Berlin, Germany, in November 2011. The success of that meeting led to three other events, each of which focused on a specific region of the world: the Latin American Wet AMD Coalition Expert Summit in Bogota, Colombia, held in March 2012 in partnership with the Pan-American Retina & Vitreous Society; the Australian

Figure 5. *Moderated discussion at Expert Summit, Hong Kong, February 19, 2013*

Wet Age-Related Macular Degeneration Coalition Expert Summit in Sydney, held in July 2012 in partnership with the Macular Disease Foundation Australia; and the Asia-Pacific Wet AMD Coalition Expert Summit, held in Hong Kong in February 2013.

Experts at these summits identified, discussed, and achieved agreement on the rationale for antiangiogenic therapy to treat wet AMD; the role of early intervention in preventing wet AMD-associated blindness; the safety of repeated, long-term therapy; and the role of chronic antiangiogenic therapy for wet AMD. Each meeting resulted in a white paper that provided an overview of the group's discussions and the key steps necessary for advancing the treatment of wet AMD using anti-VEGF therapies to maximize impact and help the most individuals possible.

Deepening the Discussion

New advances in the treatment of wet AMD have continued to push forward at a rapid pace. As researchers, clinicians, and patients acquire experience with antiangiogenic therapies and as more studies involving these treatments have been published, new questions have arisen about the best timing, dosing, and sequencing of the treatments, as well as about other matters regarding the diagnosis and long-term management of the disease.

By the end of the first quarter of 2013, the Angiogenesis Foundation determined it was time for a second international expert summit on wet AMD, one that would delve deeply into the very latest research surrounding the detection, diagnosis, and treatment of the disease. That summit was held in Berlin on June 24-25, 2013. As with all the earlier summits, this event was not a traditional scientific meeting but, rather, an interactive, professionally moderated set of short presentations and roundtable discussions that aimed to establish a dialogue and agreement among the participants.

The summit opened with two short presentations. One provided an up-to-date summary of clinical trials on wet AMD treatments. The other offered a review of the best current clinical practices for managing wet AMD. Under the direction of the moderator, the assembled experts then spent the rest of the day engaged in a series of discussions that defined and prioritized what AMD stakeholders—patients, caregivers, clinicians, payers, and policymakers—value most in AMD care. A graphic recorder captured key points of the discussion, enabling the participants to visually review the content of their

Figure 6. *International Expert Summit, Berlin, June 24-25, 2013*

conversations as they worked through the tasks at hand. During the summit's second day, the experts focused on mapping current care pathways for the treatment of AMD, starting with patient awareness and moving through diagnosis, referral, treatment, and follow-up. Differences in care pathways among countries and regions of the world were noted and discussed, as were the general barriers that impede a smooth and effective care-pathway continuum and thus hinder successful treatment outcomes. Summit participants then turned their focus on identifying, mentoring, and training the next generation of AMD leaders. This was followed by a provocative discussion about where AMD treatment and research is headed in the coming years. This white paper provides an overview of the group's discussions.

The Role of the Angiogenesis Foundation

Founded in 1994 and headquartered in Cambridge, Massachusetts, the Angiogenesis Foundation is the world's first 501(c)(3) nonprofit organization dedicated to conquering disease with approaches based on angiogenesis, the growth of new blood vessels in the body. Its global mission is to help people benefit from the full promise of angiogenesis-based medicine, and to make life-, limb-, and vision-saving treatments available to everyone in need.

As a scientific organization, the Angiogenesis Foundation is independent of any individual, institution, or commercial entity, and, as such, it takes a unique approach to achieving its mission to help people lead longer, better, and healthier lives. It has helped propel innovative research involving both angiogenesis inhibitors and stimulators. Although much of this research has been pharmacological, promising studies involving nutrition and biomarkers are also being actively pursued. In addition, the Angiogenesis Foundation is constantly looking for ways to innovate patient-centered care pathways.

Angiogenesis-related research is being conducted across a remarkably wide variety of disease states. In recent years, for example, profound angiogenesis-treatment breakthroughs have been discovered in oncology, wound care, and cardiovascular disease. But nowhere has the promise of angiogenesis-related research become more apparent than in the field of ophthalmology, most notably with treatments for retinal diseases, such as wet AMD, diabetic macular edema, and retinal vein occlusions.

The Angiogenesis Foundation recognizes the challenges of optimizing patient care and outcomes with such paradigm-shifting discoveries as angiogenesis-based treatments for retinal diseases. It also deeply understands that to meet the goal of improving global health through angiogenesis-based medicine, the complex needs of all the stakeholder groups involved, including patients, caregivers, patient-support organizations, physicians, researchers, scientists, industry leaders, regulators, policymakers, and funders, must be aligned and met. The Angiogenesis Foundation is committed to helping those groups work together to make sure that all people benefit from current and future advances in angiogenesis-based medicine.

The International Expert Summit

The International Expert Summit opened with welcoming remarks from Dr. William Li, the president, medical director, and co-founder of the Angiogenesis Foundation. He explained the purpose of the current summit and the history of the earlier ones. Dr. Li's remarks were followed by two brief presentations that offered overviews of recent developments regarding AMD research and treatment. Dr. Gemmy Cheung of the Singapore National Eye Centre presented highlights from recent clinical trials on wet AMD treatment. Dr. Patricio Schlottmann of the Organización Médica de Investigación in Argentina shared best practices for managing wet AMD.

Recent Clinical Trials on Wet AMD Treatments

Two landmark clinical trials—the MARINA[7] and ANCHOR studies[12]—dramatically changed the lives of patients with wet AMD. These phase III multi-center, randomized studies demonstrated that monthly intravitreal administration of the anti-VEGF drug ranibizumab prevented vision loss in most patients with wet AMD and, in addition, resulted in improved vision in about one-third of the cases. Because monthly injections place a significant treatment burden on patients, subsequent studies have attempted to determine if a less-frequent dosing schedule would produce comparable results. The PIER clinical trial was designed to investigate whether ranibizumab would be effective if administered monthly for three months and then quarterly thereafter.[13] They found that the benefits of the drug declined once quarterly doses began. Other studies, including PrONTO in 2009[14] and SUSTAIN in 2011,[15] have found that variable, as-needed (PRN) dosing regimes were comparatively effective and safe after the initial three-months of injections when monthly optical coherence tomography (OCT) imaging was used to guide the regimen.

In 2011, the one-year results of the CATT clinical trial were published.[7] This study compared ranibizumab with off-label use of bevacizumab. It found that the drugs were similarly effective and safe if given in the same dosing regimen (monthly or three monthly loading doses then PRN). The two-year results from CATT, published a year later, had similar findings.[16] Those extended results also showed that the continuation of monthly injections was slightly more effective than switching to PRN in the second year, although the difference was a mean of -2.4 letters. Two subsequent European trials comparing

Figure 7. *Moderated discussion at International Expert Summit, Berlin, 2013*

ranibizumab and bevacizumab, IVAN[17] and GEFAL,[18] produced findings that support those of the CATT study.

A third drug, aflibercept (also known as VEGF trap-eye), was also introduced in 2011 for the treatment of wet AMD. Two similarly designed phase III trials (VIEW 1 and VIEW 2) reported that intravitreal injections of aflibercept every two months after three initial monthly doses were as effective as monthly injections of ranibizumab at stopping disease progression and restoring visual acuity.[19] With aflibercept, therefore, clinicians and their patients have an additional—and perhaps less burdensome—treatment option.

Other recent studies (MONT BLANC[20] and DENALI[21]) have found that combining photodynamic therapy (PDT) with ranibizumab does not significantly improve vision; nor does the addition of PDT help reduce the number of injections needed by patients. Additional studies (MERITAGE[22] and CABERNET[23]) have reported that administering low-dose radiation (epimacular brachytherapy) as an adjunct to anti-VEGF injections does not decrease the need for frequent anti-VEGF retreatment, although it does appear to help stabilize vision in refractory cases. The use of stereotactic radiotherapy (SRT) in a clinical trial (INTREPID[24]) involving 230 patients found that a single dose of SRT significantly reduced the number of ranibizumab injections needed by the patients during the first year of treatment.

Researchers have also been investigating whether a higher monthly dose of ranibizumab (2.0 mg versus the standard treatment of 0.5 mg) could approve the visual acuity of patients with wet AMD. One study (HARBOR[25]) found that the higher dose had no effect on outcomes in treatment naive patients, while a second study (SAVE[26]) in patients with recalcitrant (resistant-to-treatment) wet AMD reported that the higher dose led to statistically significant gains in visual acuity, as well as anatomical improvements (a decrease in central retinal thickness).

Researchers—and clinicians—are also trying to determine how long anti-VEGF treatments need to be continued. A recent multi-center cohort study (SEVEN-UP[27]) assessed long-term outcomes of patients enrolled in the ANCHOR, MARINA, and HORIZON[28] studies. The study found that approximately seven years after the patients had begun ranibizumab treatment, one-third of patients demonstrated good visual outcomes, while another third demonstrated poor outcomes. In addition, some 68% of the patients still had active disease—a clear sign that wet AMD is a chronic condition that requires indefinite treatment. Indeed, HORIZON patients in highest quartile of post-study injections (≤11 injections) had the best mean gain in vision during years four to seven. (The mean number of injections received by HORIZON patients after the study ended was 6.8.)

Best Practices for Managing Wet AMD

AMD is a rapidly progressing and highly disabling disease. Its prevalence increases with age; it frequently affects both eyes; and in its early stages, the disease often goes undetected. The quality of life of patients with severe wet AMD is slightly comparable to that of bedridden patients with severe stroke.[29] Clinicians have at their disposal advanced technologies that can help with diagnosing and treating the disease, including optical coherence tomography (OCT) and fluorescein angiography. In addition, the development of anti-VEGF drugs has dramatically changed the natural history of wet AMD. The downward trajectory of vision loss associated with the disease can now be slowed or, in some cases, reversed. While these therapeutic agents come in many forms (some are fusion proteins, some are full or fragments of antibodies), they are all administered via intravitreal injections. The drugs work differently, and bring different results, but they can produce excellent treatment responses.

The effectiveness of anti-VEGF treatment for wet AMD can be seen in its low "number needed to treat" (NNT) number. The NNT is the number of patients that need to be treated with a particular drug or other medical treatment for one patient to experience a positive outcome. The NNT for anti-VEGF drugs is very low. For the prevention of visual loss (≤15 letters on the Snellen eye chart), one patient will receive a positive outcome for every one to two patients treated with anti-VEGF intravitreal injections. For visual improvement (≥15 letters), the ratio is 1:3. By comparison, cardiologists must treat 99 patients with the drug atorvastatin to prevent a heart attack in one patient.

The long-term effect of anti-VEGF therapies on vision, however, is not well understood. In the seven-year follow-up study to the MARINA,[7] ANCHOR,[12] and HORIZON[28] clinical trials, a third of the patients re-examined were found to have experienced a decline in their visual acuity of 15 letters or more, and two-thirds were found to still have active disease.[27] The number of injections received by patients after 24 months varied, however. The HORIZON patients had received, for

example, a mean of 6.8 injections after exiting the trial, and only 46% of the patients enrolled in all the studies were still receiving anti-VEGF treatment seven years later. As this study made clear, 24 months of treatment is often not enough. Yet, treating wet AMD patients indefinitely is not sustainable. Patients, clinicians, and the medical system itself tire of the burden of repeated examinations and injections. Clinicians have attempted to devise their own individualized treatment strategies but these efforts, coupled with an increasing patient load, have not led to improved results.[30,31,32]

One important factor related to outcomes that is often overlooked is time-to-initial-treatment. The longer the start of treatment is delayed after diagnosis of wet AMD, the more vision the patient loses.[33] In published clinical trials, treatment generally starts within seven days of diagnosis, but in clinical practice, prompt access to treatment is much less common. In many regions of the world, it can take a month or more after diagnosis before the patient gets access to and/or approval from a payer for treatment. A recent study in Argentina found that the waiting time to get approval for an anti-VEGF drug was a key factor in treatment success—or failure.[34] Other factors can also give clinical trials a false impression of treatment success. Some studies, for example, have a high lost-to-follow-up factor—sometimes as high as 50%.[35]

Good patient management of AMD patients requires several components: a diagnosis that is quick, precise, and non-invasive; initial treatment that is delivered immediately or very soon after diagnosis; an accurate response assessment so that non-responders do not keep receiving injections of the same drug; and an effective follow-up strategy to measure disease activity. In addition, treatment needs to be based on an appropriate strategy, one with a streamlined, ideally evidence-based algorithm that is practical as well as effective, and an appreciation for the chronic nature of the disease requiring follow up and treatment beyond 2 years.

All treatment strategies must be well designed, well implemented, and able to be properly measured and evaluated. The strategies should take into account evidence-based prognostic factors and treatment regimes. Many current strategies, including variations of treat-and-extend and treat-to-target, are based on limited clinical trial results.[36]

To determine treatment strategies regarding therapies for wet AMD, clinicians must, of course, rely on published clinical trials. Yet, the reasoning behind the methodologies and analyses of such trials is not always clear; nor are the methodologies comparable from one study to another. In addition, clinical trial results are often presented in relative rather than absolute terms. To provide better evidence for treatment strategies, clinicians need clinical trials that are better designed, better analyzed, and more transparent.

In conclusion, wet AMD is a highly disabling condition that relies on technology for diagnosis. Therapies vary in efficacy and safety, and are administered in a variety of treatment strategies. The evidence base is presently available at an early stage and therefore limited. The standard of care using anti-VEGF agents within ophthalmology continues to evolve. Clinicians who want to provide optimal AMD care to their patients continue to face many challenges, and many questions about the disease and its treatment remain unanswered.

Defining and Improving Value in the Treatment and Management of AMD

As the summit's opening presentations demonstrated, anti-VEGF therapies have made a remarkable difference in the lives of millions of people with wet AMD. Yet the therapies have limitations, which impact the value ascribed to them by patients, clinicians, payers, and other AMD stakeholders. In clinical trials, the value of AMD treatments are primarily determined by improvements in vision quality, as measured by eye charts. Patients, however, tend to use broader criteria—especially factors related to quality of life—to assess a treatment's value. After the opening presentations, summit participants turned their focus to defining and improving value in the treatment and management of AMD from the perspectives of the disease's various stakeholders.

The Perspective of Patients and Caregivers

Above all, patients want and value improved vision, but not necessarily the kind of improvement that is only measured by the number of lines that can be read on an eye chart, as the summit experts had pointed out. An AMD treatment is most valuable to patients when it enables them to maintain independent activities of daily living, such as reading and dressing oneself. Patients also want to be able to continue with their hobbies and interests and to retain their social contacts. The ability to recognize faces is a particularly important treatment outcome, summit participants stressed, as it means patients are able to continue to interpret nonverbal as well as verbal communication.

Patients also value treatments that minimize the physical and financial burden of care—both for themselves and for their caregivers. Thus, they want easy and equitable access to retinal specialists, therapies, and rehabilitation services. They also want more affordable treatments, as well as ones that require fewer visits to medical clinicians. The transportation and time burdens associated with current treatments are substantial for both patients and caregivers alike, and often act as barriers to timely and effective care, the summit participants pointed out.

AMD patients also want and value empathetic and individualized care from their clinicians—the type of care that requires physicians to spend more time with them than medical-care systems often permit. In addition, patients want clear and thorough information about AMD and its treatment, including information about rehabilitation services. Such information can be empowering and may help alleviate certain fears (particularly of going blind) as well as enable patients—and their caregivers—to plan better for the future.

The Perspective of Providers/ Clinicians

Retinal specialists and other clinicians providing care to patients with wet AMD value treatments that offer not just comparable or superior anatomical results, but significant improvements in both visual acuity and quality of life, the summit participants said. Clinicians, like patients, also want treatments that require fewer injections (or, preferably, no injections at all) and that have minimum side effects. Clinicians would like to have access to all drugs that they believe would help each individual patient, rather than be restricted.

Summit participants also stressed that clinicians place high value on well analyzed, unbiased, and timely information about wet AMD treatments. They discussed the need for researchers to provide access to complete data sets from studies to ensure that the results are reliable. Clinicians also value research with realistic treatment protocols that are applicable to "real-life" clinical situations.

The summit's participants also discussed how current treatments and systems of care place a burden on the quality of the professional life of clinicians who care for patients with wet AMD. As populations age, an increasing number of people are seeking treatment for the disease, and that treatment usually requires a long series of injections as well as extended follow-up care. Clinicians would like the delivery of wet AMD treatments to be more widely distributed; they would also like better coordination and collaboration of patient management among the various clinicians involved in each patient's care. Many patients with wet AMD have co-morbidities (concomitant but unrelated medical conditions) that make coordination and collaboration among clinicians particularly crucial for successful patient care. In addition, clinicians want payment systems that reward quality of care over quantity of care— in particular, systems that allow clinicians to spend more time with individual

patients. Minimizing the bureaucratic and administrative burden associated with the care of wet AMD patients would help free up more time for clinicians to spend on individual patient care, the summit participants agreed. In addition, clinicians would like better access to authorities (hospitals, regional authorities, health ministers, payers, and government regulators) to talk about how to improve the clinical treatment of patients with wet AMD and how to lift the burden of the disease for all stakeholders, especially for patients.

The Perspective of the Payer and Society-at-Large

The summit participants discussed how advances in the prevention and treatment of age-related diseases that cause vision loss are a major reason why being 70 years old does not mean the same thing, in terms of quality of life, as it did half a century ago. More people now have the possibility of experiencing old age with their vision intact. Making sure that all individuals have access to that possibility, however, comes with a significant financial cost. Private and government payers, therefore, place high value on AMD-related therapies that are both effective and efficient. In addition, payers, like clinicians, want unbiased and timely data about those therapies so that they have more accurate information for cost-benefit analyses.

For society-at-large, the value of AMD-related therapies comes from the contribution of vision-saving treatments to the quality of life of a growing elderly population. Societies benefit most when such treatments are affordable and accessible to all. Persuading societies that more resources should be allocated to saving the vision of their elderly populations is challenging, however, because so many other (and more "visible") age-related chronic diseases are also asking for those resources. Yet, patients with wet AMD often have chronic co-morbidities, such as heart disease or diabetes, so treatment to help them maintain their vision can also retain a higher quality of life. Still, AMD patient-advocates, including clinicians, need to press forward rather than relent on their efforts to convince societies of the importance of helping AMD patients get the care they need.

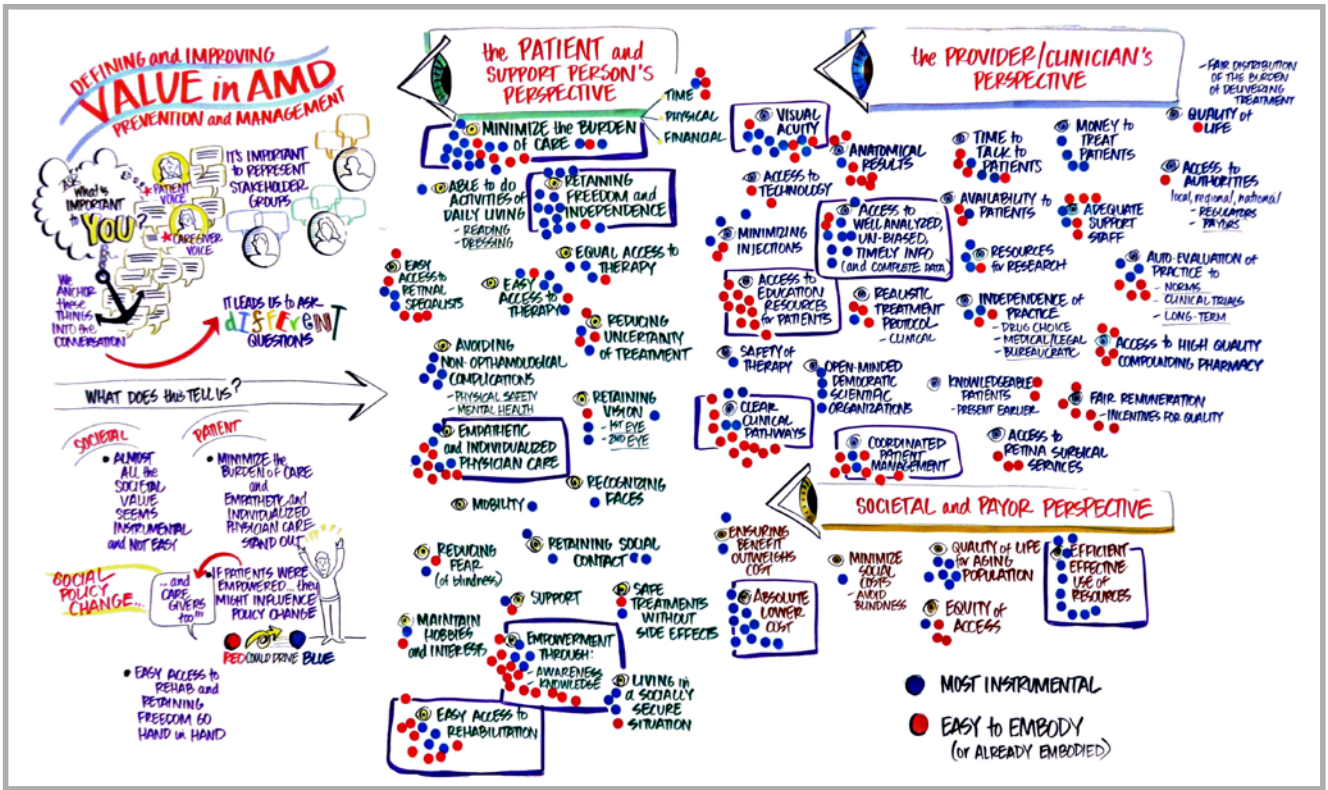

Figure 8. *Graphic Facilitation Chart: Defining Value and Improving Prevention and Management*

Improving the AMD Continuum of Care

After identifying what AMD stakeholders most value and want from treatments for the disease, the summit participants turned their focus to care pathways. They discussed the entire continuum of AMD-related care, from awareness and diagnosis through treatment and follow-up.

Current State of Awareness

The discussion started with participants summarizing their country's overall level of public awareness about AMD.

- **France** has a designated week each year that focuses on AMD screening. In addition, there are public-service announcements on French television to raise awareness about AMD. As a result, many people in France are familiar with AMD and its symptoms. These efforts have also increased public awareness of other retinal diseases.
- Public awareness in **Germany** about AMD is minimal. A survey conducted a few years ago found that less than 20% of the German population had heard of the disease. There is an awareness campaign in the country, but the effort has been underpowered and not very effective. As a result, few Germans have an understanding of the seriousness of the disease. "They think it's like a cold that you get and then fix," one summit participant noted.
- **Switzerland** is similar to Germany in terms of its public's level of awareness about AMD, but many patient organizations do not have enough resources to fund awareness campaigns. In recent years, however, information about the disease and its symptoms has begun to reach the public, and awareness is growing, although slowly.
- In **Italy**, most public awareness campaigns about AMD are regional initiatives. Tuscany, for example, has made efforts, with the help of a local association for the blind, to make older Italians and their families aware of the disease and its symptoms. A few public-service announcements about AMD have recently run on Italian television, but there is no large-scale national initiative underway. As a result, most Italians known very little about the disease. Public health officials are planning, however, to increase AMD screening through mobile clinics set up in public spaces.
- In **Poland**, an AMD advocacy group has organized public awareness initiatives, which have included placing information on billboards and in popular magazines. The group has also used the media to distribute AMD "self-tests." No proper research exists, however, on whether these efforts are leading to more people seeking early diagnosis and treatment for the disease.
- Awareness about AMD is generally quite low in **Singapore**. As a result, most Singaporeans have late-stage disease by the time they visit an eye specialist. Singapore does have an annual "AMD awareness week." The campaign is not very effective, however. It tends to reach young, educated individuals rather than its intended audience: Singapore's older (and often illiterate) population.
- There is a week-long "AMD awareness" campaign each year in **Columbia**. In addition, the Pan-American Retina and Vitreous Society sponsors an AMD awareness week every two years. Yet public awareness about AMD remains low. AMD patient-advocates and clinicians have recently undertaken new efforts to change that situation. Early in 2013, a group of advocates and clinicians met with government officials to talk about issues related to AMD, including raising awareness. An effort is underway to find a popular and well known Columbian who would be willing to serve as a national spokesperson during national awareness campaigns.
- In **Argentina**, the level of awareness about AMD is much higher in urban areas than in rural ones. In Buenos Aires, for example, awareness of the disease and its symptoms is probably comparable with that in most parts of Europe. In Argentina's rural areas, however, raising awareness about AMD must compete with other pressing health priorities, such as alleviating tuberculosis and malnutrition. Argentina runs an AMD awareness campaign every year, but it's difficult to know if that effort has had much of an impact.
- In the **United States**, March has been designated "Age-Related Macular Degeneration Month." In addition, the National Eye Institute sponsors an annual "Healthy Vision Month" in May that focuses at least in part on AMD. These and other awareness efforts have been somewhat successful in reaching and educating older Americans, but much more needs to be done. AMD receives significantly less attention from the U.S. media than other age-related diseases, including other eye diseases such as cataracts and glaucoma. High-profile individuals are needed as advocates and spokespeople, but most seem reluctant to step into that role, probably because of the "aging" and "disabled" stigmas attached to the disease.

Current Care Pathway

To enhance and deepen the dialogue, the summit's participants were divided into two subgroups. Each subgroup was instructed to discuss and map the various stages of the typical AMD care pathway. They were asked to consider such questions as:

- How do patients become aware of their disease?
- Who typically diagnoses the disease?
- To whom are patients referred after diagnosis?
- What treatments do patients typically receive, and in what order?
- Who pays for those treatments, and how much?
- What follow-up care and services do patients receive?

A summary of these discussions follows.

Stage 1: Awareness

Most patients become aware of their disease when they experience visual abnormalities, particularly vision loss that interferes with daily activities. Yet, because awareness of wet AMD is generally low, few patients recognize that AMD's telltale symptoms (e.g., a loss of central vision and straight lines appearing wavy) are an "eye emergency." Most patients, therefore, delay seeking care. Many optometrists and ophthalmologists are also unaware that patients with early symptoms need a swift diagnosis followed by immediate treatment. "When someone has a chest pain, everybody knows what to do," said one summit participant. "That's not true with vision problems."

Stage 2 & 3: Diagnosis and Referral

The pathway to a wet AMD diagnosis can be lengthy and involve several different clinicians. Patients with wet AMD symptoms may go to an optometrist, a general practitioner, a general ophthalmologist, or a retinal specialist for their initial consultation, depending on such factors as where they live, who is paying for their medical care, and how aware they are about the disease. Patients rarely visit a retinal specialist first, however. Although getting a quick and accurate diagnosis is imperative for effective treatment of the disease, some countries have complex systems for routing patients with wet AMD symptoms to a retinal specialist. A patient may visit two, three, or even four clinicians before being diagnosed. Long wait times for appointments, administrative and reimbursement barriers, and misdiagnosis by non-retinal specialists can also delay the diagnosis of wet AMD.

State 4: Treatment

In some countries represented at the summit, only retinal specialists are permitted to administer anti-VEGF injections to patients with wet AMD. In others, however, general ophthalmologists can also provide the treatments, and they are doing so in increasing numbers. That trend is welcomed in areas of the world where there are few retinal specialists (or where retinopathy is not an official medical sub-specialty), but it has also raised concerns about quality of care.

The on-label anti-VEGF drug used to treat wet AMD (ranibizumab or aflibercept) is determined by its approval status in a particular country as well as by the patient's payer or by the ability of the patient to self-pay. Drug choice also depends on whether the clinician and the patient have access to off-label therapies. The preferences of the clinician and the patient may also play a role; a patient may choose aflibercept over the other two drugs, for example, because it requires less frequent injections. At the time of diagnosis, patients are often fearful of becoming blind and thus rely on their clinician to present them with their best treatment option. Some clinicians, however, are financially incentivized to use a particular drug or dosing schedule, a factor that is usually hidden from the patient. Financial factors are, of course, also part of the cost-benefit analysis that payers consider when approving anti-VEGF drugs and dosing schedules for patients.

In some countries, the payer approval process of drugs, whether private or pubic, can be complicated and lengthy, and thus serves as a barrier to timely and effective treatment; in others, the process is simple and swift. In France, for example, wet AMD patients generally receive their first anti-VEGF injection within a week of diagnosis; in Switzerland's large eye clinics, the first injection is frequently given to the patient during the diagnostic appointment. In many regions of the world, however, patients have to chase reimbursement for wet AMD treatments or find the money to pay for the treatments themselves, processes that may cause them to delay or cut short their prescribed series of treatments.

Stage 5: Follow-up Care

Wet AMD is a chronic disease, and patients need to have their vision closely monitored and possibly treated for the rest of their lives. Many patients, however, do not complete their initial dosing schedule, let alone participate in ongoing assessments, treatment, and care. The cost, frequency, and burden of anti-VEGF treatments play a role in patients dropping out of care. Better medical-administrative systems are needed to ensure that wet AMD patients complete their dosing schedule and receive other follow-up services. In addition, clinicians need to help patients become better informed about what to expect from anti-VEGF treatment.

Patients also need easy and timely access to rehabilitation services. Getting a referral to rehabilitation services is difficult for many patients, however. Their clinician may be unaware of how or where to refer patients, and in some regions, particularly rural ones, such services may not even exist. In addition, rehabilitation services may not be reimbursable. Often it is the patient's family who must find, access, and pay for rehabilitation services. For some families, a lack of financial and other resources makes such services prohibitive.

Patients with wet AMD may also need mental health services. The prevalence of depression among patients with wet AMD is high, primarily due to activity restrictions caused by the loss of vision.[37] It's important that clinicians, as well as patients and their caregivers, be aware of the increased risk of depression among wet AMD patients. Professional counseling, particularly counseling that complements visual rehabilitation services, can greatly help patients who feel overwhelmed and frustrated with the challenge of maintaining their independence.

Barriers and Solutions

After the subgroup discussions, the summit participants reconvened as a single entity to identify barriers and solutions to improving the wet AMD continuum of care. The key points that arose out of this discussion are listed below. Some of these points are specific to certain countries or regions of the world.

Barriers to Raising Awareness

- A lack of financial resources to fund awareness campaigns.
- A lack of awareness among patients and clinicians that wet AMD can be an emergency medical condition requiring prompt care.
- An underrepresentation of patient advocates "at the table" when medical groups, government officials, and other stakeholders are drafting policies that affect wet AMD patients.
- The age of the typical wet AMD patient; older people are more difficult to reach through media campaigns directed at the general public.
- Other age-related diseases that compete for the same limited amount of funding sources.
- The lack of data on the cost of vision loss to society.

Solutions for Raising Awareness:

- Increase resources for advocacy.
- Keep awareness messages simple; focus on general vision loss and the need to see a specialist at the first sign of the disease.
- Translate awareness efforts into a successful system of triage so that patients receive timely diagnosis and treatment.
- Train general practitioners to ask AMD screening questions during routine medical visits with at-risk patients.
- Generate data on the cost of vision loss to society.

Barriers to More Timely Diagnosis and Referrals

- A complicated referral system.
- Lack of proper symptom-triage when patients are setting up appointments.
- Other eye problems (e.g., cataracts) that can make it difficult for a clinician to determine co-existing symptoms of wet AMD.
- Geographic maldistribution of retinal specialists.
- Inconsistencies in the quality of clinician readings of OCTs.
- Financial benefits to general ophthalmologists to retain patient rather than refer them to a retinal specialist.

Solutions for More Timely Diagnosis and Referrals:

- Include an Amsler grid test when patients present with vision problems; also, make the test part of routine medical check-ups with at-risk populations.
- Develop an effective triage system, similar to the algorithm used for chest pain, to help ensure that patients receive a quick diagnosis.
- Design and implement a feedback system of quality control to protect against both under- and overdiagnosis.
- Increase patient access, particularly in rural areas, to clinicians trained to diagnose wet AMD.
- Train more general ophthalmologists in the diagnosing and treating of wet AMD.
- Make sure all clinicians who read OCTs are properly trained.

Barriers to Timely and Effective Treatment

- Lack of access, especially timely access, to anti-VEGF medications.
- Differences in private and public reimbursement policies regarding wet AMD treatment.
- Complicated and lengthy systems for getting treatment approval for patients.
- Government and payer restrictions that limit treatment options for patients and clinicians.

Solutions for More Timely and Effective Treatment

- Negotiate with pharmaceutical companies to improve access to anti-VEGF medications.
- Encourage a more individualized approach to treatment, including alternative dosing or switching therapies, or the cessation of treatment for non-responders.
- Develop more detailed, evidence-based guidelines for the treatment.
- Shorten the treatment approval and reimbursement processes for patients.

Barriers to Timely and Effective Follow-up Care

- Patient and clinician treatment-fatigue.
- Advanced age and poor health status of the patient.
- Patient's fear of burdening his or her family.
- A lack of an organized system for recapturing patients who don't return for treatment and follow-up care.
- Lack of knowledge (by patient and clinician) about available rehabilitation services.
- Poor reimbursement for rehabilitation services.

Solutions for Timely and Effective Follow-up Care

- Create more transportation support to help wet AMD patients access care.
- Promote the use of software systems that send automatic reminders to patients about follow-up visits.
- Educate patients and clinicians about available rehabilitations services.
- Advocate for increased reimbursement for rehabilitation services.

With the compilation of a comprehensive list of barriers and possible improvements to the current wet AMD care pathway completed, the summit participants turned to the future to discuss who might lead the way in implementing the needed changes to realize the pathway that they had just identified. After acknowledging that opinion leaders have tended to be selected in the past by the pharmaceutical industry, the experts discussed the idea of recruiting and cultivating future leaders themselves. They also talked about the importance of recruiting patient-advocates as well as physicians and researchers for leadership roles. The discussion focused on three questions:

1) What are the key attributes of opinion leaders in this field?
2) Where can the next generation of leaders be found?
3) How can those individuals be cultivated and encouraged to take on leadership roles?

Key Attributes of AMD Opinion Leaders

The summit participants agreed that individuals with a variety of skill sets are needed for the next generation of AMD opinion leaders. Knowledge about health economics, business organization, research, and/or patient-advocacy is particularly valuable. A background in geriatric medicine is also helpful. In addition, opinion leaders need to be open-minded, pragmatic, and able to build strong working relationships with all AMD stakeholder groups. They should also be hungry for knowledge, able to develop their own ideas, willing to take a stand, and, in the case of clinician-leaders, have experience with the disease and its treatment. Being media-savvy and having general communication skills are also necessary, as is having a good, thorough knowledge of the structure and operations of various health systems. Opinion leaders should have the ability to be independent and unbiased, with full transparency of industrial ties.

Patient-advocacy leaders need to have attributes similar to those of clinician-leaders, the summit participants agreed. Because they need to be able to represent data and issues related to AMD accurately, clearly, and without exaggeration, good communication and organization skills are particularly useful. They also need to be good collaborators, as they must work with many different kinds of stakeholders.

Finding and Developing AMD Opinion Leaders

Next, the summit participants discussed where to find and how to develop a new generation of AMD opinion leaders. It was agreed that such leaders are often found in research hospitals and centers, but they may also emerge from other settings. Many can be found making presentations on AMD-related topics at professional meetings and academic colloquia. Patient-advocacy leaders, the summit participants noted, are often found within journalism or other professions that require individuals to communicate effectively with the public.

To develop the next generation of AMD opinion leaders, the summit participants recommended that current leaders serve as mentors, advising promising researchers and clinicians on how to prepare presentations and speeches, for example. Mentors could also help arrange for potential leaders to attend professional meetings so that they can expand their knowledge of the field and its key players and issues. Special training in biostatistics, advocacy lobbying, negotiations, and the workings of the media would also be beneficial.

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