



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

A Report Based on a Latin American Expert Summit
Convened in Bogota, Colombia, March 2012



Pan-American Retina & Vitreous Society
The Angiogenesis Foundation

Key points

1. Although not as well-known as many other diseases, Age-related Macular Degeneration (AMD) is the world's leading cause of vision loss and blindness in adults over the age of 65.
2. The percentage of Latin Americans aged 65 and older is projected to triple from 6.3 percent in 2005 to 18.5 percent in 2050.
3. During the past decade, new therapies and diagnostic techniques—VEGF-targeted antiangiogenic therapy and Spectral Domain Optical Coherence Tomography (SD-OCT)—have produced a paradigm shift in the diagnosis and treatment of wet AMD. Patients now have effective treatment options that can help keep them from going blind.
4. The majority of patients with wet AMD, including those living in Latin America, are not receiving the optimal care that is needed to maintain vision and prevent progressive vision loss. The treatment window for wet AMD is relatively short, and any delay can mean the difference between retaining vision and blindness.
5. The barriers in Latin America to receiving timely and optimal care are many. They include:

- The high long-term cost of licensed anti-VEGF treatment to patients.
- The lack of both government and private insurance reimbursement for wet AMD treatments.
- The limits placed on treatment options by national health authorities.
- Limited patient access to retinal centers and retinal specialists.
- A lack of awareness among the public as well as among optometrists, general ophthalmologists, primary care physicians, and other non-retinal healthcare providers about the disease.

Key points

6. As a result of these and other barriers

- Patients are struggling with the burden that comes with requiring monthly care involving an effective but costly and invasive therapy.
- Retinal specialists are coping with a flood of patients that threatens to overwhelm their capacity to provide effective therapy.
- National healthcare systems and private insurers alike in Latin America are staggering from the sudden and growing expense of effective therapies that for most patients will require a lifetime of therapy.

7. Overcoming the substantial current challenges to the early diagnosis and effective treatment of wet AMD will require the concerted efforts of all Latin American stakeholders: patients, caregivers, physicians, researchers, scientists, industry leaders, regulators, policymakers, payers, the media, and society at large.

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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 needed to read, recognize faces, drive, and in general see most anything clearly. 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 needed to see fine details.

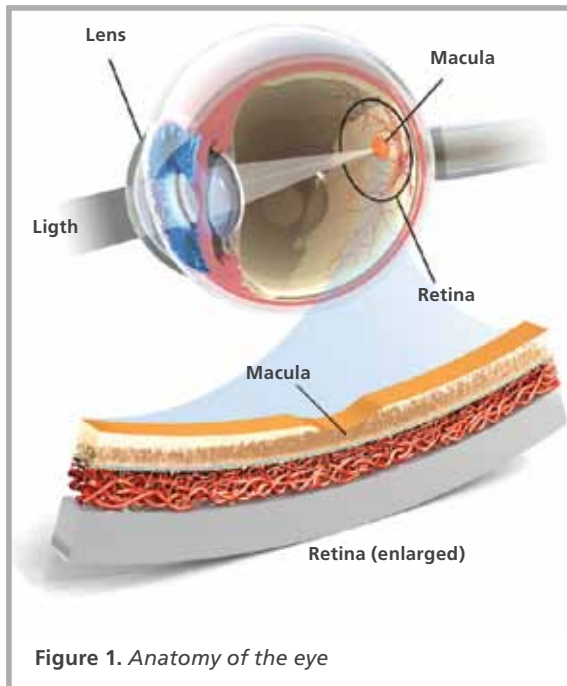


Figure 1. Anatomy of the eye

There are two types of AMD, known as 'dry' AMD and 'wet' AMD. Both forms can occur in one or both eyes, although the development of AMD in one eye appears to increase the risk that AMD will develop in the second eye. Neither form of AMD is painful and as a result can go undetected until it produces marked changes 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.

Dry AMD, the more common form of macular degeneration, is characterized by the accumulation of drusen, small yellowish deposits that build up beneath the macula. As the number of drusen or their size increases, cells in the retina may become damaged, producing distortions in vision that are most apparent when reading. Dry AMD does not usually cause total loss of central vision.

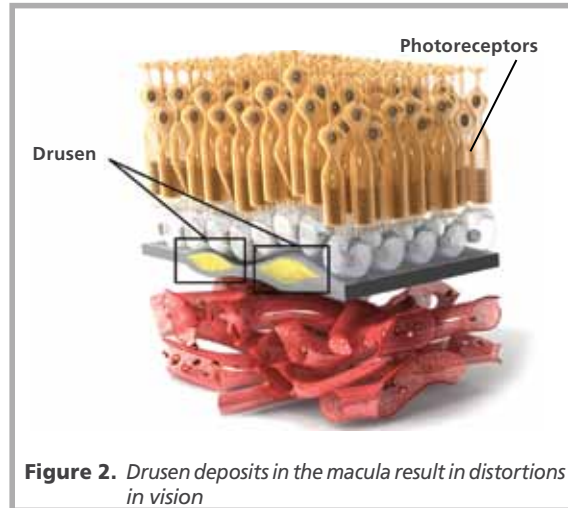


Figure 2. Drusen deposits in the macula result in distortions in vision

Wet AMD is the more serious form of the disease. For reasons that are as yet unclear, 10 percent to 15 percent of adults with dry AMD will go on to develop wet AMD and experience abnormal blood vessel growth under the macula. The growth of new blood vessels, known as angiogenesis or neovascularization, eventually leads to blood and fluid leakage that can scar the macula and retina, producing rapid and permanent loss of central vision in as little as three months. An early symptom of wet AMD is that straight lines appear wavy.

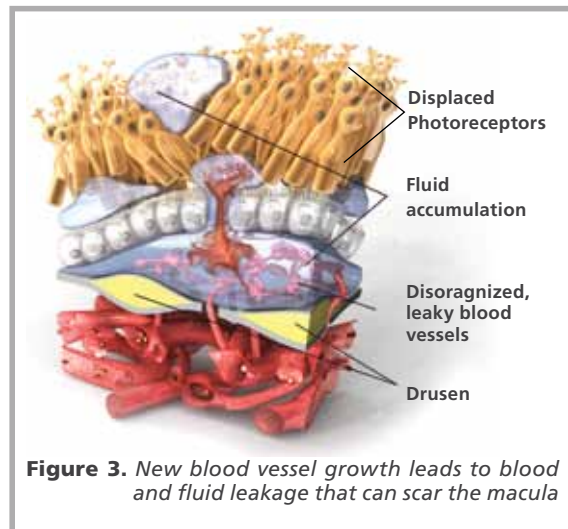


Figure 3. New blood vessel growth leads to blood and fluid leakage that can scar the macula

In most parts of the world, AMD is a relatively unappreciated disease, yet it is the leading cause of vision loss and blindness in adults over the age of 65. The World Health Organization (WHO) estimates that wet AMD affects 3 million people globally, accounting for 8.7 percent of all blindness and 50 percent of blindness in

industrialized countries.¹ The WHO projects that these numbers will double by 2020 as the population of industrialized countries ages.

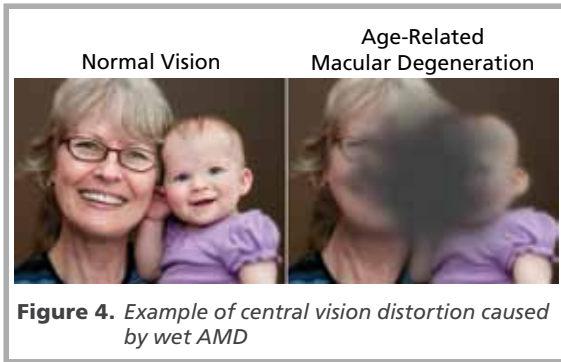


Figure 4. Example of central vision distortion caused by wet AMD

Paradigm Change

The field of research focused on angiogenesis, which began in the early 1970s, made dramatic advances in the late 1990s, culminating in the identification of specific treatment approaches to control undesirable blood vessel growth in diseases ranging from cancer to skin disease to blinding disorders caused by abnormally growing blood vessels, such as wet AMD. Presently, more than 10,000 laboratories around the world are involved in angiogenesis research, and over 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. Ten years ago, AMD was a significant cause of blindness in the elderly. Today, vision loss and blindness from wet AMD is largely preventable with early, appropriate care.

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 pegaptanib slowed the rate of vision loss caused from wet AMD.² Antiangiogenic therapies, aimed at halting abnormal blood vessel growth, became recognized as an entirely new class of disease treatment.

In June 2006, an even more effective drug, ranibizumab, became approved for the treatment of wet AMD. Ranibizumab, as well as pegaptanib, interfere with a small protein known as vascular endothelial growth factor (VEGF). This growth factor stimulates the very angiogenesis that lies at the heart of wet AMD. Clinical trials had

demonstrated that 95 percent of patients treated with a once monthly injection of ranibizumab into the eye maintained their vision as long as the injections continued over the course of the trial.^{3,4} In addition, some 40 percent of those treated with ranibizumab for a year experienced a significant improvement in visual acuity, enough to restore their vision to 20/40 in the treated eye. Today, Ranibizumab is approved in over 80 countries on every continent except Antarctica.

For the first time, physicians could offer their patients the opportunity to save their vision, and even reverse lost vision in some individuals. The major drawback to this new therapy, however, was 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 by the FDA, retinal specialists began experimenting with another anti-VEGF agent, bevacizumab. It had received FDA approval in 2004 for the treatment of colorectal cancer, and was later approved for the treatment of other cancers as well. Bevacizumab is a larger molecule known as a monoclonal antibody, from which ranibizumab, a smaller size molecule, 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 effective for the treatment of wet AMD and is used off label for this purpose at a cost of about USD\$50 per injection.⁵ (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 compounding pharmacy into the much smaller, diluted quantities needed for treating the eye. Numerous documented cases of infection from bevacizumab use in the eye have been reported. These cases are likely due to poor pharmacy practice when dividing the product, not the molecule itself. The Colombian government has also issued a warning about the use of bevacizumab in the eye.^{5a} Clinical trials comparing ranibizumab with bevacizumab have suggested, however, that both drugs are effective at stopping disease progression and restoring visual acuity, at least when dosed monthly during the first year of treatment.⁵

On November 18, 2011, a third anti-VEGF drug, VEGF Trap-Eye (aflibercept intravitreal Injection) received U.S. FDA approval for the treatment of wet AMD.⁶ Based on a fusion protein that

neutralizes VEGF and blocks the mechanism of pathological angiogenesis, VEGF Trap-Eye is designed to be administered by intraocular injection every two months following three initial monthly injections. In March 2012, Australia became the second country to approve VEGF Trap-Eye for AMD treatment, and regulatory applications are pending in other countries, including those in Latin America.

The globally expanding use of anti-VEGF therapies is dramatically improving the quality of life for countless numbers of individuals with wet AMD worldwide. Many more people are now able to retain their vision and, consequently, their independence. But more innovations are needed in order to improve existing therapies and health care systems.

The sudden emergence of effective therapies has set in motion a chain of events that has dramatically impacted the professional lives of ophthalmologists who specialize in retinal diseases and is straining healthcare budgets at a time when many industrialized countries are dealing with a growing number of fiscal challenges. Many patients do not have access to licensed anti-VEGF therapies, and those who do may face severe challenges related to their ability to maintain continuous treatment and necessary monitoring of their condition. Those benefits of the paradigm shift for wet AMD do not come without a heavy burden on the patient

and their caregivers. Therefore, the strategic assessment of the benefits and challenges to improving the lives of patients with wet AMD is timely and important.

The Latin American Expert Summit

Given the changes that have come with the advent of multiple effective therapies, and the fact that these therapies have revolutionized a field in the blink of an eye, it is perhaps an opportune time for the AMD stakeholder community to take a step back and review the progress it has made, the challenges it faces, and the questions that it needs answered to best meet the needs of those with wet AMD. The Angiogenesis Foundation, a scientific nonprofit organization whose mission is to conquer disease through the control of neovascularization, is well positioned to play the role of a neutral facilitator of such a review.

Starting in 2009, the Angiogenesis Foundation immersed itself in the field of macular degeneration and began looking at how it could apply the lessons it learned from its interactions with the oncology and wound healing communities to this new area of clinical opportunity. As its first major global step, it assembled an interdisciplinary



Figure 5. Moderated discussion at Expert Summit, Bogota, Colombia, march 2012

group of international leaders in AMD treatment and translational science and convened the first International Expert Summit for Age-Related Macular Degeneration in Berlin, Germany, on November 14-15, 2011. At this meeting, the 16 chosen experts identified, discussed, and achieved agreement on the rationale for angiogenic 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 suppressive antiangiogenic therapy for wet AMD. A White Paper was produced as a result of that meeting. It provided an overview of the group's discussions and presented the key steps that are needed to advance the treatment of wet AMD using anti-VEGF therapies to impact the greatest number of individuals possible.

It was clear from the Berlin summit that different regions of the world face their own specific challenges regarding AMD prevention, diagnosis, and treatment. To assist the various regions in identifying and finding solutions for these challenges, the Angiogenesis Foundation, and regional leaders, will organize a series of regional summits. The first of these, in partnership with the Pan-American Retina & Vitreous the Latin American Wet AMD Coalition Expert Summit, was convened in Bogota, Colombia, on March 10, 2012. At this meeting an interdisciplinary group of 12 Latin American leaders in AMD treatment and translational science:

- Analyzed the current status of AMD prevention, diagnosis, and treatment in the region.
- Defined where the region wants to be in terms of detecting and treating wet AMD.
- Outlined the barriers that lie in the path of achieving that state; and
- Identified the immediate and long-term steps that need to be taken in the region to overcome those barriers.

The summit was not a traditional scientific meeting, but rather an interactive, professionally moderated set of short presentations and roundtable discussions that aimed to establish a dialog and agreement among the participants. The summit began with four short presentations recapping the current status of wet AMD therapy, the current understanding of wet AMD biology and angiogenesis, and how AMD evidence can be translated into public health policy in Latin America. Under the direction of the moderator,

the assembled experts then spent the rest of the morning engaging in a series of discussions that defined where the field wants to be in terms of detecting and treating wet AMD and outlined the barriers that lie in the path of achieving that state. The moderator captured key points of the discussion, enabling the participants to visually review the content of their conversations as they worked through the tasks at hand.

During the summit's afternoon session, the experts focused on developing solutions to overcoming the barriers identified earlier in the day. An emphasis was placed on overcoming barriers for the early detection of wet AMD and for improving access to effective interventions. Current practices were discussed. The group then engaged in an analysis of what would define successful treatment outcomes for key stakeholders in the AMD community, especially, of course, patients. Working off the foundation laid by these discussions, the experts then developed a research agenda specific to Latin America that could move the field toward the desired future state of AMD prevention, diagnosis, and treatment. This White Paper provides an overview of the group's discussions.

The Role of the Angiogenesis Foundation

Founded in 1994, The Angiogenesis Foundation is the world's first 501(c)(3) nonprofit organization dedicated to conquering disease using a new approach based on angiogenesis, the growth of new blood vessels in the body. Based in Cambridge, MA USA, the Angiogenesis Foundation is committed to helping people around the world 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. The Foundation has extensive insights into key success factors with angiogenesis stimulating and inhibiting therapies, across multiple disease states, and the challenges of optimizing care and outcomes with paradigm shifting technologies. With the expertise, time, and resources needed to deeply understand the complex needs of multiple

stakeholders, including patients, caregivers, physicians, researchers, scientists, industry leaders, regulators, policymakers, payers, and financiers, the Angiogenesis Foundation facilitates processes that achieve increasingly better outcomes for patients. Its guiding philosophy is that patients collectively benefit when the needs of the different groups involved, in both developing and delivering treatment, are well aligned and met.

The Role of the Pan-American Retina & Vitreous Society

Founded in 2004, the non-profit Pan-American Retina & Vitreous Society (PRVS) is the leading retina and vitreous organization in Latin America. Its mission has four parts: 1) to promote and encourage the prevention, treatment, and rehabilitation of diseases that affect the retina and vitreous; 2) to promote and encourage the exchange of knowledge between retina and vitreous specialists in North, Central, and South America; 3) to conduct regular medical and scientific meetings with specialists and guests from its member countries; and 4) to participate in symposia, courses, and other meetings organized by the Pan-American Association of Ophthalmologists.

Current Status

To open the Latin American summit, three experts gave four 15-minute presentations as background for the subsequent roundtable discussions. Dr. Francisco Rodriguez, the scientific director of Fundación Oftalmológica Nacional in Colombia and former president of the Pan-American Retina & Vitreous Society, described the current status of AMD management and presented a comparative analysis of wet AMD therapies. Dr. Patricio Schlottmann, of the Organización Médica de Investigación in Buenos Aires, Argentina, summarized the current understanding of AMD biology and progression. Dr. Juan Manuel Lozano, of the Florida International University in the United States, discussed the nature of AMD-related evidence and how it can be translated to public health policy in Latin America.

conducted in Latin America regarding AMD and vision loss, one Colombian study has found that AMD is becoming more common as that country's life expectancy lengthens and as its population ages.⁷

There is clear evidence that if wet AMD is left untreated, the visual prognosis for patients is poor, and that the natural progression of the disease is dramatic. Studies have shown that 12 months after diagnosis of wet AMD, untreated patients lose an average of two to three lines of vision.⁸ A recent study looking at a variety of factors found that age, smoking, body mass index, drusen size, the presence of advanced AMD in one eye, and single nucleotide polymorphisms in five different genes were all independently associated with progression.⁹ In addition, taking high-dose supplements of vitamins C and E, beta carotene, and zinc has been found to slow the progression of late-stage AMD.¹⁰ Another study found that particular drusen characteristics were also predictors of a high risk for progression.¹¹

Defining the State of AMD Management

Aging is considered the most important risk factor for AMD. In the developed world, AMD is a leading cause of irreversible blindness among people aged 50 and older, and it is the leading cause of blindness in people over the age of 65. Although no epidemiology studies have been

The good news is that the natural progression of wet AMD is not set in stone. Multiple clinical trials have now shown that antiangiogenic therapy targeting VEGF stops disease progression and, in some patients, can partially reverse lost vision. In two different clinical trials,^{3,4} the average patient

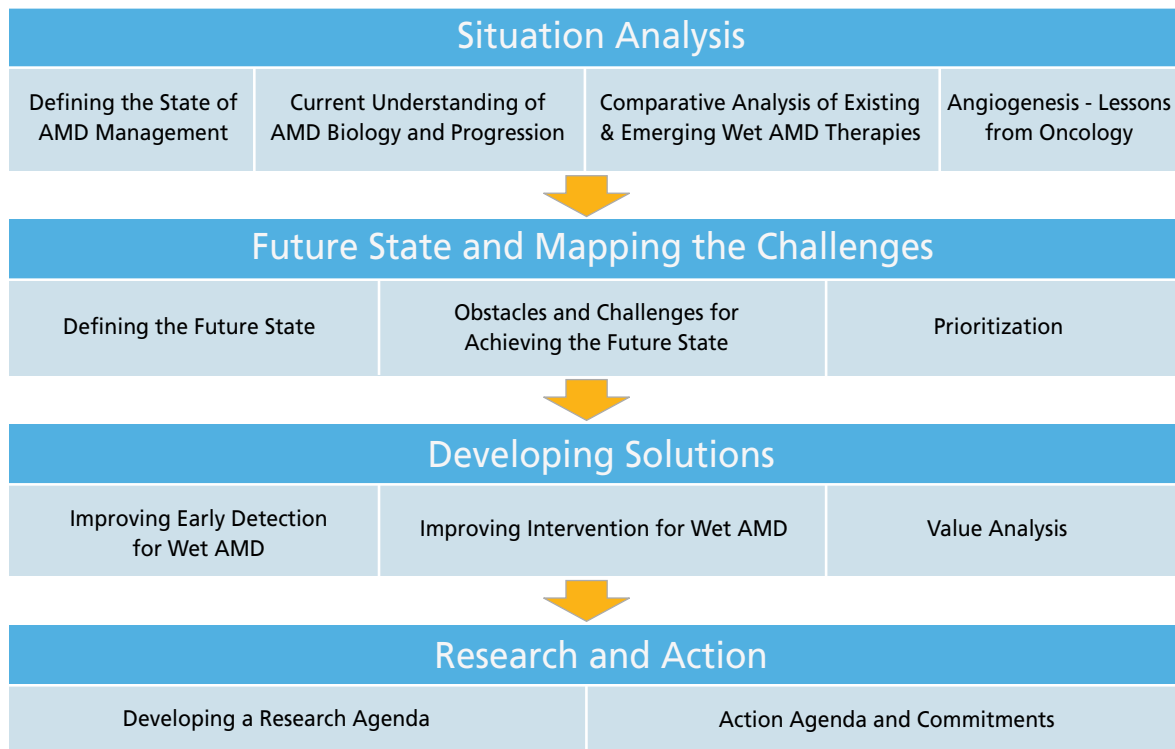


Figure 6. Schematic Flow of the International Expert Summit

receiving monthly injections of ranibizumab experienced a rapid gain in visual acuity. After a year of therapy, the average patient gained nearly two lines of vision, and this gain was stable at 24 months.

Another clinical trial showed that about 40 percent of patients receiving ranibizumab can maintain their gains in visual acuity with less frequent dosing after three initial injections.¹² The distinction between those patients that do and do not maintain their gains with less frequent injections becomes apparent about 60 days after the third injection. Given the chronic nature of AMD, it is not clear yet how infrequent dosing can be or if there are some patients who will be able to discontinue therapy altogether at some point. The pooled results of two clinical trials presented publicly, have shown, however, that injections of the newest VEGF inhibitor, VEGF Trap-Eye, can be administered every two months, following a monthly application during the first three months of treatment, with results comparable to monthly ranibizumab injections.^{13,14}

While it is clear that anti-VEGF therapy can successfully treat and even reverse the symptoms of wet AMD, there are a number of concerns with current therapy options. Wet AMD is a chronic disease with differing individual response to therapies, which result in a high rate of retreatment, therefore placing a remarkable burden on both patients and retinal specialists. The high cost of therapy is creating economic challenges for many national healthcare systems, including those in Latin America, that are already under strain. In addition, the optimal treatment regimen for specific subsets of patients has yet to be defined in clinical trials, and many patients fail to understand that AMD is a chronic disease that requires lifelong medical care. Finally, gains in visual acuity do have a limit, and a small subset of patients with wet AMD do not appear to respond, whether functionally or anatomically, to current anti-VEGF therapy. Separate management of care is needed for non-responders.

Current Understanding of Wet AMD Biology and Progression

AMD does not appear suddenly in patients. In the disease's earliest stages, patients may not realize that it's their vision itself that has changed and may comment or complain instead about eyeglasses that "no longer work." Optometrists,

general ophthalmologists, and primary care physicians need to be attuned to these subtle suggestions of early disease as well as to its clinical presentation to ensure that patients receive timely and effective treatment.

Research has established that AMD is related to certain changes in the aging eye. Drusen, a complex mix of various proteins and lipids as a result of natural shedding of cellular debris, are the hallmark features of dry AMD, and they reflect the microenvironment of the retina. Data from a multi-center clinical trial involving more than 3,600 participants found that the shape and size of the drusen appear to correlate with disease stages of dry AMD, which are predictive of progression to wet AMD.¹⁰ During the five-year course of the trial, only 1 percent of participants with "mild" drusen in one eye progressed to wet AMD, while 6.3 percent of those with "intermediate" drusen in one eye and 26 percent of those with "intermediate" drusen in both eyes went on to develop wet AMD. Among the trial's participants with "advanced" drusen in one eye, 43 percent progressed to wet AMD. Beyond these correlations, however, there is presently no clear consensus of how drusen are related to neovascularization and the development of wet AMD.

Nor is it known if the disease presents or progresses similarly in different population groups. A meta-analysis of nine studies involving four Asian populations found that the age-specific prevalence of late AMD among those populations was comparable to those among white populations, but that early signs of AMD were less common among the Asian groups.¹⁵ As the authors of the meta-analysis noted, these findings suggest possible ethnic differences in AMD phenotypes or subtypes.

Indeed, although age is the primary risk factor associated with wet AMD, it is not the only one. Other risk factors include genetics, smoking, gender, cardiovascular disease, diet, ametropia (refractive error), sunlight exposure, and a history of cataract surgery.

The current view of the pathogenesis of AMD is that it is a progressive disorder that may start with inflammation, perhaps in response to oxidative stress, that affects the extracellular matrix in the retinal region.¹⁶ As the disease progresses, these changes in the extracellular matrix may be altering the balance of pro- and antiangiogenic substances that include VEGF, which stimulates blood vessel growth, and another substance known as pigment epithelium-derived growth factor

(PEDF) that inhibits it. Research also suggests that endostatin, another inhibitory protein involved in regulating angiogenesis, may be decreased in the pathology of wet AMD.¹⁷

There are additional processes likely to be involved in the progression of AMD. Various studies have shown that the complement system and macrophages involved in inflammation promote neovascularization in the retina. In one set of experiments, for example, researchers demonstrated that impairing macrophage recruitment in the retina allowed various complement factors to accumulate, which in turn, induced VEGF production in the retina.¹⁸

While the current state of knowledge about wet AMD is far from complete, it is clear that angiogenesis is a key process in the development of the disease. Combination therapies targeting different aspects of the biology of neovascularization in wet AMD may lead, therefore, to improved and more durable clinical outcomes in the future.

Comparative Analysis of Existing and Emerging Wet AMD Therapies, with a Focus on Anti-VEGF Therapies

As of March 2012, three anti-VEGF drugs have received regulatory approvals for use in humans. Pegaptanib was the first of these drugs approved for intraocular injection to treat wet AMD¹⁹, but it is used rarely today because ranibizumab has proven superior in clinical practice in every respect.²⁰ VEGF Trap-Eye was approved in the United States in November 2011⁶ on the basis of demonstrating non-inferiority to ranibizumab in clinical trials.^{12,13} License applications are pending in Colombia and other Latin American countries. Clinical trials have demonstrated that VEGF Trap-Eye is effective when administered every two months after the initial three monthly applications, whereas ranibizumab has only been studied in clinical trials using a monthly injection regimen. In addition, while pegaptanib and ranibizumab target VEGF-A, the key member of the VEGF family of growth factors, VEGF Trap-Eye has a broader spectrum. It links VEGF-A and two other related growth factors—VEGF-B and PIGF (placenta growth factor).^{20a}

Although there have been multiple clinical trials studying ranibizumab, there is only one published comparative randomized clinical trial comparing ranibizumab with bevacizumab, the Comparisons of Age-Related Macular Degeneration Treat Trials (CATT).⁵ All of the current randomized clinical trials are limited in their conclusions, and there have been no truly long-term follow up studies for any of the approved drugs in the chronic disease management setting (>5 years), an important consideration because wet AMD is considered a chronic disease. Another limitation of the trials conducted to date is that they do not reflect nor compare the spectrum of dosing schedules currently in use. The results of the VEGF Trap-Eye phase III trial have not yet been published in a journal, though they are included in the VEGF Trap-Eye package insert.²¹

From the clinical data that has been presented, it is clear that treatments with ranibizumab, bevacizumab, and VEGF Trap-Eye all produce meaningful functional improvements in vision as measured by changes in visual acuity, but with different requirements in the frequency of injections. To date, VEGF Trap-Eye is the only drug that has been demonstrated in clinical trials to be efficacious when administered every two months, rather than monthly. Data from CATT show that over the first 12 months and in the population treated, monthly ranibizumab and monthly bevacizumab were comparable in terms of functional gains. Two-year CATT data have yet to be published. Clinical trial data show that VEGF Trap-Eye injections every two months are equivalent to monthly injections of ranibizumab in terms of functional gains. In terms of anatomical gains, as measured by a change in the total lesion area, monthly ranibizumab and monthly bevacizumab appear comparable at stabilizing the anatomical impact of wet AMD. The VEGF Trap-Eye trials used a different measure of anatomical change that cannot be compared to total lesion area, but by that measure VEGF Trap-Eye treatment has been shown to reduce the size of anatomical lesions.

In summary, one-year clinical data published so far shows that ranibizumab, VEGF Trap-Eye, and bevacizumab produce comparable improvements in visual acuity and lesion growth and that use of these anti-VEGF therapies produce the best clinical outcomes in the treatment of wet AMD. There appear to be no serious short-term concerns about intraocular safety for the registered therapies (ranibizumab, VEGF Trap-Eye and pegaptanib), and the overall potential for associated systemic adverse events appears acceptable over the short term. There is less certainty about safety

and complications arising from off-label use of bevacizumab, which is dispensed for cancer use and diluted by local pharmacies into smaller quantities for injections into the eye. It is clear, however, that long-term studies are needed to confirm both efficacy and safety findings, and that research needs to be done to determine if there are ways to avoid trading good outcomes for fewer treatments by using alternative dosing strategies. Currently, many retinal specialists begin to prolong the time between injections once a patient's disease has stabilized or shown improvement. In addition, it would be helpful if clinical trials more accurately reflected the "real world" of clinical practice.

Translating Evidence to Public Health Policy in Latin America

The development in recent years of several different types of angiogenesis-based treatments has brought new hope to patients with wet AMD. But translating the evidence regarding those treatments into public health policy, specifically in Latin America, presents several challenges.

Several factors must be considered during the formation of public policy: the quality of the evidence, its applicability to a particular setting, and the trade-offs between desired and undesired

effects. Policymakers must determine whether a particular policy or program is technically, administratively, and financially feasible, and whether it is in agreement with the predominant values and political climate of the country or region where it is being considered for implementation. In addition, the policymaking process must be systematic and transparent. And it must also include input from all relevant stakeholders: healthcare providers, payers (private and public), patients, and the society at large.²²

This weighing of the evidence regarding risks and benefits can be seen in the various policies in Latin American concerning anti-VEGF treatments for wet AMD. In Brazil, for example, many payers in the private health system have decided that the safety risk associated with the off-label use of bevacizumab for treating wet AMD outweighs the benefits of the lower cost. This decision was made after a law was passed that obliged private payers to cover wet AMD treatments starting in January 2012, and the payers recognized liability issues. Bevacizumab is, therefore, currently not reimbursable in Brazil in many HMOs and private insurance plans as well as is not available in the public health system, although patients can still be treated with the drug if they pay for it out-of-pocket. In other Latin American countries, however, bevacizumab remains the main treatment drug for wet AMD, primarily because of its lower cost and because of the requirement that patients must pay for treatments not available or covered in their health system.

Where We Want to Be

Anti-VEGF therapy is undoubtedly making a remarkable difference in the lives of patients with wet AMD, including those in Latin America. However, there is plenty of room for improvement in terms of how patients are brought into the treatment system and how they are treated once their condition is diagnosed. The healthcare system itself, particularly the retinal specialists who suddenly found themselves both empowered and overwhelmed when the first effective treatments for wet AMD became available, was not designed to provide optimal care to the sudden flood of patients that the advent of anti-VEGF therapy brought through clinic doors.

To open the discussion on how to improve the treatment and outcomes for wet AMD in Latin America, the summit participants reviewed the findings of an informal survey that they had completed before arriving at the summit. The survey had asked questions about the current state of AMD treatments and outcomes in the participants' countries. It had also asked the participants to identify the top barriers in their countries that are impeding efforts to improve those treatments and outcomes. The survey's findings proved a useful "warming up" exercise for the conversation that followed.

The Desired Future State of AMD Treatment in Latin America

After the survey's findings were presented, participants were asked to discuss the first key question of the summit: In their opinion, as leading practitioners in this field who treat or interact with AMD patients every day, what would be the desired future state of a patient-centered system in Latin America that would provide the best outcomes for patients with wet AMD?

The participants agreed that one of the central features of this ideal future state would be a longer-lasting treatment, perhaps one that was taken orally or in the form of eye drops rather than as an injection. Such a treatment would reduce the burden on patients and caregivers associated with having to make monthly visits to retinal specialists, and could decrease the cost of therapy, both for the patient and the healthcare system. Such a therapy would also greatly reduce

the burden that Latin America's limited number of retinal specialists are experiencing in trying to meet the demands of repeatedly treating and monitoring a growing number of patients with wet AMD.

Not all of the summit's participants were convinced, however, that a less invasive, therapy, although desirable, would lead to better overall compliance with treatment. It was pointed out that patient compliance is not always strong with topical treatments, as illustrated by the difficulty healthcare professionals encounter with getting glaucoma patients to adhere to their at-home eye drop therapy.

Participants did agree, however, that in the desired future state of a patient-centered AMD treatment system, health care systems would recognize the value of these treatments to society and offer full access to reimbursable treatments. The high cost of current treatments was repeatedly cited throughout the summit as a major barrier to the timely and effective treatment of wet AMD in Latin America. Also discussed was the emotional and financial burden that patients and their caregivers incur as they attempt to maneuver through the current system of getting approval and reimbursement for treatment.

Another feature of the desired future state, participants agreed, would be a greater awareness of AMD, both by the public and by members of the non-retinal specialist physician community. If both these groups were more knowledgeable about AMD, there would be an increase in the number of individuals coming in for screening at the earliest signs of vision loss and in the number being referred to retinal specialists for therapy while wet AMD is most treatable. Some patients have said that they waited to go to the doctor because they thought they needed new glasses. They did not realize that they were experiencing a major compromise of vision and had a short window of opportunity to get treatment and save their eyesight. Too many individuals go blind in one eye before understanding the full and devastating consequences of not seeking treatment early in the course of the disease.

A better understanding of the disease would also improve compliance. If patients and caregivers knew how the disease worked, they might be more proactive in seeking access to regular care. In addition, a more knowledgeable public might

also inspire policymakers to lift some of the current cost and bureaucratic barriers to timely and effective treatment. By raising awareness of the value of eyesight in the elderly, policy makers would understand how vision is linked to the economy of their countries. With the growing aging population, vision plays a key role reducing the costs associated with aging. For example, poor vision can lead to falls and accidents that require expensive hospital stays. It can also reduce the independence of older individuals, causing them to be a financial burden to society earlier than needed.

Taking into account the high costs of nursing home care and the need to keep the elderly population as contributing members of society, the costs of treatment do not seem as consequential. Because of its significance to global economies, preventable blindness is a key agenda item in the Non-Communicable Disease meetings of the World Health Association. To help improve the situation in Latin America, it was suggested that Latin American countries initiate AMD-related public awareness campaigns similar to those that have successfully raised awareness in the region about the need for the early detection and screening of breast cancer.

One participant pointed out that Colombia has a national Day of Vision on which individuals are encouraged to test their own vision; this program has dramatically increased the number of people who go to the doctor for an eye examination. That country is also using social media to reach young people and encourage them to talk to their parents and grandparents about AMD. In addition, the Colombian Vitreo-Retinal Association has a program for training primary care physicians and optometrists, and has worked with the pharmaceutical industry to educate cardiologists and gerontologists about AMD.

An essential component of any public awareness campaign, the participants agreed, is a concerted effort to explain to patients, their families, and the public at large that AMD is a chronic condition, one that, like heart disease and diabetes, requires ongoing medical surveillance and care. Patients must also be made aware of the disease's natural progression so that they understand how crucial it is to receive treatments in a timely fashion and what to realistically expect from those treatments. Of particular importance is that patients understand

that it is unlikely that injections will completely restore sight that's already been lost.

Yet another feature of the desired future state would be more timely access to treatment. After wet AMD is diagnosed, the window for successfully treating the disease is relatively short. Any delay, including ones due to health policies and reimbursement barriers, can mean the difference between patients retaining their sight or becoming blind. The summit participants also agreed that treatment should include vision rehabilitation so that each patient's quality of life remains as high as possible after diagnosis. Such rehabilitation includes access to vision-enhancing tools.

To improve access to treatment, less expensive and more widely available AMD-related diagnostic technologies are also needed. Such technologies would not only help with the diagnosis of AMD, but would also help predict its disease course in a way that would reduce the burden on retinal specialists to screen and monitor patients. While SD-OCT is a highly accurate and effective technology, it requires expensive equipment and extensive training that precludes its widespread use by general ophthalmologists and primary care physicians.

A deeper understanding of the complex etiology of AMD, particularly wet AMD, was identified as an additional feature of a desired future state of patient-centered AMD care. Today, little is known about the underlying sequence of molecular events that leads to the deposition of drusen and the onset of abnormal angiogenesis in the retina. And though it is clear that genetics plays a major role in determining disease susceptibility and that some populations are more likely to develop wet AMD than others, the role that specific genes play in the pathology of the disease has yet to be uncovered. In addition, little is currently known about why many wet AMD patients do not respond to anti-VEGF treatment. In a desired future state, the summit participants agreed, not only would health professionals understand why some patients are non-responders, but they would also have effective alternative treatments for those patients.

Finally, the summit's participants stated that the desired future state would include epidemiological studies about AMD in Latin America. Such studies have not yet been conducted, so little is known

or understood about the incidence, prevalence, or progression of the disease in this area of the world. What is known, however, is that the elderly population in Latin America is growing at a rapid rate. The United Nations, for example, projects that the percentage of people aged 65 and older in Latin America will triple by mid-century, from 6.3 percent in 2005 to 18.5 percent in 2050.²³ Since AMD is a primarily a disease of the aging eye, these statistics suggest that AMD will be requiring an increasing amount of Latin America's medical resources. It also points out the urgency of developing healthcare systems that will be equipped to handle the substantial number of individuals who will need treatment for AMD in the coming years.

In summary, the ideal future state of a patient-centered AMD treatment system in Latin America would have:

- Longer-lasting, less-invasive treatments at low or no cost to patients.
- A public that is well educated about all aspects of AMD diagnosis and treatment.
- Policy makers that understand the impact of vision on a country's economies.
- Timely, technologically advanced, and more easily accessible diagnostic tools, as well as better trained diagnostic clinicians.
- Deeper scientific understanding of AMD, including its genetic and biological causes.
- Epidemiologic knowledge about the incidence, prevalence, and progression of AMD in Latin America.
- A health care system that would offer full access to reimbursable treatments with limited barriers to accessing care.

Existing Barriers

With the desired future state in Latin America defined, the moderator asked participants to list barriers that stand in the way of the region reaching it. The key barriers identified were the following.

Barriers Related to Early Diagnosis and Treatment

- Incomplete knowledge of the pathology and underlying causes of the disease
- Lack of Latin America-specific epidemiologic data about the disease
- Lack of effectiveness data for diagnostic screening
- No clear guidelines about when patients should be referred to retinal specialists
- No universally followed treatment guidelines
- Lack of priority for treating AMD when co-morbid conditions exist
- Lack of treatment options for dry AMD
- Poor prognostic indicators
- All current therapies are short-acting and thus require repeated injections

Barriers Related to Patients

- Health insurance bureaucratic systems that limits, and at times blocks, access to licensed AMD treatments
- Complicated reimbursement systems that often end up delaying treatment
- Lack of awareness about AMD among the general public and non-retinal physician specialists
- Poor patient compliance, which is made difficult because patients do not want to be a burden on their families given the cost of treatment and the difficulties of securing transportation to appointments for treatments
- Poor patient understanding of what to expect from treatment
- Poor caregiver understanding of how to help their family members
- Lack of organizations in each country advocating for patient rights

Barriers Related to the Healthcare System

- Lack of understanding among policymakers about the economic impact from vision loss in the elderly
- The failure of insurers to consider wet AMD as a priority disease
- The high cost to healthcare systems of screening equipment and anti-VEGF treatments
- Insufficient AMD-related training for optometrists, general ophthalmologists, primary care physicians, gerontologists, and other medical “gatekeepers”
- Poor geographic dispersal of retinal centers
- Limited access to vision rehabilitation specialists
- Lack of communication among doctors treating patients with co-morbidities, such as diabetes and heart disease
- Regulatory decisions that limit treatment options in some countries
- Lack of transparency by governmental agencies, pharmaceutical companies, physicians, and others about decisions regarding how wet AMD is going to be diagnosed and treated

Developing Solutions in Latin America

With key barriers defined, the summit participants engaged in a discussion about their findings. They talked about how these barriers might be overcome with improvements to current practices regarding the awareness, early detection, and treatment of wet AMD. They then discussed how to define success regarding treatment outcomes and what research needs to be undertaken to help reach outcomes that would be valued by all stakeholders.

Improving Awareness and Early Detection

A major barrier to improving early detection of wet AMD in Latin America is the lack of awareness about the disease on the part of both the patients and the physicians, other than retinal specialists. Getting patients into the clinic for treatment at the earliest appearance of wet AMD and retaining them in treatment will keep the majority of individuals from losing their vision.

Some efforts to improve the public's awareness of AMD are, of course, already underway in Latin America. Colombia's Day of Vision has an objective of getting patients into the health system early, with wet AMD designated as a "priority condition." Physician members of the Colombian Society of Ophthalmology make a point of doing media interviews as often as possible. In Brazil, information about wet AMD is disseminated to the public through Retina Brasil and the AMD Alliance International; these organizations promote an "AMD Awareness Week" each September. Other country-specific non-profit organizations attempt similar campaigns, but it was generally agreed by the summit's participants that a larger, more cohesive effort—perhaps one held simultaneously throughout the region—would have a more profound impact on raising public awareness. Participants discussed modeling such a campaign after successful efforts to educate the public about AIDS and breast cancer. They also discussed the importance of involving all stakeholders in such efforts, including physicians, patients, policymakers, the pharmaceutical industry, and the media.

It was also agreed that epidemiological studies about the incidence and prevalence of AMD among Latin American populations would greatly enhance the effectiveness of any public awareness

campaign about the disease. The data from such studies could be used to underscore—particularly, perhaps, for policymakers—the projected growth in Latin America's aging population and the exploding need this growth will create for an increase and improvement of AMD-related services. Such data could also be used to point out the long-term cost-effectiveness of early detection and treatment.

Improving the early detection of wet AMD also requires educating optometrists and non-retinal physicians, in particular general physicians, geriatric physicians, cardiologists, and other medical professionals with large elderly patient groups, about the disease's earliest signs and symptoms. These medical professionals must also be trained to know when to refer patients with suspected AMD to a retinal specialist—and health insurers should encourage such referrals. Delayed referrals are a leading cause of unnecessary vision loss among AMD patients. Right now, Latin America does not have enough trained healthcare professionals, particularly in rural areas, to handle the demand for AMD screening, the summit's participants stressed.

To accommodate the growing number of Latin Americans who will be requiring AMD screening in upcoming years, more and better diagnostic equipment will also be needed. The cost of the equipment must come down, however, so that it can be more widely distributed. In the meantime, expanding the use of telemedicine technologies (the use of electronic communications to exchange medical information from one site to another) might help address some of the demand for AMD screening. One summit participant noted that the medical community in Chile uses telemedicine to help with the diagnosis of diabetes; something similar might be tried with wet AMD.

A final underlying issue that summit participants saw as a barrier to early detection was the lack of clear definitions for early-stage wet AMD. Different countries use different terminology and diagnostic criteria in their guidelines. For example, the Colombian Society of Ophthalmology has published its own guidelines, while physicians in Costa Rica use the preferred practice patterns of the American Academy of Ophthalmology. Summit participants agreed, however, that it remains unclear how widely any of the existing AMD diagnostic and treatment guidelines are used in their countries. They also agreed that a

cross-regional set of guidelines—one that would then be broadly distributed and implemented—might be an important project for Latin America’s medical societies to undertake.

Improving Access to Effective Intervention

Early diagnosis and prompt and aggressive treatment of wet AMD, particularly within the first year of disease, are essential for improving visual outcomes for patients.²⁴ The majority of Latin American patients with wet AMD, however, are not receiving the optimal medical care that is needed to maintain vision and prevent progressive vision loss. A number of factors are at play.

To begin with, most Latin Americans—up to 95 percent in some countries—receive their health care through government programs or through social security programs offered through their employers. These programs may not offer access to treatments for wet AMD or, if they do, they make accessing those treatments a bureaucratic nightmare. In Brazil, for example, it can take two to three months for individuals to bring the necessary legal actions against the state to receive anti-VEGF treatment after diagnosis. Most patients, particularly those who lack mobility and/or easy access to transportation, give up on getting anti-VEGF treatment after diagnosis because of these bureaucratic hurdles. For others, the process takes so long that treatment occurs too late to save their vision.

Accessing anti-VEGF treatment for wet AMD is also difficult for many Latin American patients with private insurance. One patient advocate from Colombia spoke movingly at the summit about her struggle to get access and reimbursement to timely anti-VEGF treatments for her husband after he was diagnosed with wet AMD. She was directed from agency to agency in her attempt to complete the complicated and redundant paperwork that her insurer required for the authorization of payment for treatment, even requiring the couple’s wedding license as proof of identity. This effort took months. Fearful that the window for successful treatment of the disease was closing, the couple opted to pay for the first two months of treatments out of pocket, at a cost of approximately USD\$2,000 each. Few individuals in Latin America however are able to navigate this system, not only because of the multiple bureaucratic barriers but few are able to provide the costly private payment without reimbursement.

Both private and public insurers put up other barriers that have the effect of impeding successful outcomes from anti-VEGF treatments for wet AMD. For example, although wet AMD typically requires, depending on the patient’s response rate and the chosen drug treatment, 5 to 12 anti-VEGF injections a year, insurers often cover only a limited number of treatments, sometimes as few as one or two. Patients must pay for subsequent treatments out-of-pocket, an expense that is prohibitive for most elderly Latin Americans and their families. Even in the rare cases when insurers cover all treatments, the co-pays can be very high.

Because Latin American patients must often bear the financial burden of anti-VEGF therapies, many are choosing to receive bevacizumab, which is not indicated for eye diseases but is used off-label for wet AMD, primarily because of its significantly lower cost. Although the initial findings from a clinical trial comparing bevacizumab with ranibizumab suggests the two drugs are both effective at preserving and improving visual acuity, at least during the first year of treatment,⁵ concerns have been raised about bevacizumab’s safety. It is not available from the manufacturer in a standard dose or formulation suitable for treatment of wet AMD and thus must be divided into smaller doses by pharmacists, a process that can introduce the risk of bacterial contamination. Improper dilution and manipulation of the drug is a particular concern in Latin America, and Colombia has issued a warning about using bevacizumab in the eye.^{5a}

After weighing these safety concerns, many HMOs and insurance companies in Brazil decided that ranibizumab would be the only anti-VEGF agent to be covered and reimbursed as of January 1, 2012. Patients may still request bevacizumab, but those companies will no longer pay for the drug. In Colombia, bevacizumab is not approved to be used in eye diseases and the national regulatory agency, INVIMA, issued a warning about the risk of using bevacizumab in ophthalmology.^{5a} Recently, however, the original value that healthcare providers would be reimbursed for ranibizumab was reduced by 85 percent. This has led some insurers to offer coverage only for bevacizumab. In Latin American countries where there is little access or coverage for anti-VEGF medication, the percentage of patients using bevacizumab over ranibizumab is quite high: 80percent in Argentina, for example, and 90 percent in Peru, according to the estimates of the summit’s retinal specialists.

Discussions around getting the cost down for anti-VEGF therapies was a repeated topic of discussion during the summit, yet there was agreement that more discussion is needed to identify workable solutions. Suggested starting points included the possibility that Latin American health agencies could attempt to negotiate and purchase government-approved anti-VEGF agents in bulk—and thus at a lower price. However, because the purchasing systems for countries differ, this proposal would require a high level of coordination among government agencies. Alternatively, because vision is essential to keeping the elderly independent, governments could provide subsidies to help pay for the costs of treatment. Other suggestions encouraged a more innovative approach, such as public-private partnerships where governments, patient organizations, and pharmaceutical manufacturers work closely to develop a new solution, it was agreed upon though that there is much more needed discussion to identify innovation solutions to address the cost of treatments.

It was also noted that the newest anti-VEGF agent, VEGF Trap-Eye, might prove less expensive than ranibizumab. Not only are VEGF Trap-Eye's individual injections currently priced in the United States at about USD\$100 less than those of ranibizumab, clinical trial data on VEGF Trap-Eye suggest that after a monthly application during the three first months of treatment, the medication can be administered every two months instead of monthly, which in turn may lessen the burden of both the patient and the retinal specialist due to fewer required office visits. VEGF Trap-Eye is not currently licensed in any Latin American countries, but it is expected to become so soon.

Another factor that impedes the timely and aggressive treatment of wet AMD in Latin America is poor compliance among patients. While some of this compliance failure can be explained by both accessibility and cost barriers, the lack of understanding among patients about the pathology and progression of wet AMD also plays a role. Patients often do not know nor understand how anti-VEGF treatments work or why the schedule of those treatments is so essential to a successful outcome. When they do not see an immediate improvement after their initial treatment, many patients do not return for a second dose. (The summit's participants did note, however, that patients who have lost their vision in one eye to the disease are almost always fully compliant about treatment for the second eye.) In addition, non-retinal physician specialists

sometimes give patients inaccurate descriptions of what to do in regards to treatment and what to expect from the results. One solution to this pressing problem about patient compliance, the summit participants agreed, would be standardized clinical practice guidelines, including a set addressed specifically to patients and their families. These guidelines would spell out the exact steps involved in the treatment of wet AMD.

Summit participants also discussed what is known about AMD prevention, since prevention would be the best intervention of all. Prevention-related studies have been undertaken to help determine how the disease might be mitigated, but results have been discouraging. Among modifiable risk factors, smoking has been found most consistently to be associated with AMD. One recent study reported that current smokers were four times more likely than their peers who never smoked to develop late, but not early, AMD.²⁵ Other research has suggested that a diet rich in high amounts of antioxidants, particularly the carotenoids, lutein and zeaxanthin (found in green, yellow, and orange fruits and vegetables), might also decrease the incidence of late, but not early, AMD.²⁶ Perhaps most promising was a 10-year randomized clinical trial that found a significant reduction in the risk of developing advanced AMD among high-risk people who took supplements containing several antioxidant vitamins and zinc.¹⁰ ("High risk" was defined in the study as having intermediate AMD in one or both eyes or advanced AMD in one eye.) But the safety of taking such supplements in high doses, particularly over a long period of time, is unclear. Furthermore, high-dose vitamins are not always available without a prescription in Latin America. They cannot be sold over the counter in Argentina and Brazil, for example, and only recently became available without a prescription in Colombia.

Value Analysis: Defining Successful Outcomes

After discussing possible solutions for improving the diagnosis and treatment of wet AMD, the summit's participants turned their focus to how they would define success regarding the outcomes of such efforts. What are the desirable patient-centered outcomes for wet AMD treatment? And are there actions that can be taken at the national health or payer level to improve the value of treating wet AMD?

The moderator explained that different stakeholders involved in the treatment of wet AMD—patients, physicians, payers, and the society at large—may place higher or lower values on different outcomes. This led to a discussion of what is currently used as the primary endpoint of the effectiveness of anti-VEGF treatment: improvement in visual acuity, which is measured by the familiar eye chart with its 11 lines of block letters (“optotypes”).

But, as several summit participants pointed out, visual acuity may not reflect the true vision of patients. Patients who are receiving treatment for their wet AMD value more “real-life” functional endpoints, such as the ability to read, sew, dial the phone, or see the faces of their grandchildren. They’re not necessarily interested in how many more letters they can or cannot read on an eye chart. AMD-related clinical trials have sometimes included quality-of-life measurements,¹⁰ but those findings have not been translated into usable endpoints for measuring the success of treatments.

SD-OCT, which produces high-resolution, cross-sectional images of the retina, is also commonly used to measure the effectiveness of anti-VEGF drugs, and has recently been added to clinical trials as a secondary endpoint. SD-OCT can identify fluid leakage from blood vessels.

Safety was also discussed as a value that needs to be considered when comparing various wet AMD treatments and their outcomes. At what point do the risks of wet AMD treatment outweigh the benefits? Major side effects associated with anti-VEGF medications include conjunctival hemorrhage, retinal detachment, eye pain, floaters, and increased eye pressure. Bacterial endophthalmitis is also a concern, particularly when bevacizumab is used, due to the way bevacizumab has to be prepared. These potential adverse events point out the need for 1) more research on the long-term systemic effects of these drugs and 2) better guidelines on how to use the research-to-date to determine an individualized risk-benefit analysis for the treatment of patients diagnosed with wet AMD.

Cost-effectiveness analyses are also needed. How much is an eye worth—to individuals and to society? The summit’s participants noted that some patients decide the cost of AMD treatment

is too high to justify saving both eyes, and often opt to only have only one eye treated. But this is actually a ‘take it or leave it,’ choice scenario for if those patients had comprehensive and inexpensive access to care, they would not need to make it.

Setting a Research Agenda

A constant theme voiced throughout the summit was the need for more research, and as a final item of business the summit participants listed research priorities in the areas of basic understanding of disease, translational science, and the delivery of health services. This discussion ended with a discussion of current knowledge gaps, particularly as they relate to improving outcomes for Latin Americans with wet AMD.

Globally, the ultimate goal of an AMD research agenda must be to develop a cure for this disease, as well as ways to achieve primary prevention. However, because AMD is a chronic disease of aging, new and better therapies are critical. A better understanding of how the pathological changes relate to functional changes remains to be elucidated. While SD-OCT reveals structural changes, the relationship between structural changes and functional changes still needs to be fully understood. Reaching this goal will require a detailed understanding of the pathology of the disease. Given that 50 percent to 70 percent of the pathogenesis of AMD may be driven by genetic factors in certain populations,^{27,28} there should be a significant investment in efforts to correlate genotype and phenotype both to get at the root causes of AMD but also to identify subtypes of the disease based on genetics. Understanding the molecular biology of the disease should also lead to the development of better animal models for the disease and perhaps lead to the identification of intraocular or circulating biomarkers for AMD.

Critical unanswered questions concern disease progression, particularly the transition from dry AMD to wet AMD. Understanding the molecular and genetic events involved in disease progression would not only provide new drug targets and routes for preventing and in the future curing AMD, but also molecular markers—in addition to visual acuity measurements—to judge the effectiveness of drug therapy. Such research is likely to discern the role that growth factors

other than VEGF—such as PDGF (platelet-derived growth factor), PlGF (placental growth factor), FGFs (fibroblast growth factors) — play in neovascularization and identify the molecular pathways that trigger aberrant angiogenesis.

Similar to other fields of targeted therapy, research on disease outliers is likely to be productive. Understanding why some people are good responders to anti-VEGF therapy while others may only respond poorly or are not respond at all, is important. An even more fundamental question is why some aging individuals never develop drusen or other changes in the retina. It may also be fruitful to understand how age-related changes in the retina may be connected to age-related changes in other parts of the body. In addition, more knowledge is needed about the role that co-morbidities play in the progression of AMD and in patient response to treatment. Such co-morbidities include high blood pressure, high cholesterol, atherosclerosis, arthritis, coronary heart disease, cataracts, and glaucoma.²⁹

In the area of translational science, the summit participants stressed the need for the global development of improved drug delivery and longer lasting therapeutic modalities. Advances in fields such as nanotechnology, microfluidics, and cell biology need to be brought to bear on the delivery of drugs into the eye. Support should also be given to efforts to develop new and less expensive screening instruments that could be used effectively by general practitioners, ophthalmologists, and optometrists. Research is also needed to develop efficient and cost-effective methods of delivery of diagnostic, treatment, and monitoring services to an aging population.

Summit participants then composed a list of research-related questions that need to be specifically addressed in Latin America:

- How does wet AMD affect the region? Are there any genetic or other AMD-related risk factors that are more prevalent in Latin America? Also, how do co-morbidities, such as diabetes and cardiovascular disease, affect the incidence and progression of wet AMD among Latin American populations?
- What are the AMD-related biomarkers among Latin American populations?
- What are the quality-of-life endpoints most valued among the Latin American population with wet AMD? (Summit participants pointed out that the current reliance on questionnaires from other areas of the world, particularly from the United States, to assess quality-of-life issues leads to inaccurate findings due to cultural differences.)
- What AMD-related patient-compliance problems are unique to Latin America, and what specific actions would be most effective in addressing those problems?
- Are there safety concerns about anti-VEGF therapies that should be of particular concern in Latin America? For example, are there any genetic factors among Latin America's ethnic groups that raise specific safety concerns?
- How can the number of available AMD-related clinical trials of Latin Americans be increased? (Participants pointed out that the clinical trial retention rate tends to be higher in Latin America than in the United States.)

The summit participants agreed that the filling of these and other AMD-related knowledge gaps requires a unified effort of all interested stakeholders.

Summary of Desired Actions

Over the course of the daylong summit, the assembled experts agreed that certain key actions should be taken to improve the care—and the quality-of-life—of the growing number of Latin Americans diagnosed with wet AMD.

1. Improve awareness and early detection of wet AMD.

- Enact public awareness campaigns to increase the general public's knowledge about the early signs of wet AMD and the importance of self-testing.
- Work with primary care physicians and general ophthalmologists to improve early detection of wet AMD and increase referrals to retinal specialists for follow-up exams and treatment.
- Develop comprehensive programs for diagnostic training that will reach a wider range of physicians beyond ophthalmologists specializing in retinal diseases.
- Increase access to diagnostic technologies for all patients throughout Latin America.
- Increase understanding among policy makers of the economic impact of vision loss in the elderly.

2. Improve access to effective interventions.

- Ensure full access to licensed anti-VEGF therapies.
- Establish unencumbered reimbursements systems that will ensure timely treatments and allow for full patient compliance.
- Develop better practice guidelines that will retain more patients with wet AMD in the medical system so that they can receive optimal treatment and avoid losing their vision.
- Improve the coordination throughout Latin American healthcare systems for managing co-morbidities associated with wet AMD.
- Improve access to vision rehabilitation treatments, including access to vision enhancement tools.

3. Improve value for stakeholders.

- Ensure that the benefits and risks of anti-VEGF medications are openly discussed between retinal specialists and their patients.
- Ensure that new practice guidelines are patient-centric, that is, they work to minimize the burden to the patient while maximizing therapeutic outcome.
- Determine which outcome measurements are of most value to Latin American patients specifically.
- Develop the knowledge base to determine the cost-effectiveness of different treatment options.

4. Improve translational research.

- Initiate epidemiological studies to gain more knowledge about the incidence, prevalence, and progression of AMD among Latin American populations.
- Promote research that elucidates the pathogenesis of AMD and its progression from dry to wet forms.
- Establish quality-of-life endpoints most valued among the Latin American population with wet AMD.
- Increase the number of clinical trials initiated in Latin America.

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This report was made possible by the support of Bayer Healthcare and Edelman Latin America.



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