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

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A Report Based on an International Expert Summit  
Convened in Berlin, Germany, November 2011

# Key Points

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1. The majority of patients with wet AMD are not receiving the optimal care that is needed to maintain vision and prevent progressive vision loss.

- Early diagnosis and aggressive early treatment improves visual outcomes, but these require ready access to retinal specialists, appropriate treatments, and regular monitoring following initiation of therapy.
- Access to licensed anti-VEGF therapies needs to be more uniform.
- Co-payments required of patients to receive anti-VEGF therapies or monitoring with OCT present financial hardships or are unaffordable to many.
- Even where anti-VEGF therapies are available, the number of injections a patient can receive may be limited depending upon what is covered by payers.
- 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.

2. New targeted therapies and diagnostic technologies – VEGF-targeted anti-angiogenesis therapy and Spectral Domain Optical Coherence Tomography (SD-OCT) – have produced a true paradigm shift in the diagnosis and treatment of wet age-related macular degeneration (wet AMD), the leading cause of blindness in older adults. Some 500,000 new cases of wet AMD are diagnosed globally each year. The enormous impacts of this revolution in the detection and treatment of the leading cause of vision loss in older adults are still being felt by a field that went from having no truly effective treatments to having four highly effective therapies (pegaptanib, ranibizumab, bevacizumab, aflibercept) over a mere seven-year period.

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

# Key Points

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**3.** With no clear practice guidelines in place, a frontier mentality pervades the field. Already, retinal specialists in different countries, or even different regions in the same country, are developing unique approaches to diagnosing and treating wet AMD. While experimentation with different therapeutic regimens is to be expected – and even encouraged – during a paradigm shift, the field needs to develop consensus guidelines that will ultimately benefit patients, retinal specialists, and healthcare payers alike.

- Retinal specialists and general ophthalmologists need comprehensive training to use SD-OCT and guidelines for interpreting SD-OCT images.
- Consensus panels must set clear definitions of disease stages and therapeutic responses.
- A strong professional association or consortium of associations should create practice guidelines that set out the most effective approaches to therapy for different patient groups.

**4.** There is a critical need for both basic research and translational science to address unanswered questions that act as barriers to the optimal diagnosis and treatment of wet AMD even with the advent of today's effective therapies.

- The pathobiology and molecular biology of AMD are still not well understood.
- There are no biomarkers for the early detection of AMD, conversion of dry AMD to wet AMD, or response to therapy.
- The full role of VEGF and other growth factors in the etiology of wet AMD is unclear.
- Long-term outcomes of anti-VEGF therapy have not been established.
- The differences among non-responders, patients who need long-term treatment, and those who can successfully end therapy have not been identified.

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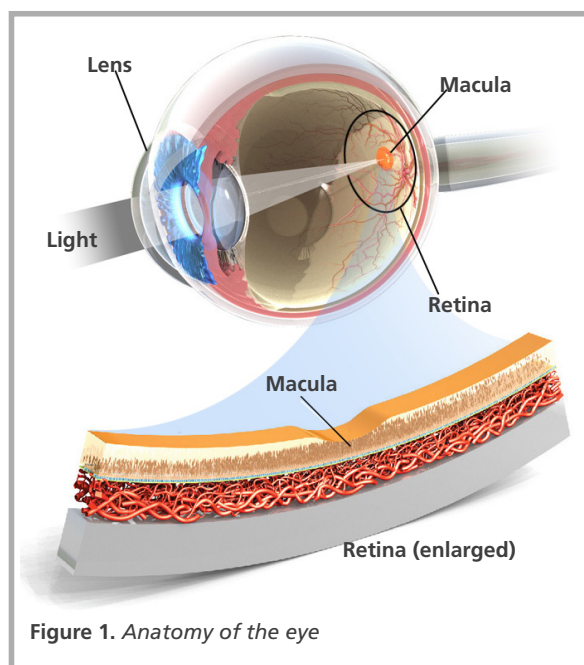
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# Introduction

## What is AMD

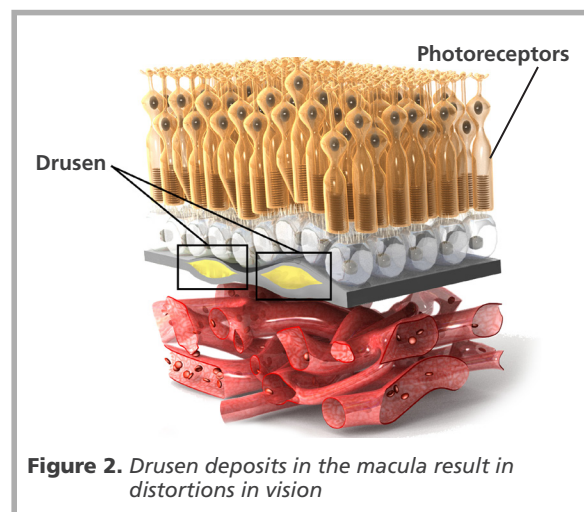
Age-related macular degeneration (AMD) is a disease associated with aging that gradually destroys sharp, central vision needed to read, recognize faces, drive, and in general see most anything clearly. As its name implies, AMD affects the macula, which is located in the center of the retina, the light-sensitive tissue at the back of the eye. The macula is the part of the eye needed to see fine details.



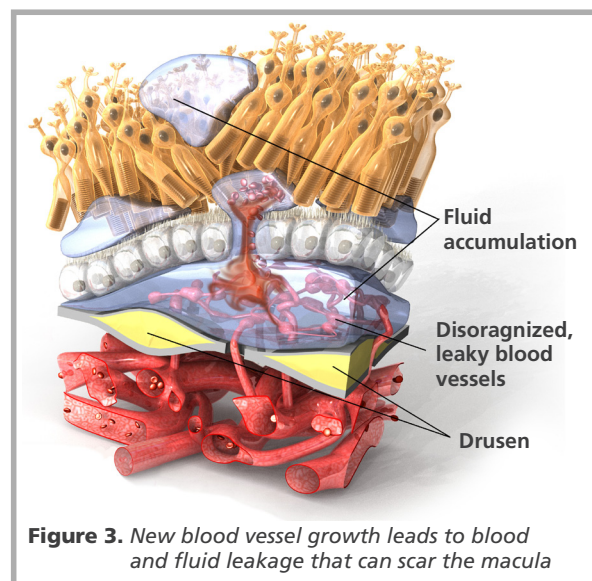
There are two types of AMD, known as 'dry' AMD and 'wet' AMD. Both forms can occur in one or both eyes, although the development of AMD in one eye appears to increase the risk that AMD will develop in the second eye. Neither form of AMD produces pain and as a result can go undetected until they produce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

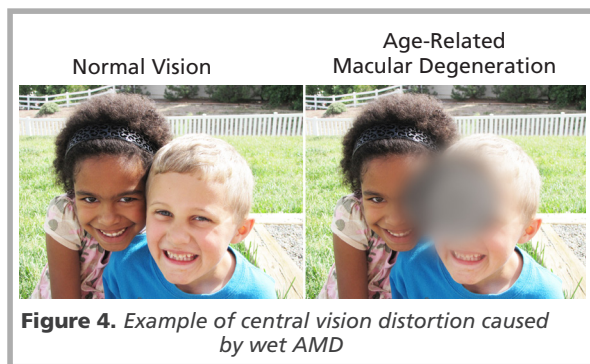


Wet AMD is the more serious form of the disease. For reasons that are as yet unclear, 10 to 15 percent of adults with dry AMD will go on to develop wet AMD and experience abnormal blood vessel growth under the macula. The growth of new blood vessels, known as angiogenesis or neovascularization, eventually 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.



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. In 2009, the U.S. Centers for Disease Control and Prevention (CDC) estimated that some 1.8 million Americans are affected by wet AMD and an additional 7.3 million are at substantial risk of developing the disease. Some 200,000 Americans are diagnosed with wet AMD annually, and the CDC estimates that the number of people with wet AMD will reach 2.95 million in 2020.

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



## Paradigm Change

The field of research focused on angiogenesis, which began in the 1960s, 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. The potential for angiogenesis-based medicines to advance modern medicine has been compared to that of antibiotics, which in the 20<sup>th</sup> century conquered many different previously untreatable diseases using a common approach.

In December 2004, the world changed for patients with wet AMD and the retinal specialists who treat them when the U.S. Food and Drug Administration (FDA) approved Macugen® (pegaptanib), the first inhibitor of angiogenesis to be successfully developed for wet AMD, which slowed the rate of vision loss. Antiangiogenic therapy, 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 Lucentis® (ranibizumab) became approved for the treatment of wet AMD. Lucentis, as well as Macugen, 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 Lucentis into the eye maintained their vision as long as the injections continued over the course of the trial. In addition, up to 40 percent of those treated with Lucentis for a year experienced a significant improvement in visual acuity, enough to restore their vision to 20/40 in the treated eye. Today, Lucentis is approved in over 100 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 was its price, about USD\$2,000 per injection, and the burden that receiving a monthly injection places on the patient and caregivers. Just before Lucentis became approved by the U.S. FDA, retinal specialists began experimenting with another anti-VEGF agent, Avastin® (bevacizumab), that was a major breakthrough for cancer treatment and had been approved in 2004 to treat colorectal cancer, and now is approved for other cancers as well. Avastin is a much larger molecule known as a monoclonal antibody, from which Lucentis, a smaller drug, is derived.

Avastin is not indicated for eye diseases, however, and is not available from the manufacturer in a standard dose or formulation that has been approved by regulatory authorities for use in the eye. It has nonetheless proven to be effective, and the off-label use of Avastin to treat wet AMD costs about USD\$50 per injection. It requires that Avastin as supplied for treating cancer be divided into the smaller, diluted quantities needed for treating the eye.



There have been concerns arising from reported cases of infection associated with Avastin use, thought to be due to poor pharmacy practices during dilution. Clinical trials comparing Lucentis with Avastin suggest they are both effective at stopping disease progression and restoring visual acuity, at least during the first year of treatment.

On November 18, 2011, a third anti-VEGF drug, Eylea® (aflibercept) received U.S. FDA approval for the treatment of wet AMD. Based on a drug technology fusing proteins together for neutralizing VEGF and blocking angiogenesis, Eylea is designed to be administered by one intraocular injection per month for three consecutive months followed by one injection every two months. Regulatory review of Eylea is pending in the EU, Australia and Japan.

Seven years into the new paradigm of treating wet AMD with vision-saving VEGF-targeted anti-angiogenesis therapy, it would be easy to assume that this is now a mature field that is well on its way to preventing the leading cause of blindness among older adults. Certainly, the globally expanding use of anti-VEGF therapies is improving the quality of life for countless numbers of individuals with wet AMD worldwide. However, 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. And while patients undoubtedly benefit markedly from therapy, many do not have access to licensed anti-VEGF therapies, and those who do may face severe challenges related to payment and 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 Expert Summit

Given the opportunities and tribulations 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



**Figure 5.** Moderated discussion at Expert Summit, Berlin, Germany, November 14, 2011

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 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 anti-angiogenic therapy for wet AMD. This White Paper provides an overview of the group's discussions and presents a number of steps that are needed to advance the treatment of wet AMD using anti-VEGF therapies to impact the greatest number of individuals possible.

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 and the current understanding of wet AMD biology and angiogenesis. Under the direction of the professional moderator, the assembled experts then engaged 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. A graphical facilitator 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. The group then prioritized those barriers according to two criteria: which ones if eliminated or reduced would have the biggest impact on the desired future state of the field, and those barriers that would yield to joint action by the AMD community.

Over the course of the summit's second day, the experts focused on issues specific to the

early detection of wet AMD, intervention in the disease process, and maintaining patient compliance. The group then engaged in an analysis of the value proposition for key stakeholders in the AMD community, including patients and their caregivers, treatment providers, and payers. Working off the foundation laid by these discussions, the experts then developed a research agenda and set of action items that together could move the field toward the desired future state in which the maximum number of individuals would be treated in the most effective and efficient manner possible.

## **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.



# Current Status

To open the summit, four experts gave 15-minute presentations as background for the subsequent roundtable discussions. **Dr. Francesco Bandello**, of the University Vita-Salute and the Scientific Institute San Raffaele in Milano, Italy, described the current status of AMD management. **Dr. Gemmy Chueng**, of the Singapore National Eye Center, summarized the current understanding of AMD biology. **Dr. Stephan Michels**, of the Triemli Hospital in Zurich, Switzerland, presented a comparative analysis of wet AMD therapies. **Dr. William Li**, of the Angiogenesis Foundation, discussed the lessons learned from anti-angiogenic therapy for cancer.

they lose their independence, and become dependent upon and a burden to family members and society at large.

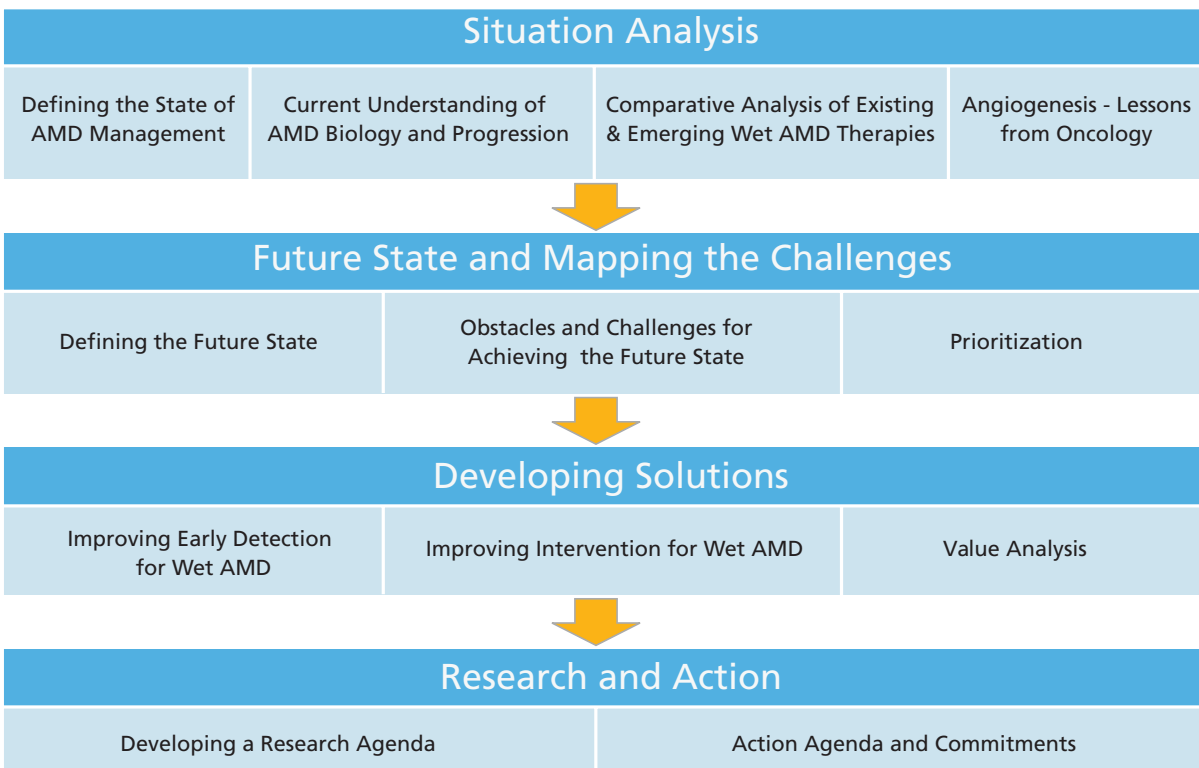
There is clear evidence that left untreated, the prognosis for patients with wet AMD is poor, and that the natural history of the disease is dramatic. Over the course of a year following diagnosis of wet AMD, untreated patients will lose on average two to three lines of vision<sup>1</sup>. A recent study 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<sup>1</sup>. Another study found that particular drusen characteristics were also predictors of a high risk for progression to wet AMD.

The good news is that the natural history of wet AMD is not set in stone. Multiple clinical trials have now shown that antiangiogenic therapy targeting VEGF stops disease progression, and in

<sup>1</sup> Changes in visual acuity are measured in terms of the number of letters and lines lost or gained in reading an ETDRS (Early Treatment Diabetic Retinopathy Study) standardized eye chart. Each line in the ETDRS chart contains 5 letters.

## Defining the State of AMD Management

Elderly patients need their eyesight to maintain their independence, to take care of their co-morbid medical conditions such as heart disease and diabetes, among other disorders. When wet AMD is undiagnosed and untreated,



**Figure 6.** Schematic Flow of the International Expert Summit

some patients, can partially reverse lost vision. In two different clinical trials, the average patient receiving monthly injections of Lucentis 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 over the additional year that the patients were observed<sup>2,3</sup>.

Another clinical trial showed that about 40 percent of patients receiving Lucentis can maintain their gains in visual acuity with less frequent dosing after three initial injections<sup>4</sup>. 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.

While it is clear that anti-VEGF therapy can successfully treat and even reverse the symptoms of wet AMD, there are a number of problems with current therapy options. The high rate of retreatment, for one, places a remarkable burden on both patients and retinal specialists, while the high cost of therapy is creating economic challenges for national healthcare systems that are already under strain. In addition, the optimal treatment regimen for specific subsets of patients has yet to be defined in clinical trials. 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.

## **Current Understanding of AMD Biology and Progression**

Drusen, a complex mix of multiple proteins and lipids, are the hallmark features of dry AMD, and they reflect the microenvironment of the retina. Meta-analysis of data from several studies has shown 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. Only one percent of patients who have “mild” drusen in one eye progress to wet AMD, while 26.4 percent of patients with “intermediate” drusen in both eyes progress to wet AMD. Over 40 percent of

patients with “advanced” drusen development in one eye will progress to wet AMD over the next five years. Beyond these correlations, however, there is presently no clear idea of how drusen are related to neovascularization and the development of wet AMD.

The current view of the pathogenesis of AMD is that it is a progressive systems disorder that may start with inflammation perhaps in response to oxidative stress, that affects the extracellular matrix in the retinal region. As the disease progresses, these changes in the extracellular matrix may be altering the balance of pro- and anti-angiogenic substances that include VEGF, which stimulates blood vessel growth, and another substance known as pigment epithelium-derived growth factor (PEDF), which inhibits it. Some studies have shown, for example, that PEDF levels are deficient in the eyes of patients with wet AMD. Other studies suggest that endostatin, another inhibitory protein involved in regulating angiogenesis, may be decreased in the pathology of wet AMD.

What is known from studying tumor development and other diseases, as well as healthy processes involving angiogenesis is that multiple growth factors, receptors, and other proteins and signaling molecules are involved in regulating angiogenesis in the body. Classes of enzymes, matrix metalloproteinases (MMPs) for example, are needed to breakdown the extracellular matrix so that new blood vessels can grow. Experiments that knock down levels of two specific MMPs – MMP-2 and MMP-9 – reduced angiogenesis in the eye, as did systemic administration of a molecule that interfered with the function of a molecule known as the  $\alpha_5\beta_1$  integrin, which is involved in cell adhesion.

It may be that processes other than angiogenesis are 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.

While the current state of knowledge about wet AMD is far from complete, angiogenesis is a key process in the development of the disease. It also raises the possibility that combination therapies targeting different aspects of the biology of wet AMD may result in improved and more durable clinical outcomes in the future.

## **Comparative Analysis of Current and Emerging Wet AMD Therapies**

As of November 2011, four anti-VEGF drugs have received regulatory approvals for use in humans. Macugen® was the first of these drugs approved for intraocular injection to treat wet AMD<sup>5</sup>, but it is used rarely today because Lucentis<sup>6</sup> has proven superior in clinical practice in every respect. Eylea was approved in the United States recently on the basis of demonstrating non-inferiority to Lucentis in clinical trials. An important distinction between these two drugs is that, in the relevant clinical trials, Eylea was administered bimonthly, whereas Lucentis was administered via monthly injections.

There have been multiple clinical trials studying Lucentis. Presently there is an important ongoing randomized clinical trial comparing Lucentis with Avastin – the Comparisons of Age-Related Macular Degeneration Treat Trials (CATT); the first year's results have been published<sup>7,8</sup>. All of the current randomized clinical trials are limited in their conclusion for some relevant outcomes, as they do not reflect nor compare the spectrum of dosing schedules currently in use. The year one results of the Eylea phase III trial are included in the Eylea package insert<sup>9</sup>.

From the clinical data that has been presented, it is clear that treatments with Lucentis, Avastin, and Eylea 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, Eylea is the only drug that has been shown to be efficacious in registrational trials when administered bimonthly, rather than monthly. Data from CATT show that over 12 months and in the population treated, monthly Lucentis and monthly Avastin were equivalent in terms of functional gains. Data comparing Eylea and Lucentis, show that these two drugs appear equivalent in terms of functional gains, but with differences in frequency of injections required<sup>1,7</sup>. In terms of anatomical gains, as measured by a change in the total lesion area, monthly Lucentis and monthly Avastin appear equivalent at stabilizing the anatomical impact of wet AMD.

In summary, clinical data published so far shows that Lucentis, Eylea, and Avastin 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 (Lucentis, Eylea), 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 Avastin, 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.

## **Angiogenesis – Lessons from Oncology**

Anti-angiogenesis therapy, primarily via the inhibition of VEGF function, has become a mainstay in the treatment of various forms of cancer, and there are lessons that the ophthalmology community can learn from the oncology community's experience with anti-VEGF agents. It is clear, for example, that VEGF induces vascular permeability in tumors and that anti-VEGF therapy can not only reduce the tumor vasculature but also can decrease intratumoral edema.

One of the key lessons learned from the use of anti-VEGF therapy to treat cancer is that VEGF trap and anti-VEGF antibodies have different biological effects on angiogenesis. Laboratories studies have shown these drugs result in different patterns of blood vessel inhibition after their administration. One possible reason is their different mechanisms of action. Avastin is a humanized monoclonal antibody and Lucentis is a smaller humanized monoclonal antibody fragment of the antibody. Both bind tightly and exclusively to the A-isoform of VEGF (VEGF-A). Eylea, or VEGF trap, is a fusion protein (also called 'soluble decoy receptor'), formed by fusing normally separate regions of two different VEGF receptors with part of an antibody molecule. Preclinical studies suggest

this enables the drug to bind more tightly to VEGF-A compared to the antibody-based drugs, such as Lucentis. In addition, Eylea also binds to VEGF-B and placental growth factor (PlGF), another member of the VEGF family. The broader targeting is considered advantageous, as these factors may also play a role in abnormal blood vessel growth in both cancer and wet AMD.

Another lesson from oncology is that maintenance treatment is important for sustaining the clinical benefits of therapy. In fact, some experiments suggest that stopping therapy can result in a rapid regrowth of blood vessels through invisible sleeves left by the original inhibited blood vessels. However, even if therapy is continued unabated, escape from suppression may occur eventually through the upregulation of other factors, including other forms of VEGF and PlGF. One human study in colon cancer, in fact, suggests that increasing circulating

levels of VEGF-C may be a predictive marker for the development of tumor resistance to Avastin.

As far as wet AMD is concerned, the main challenge will be to develop new therapeutic strategies that produce longer-lasting effects without the need for closely repeated injections. This would reduce the burden on both patients and retinal specialists that come with the need for monthly injections and follow up office visits, as well as potentially reduce healthcare costs associated with frequent office visits, injections, and monitoring. Such strategies will require a better understanding of the targets and pathways involved in retinal angiogenesis, as well as identifying the molecular mechanisms that trigger neovascularization in the first place. The development of longer-lasting or less invasive methods for delivering drugs into the eye will also be an important part of any strategy going forward.

# Where We Want to Be

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Anti-VEGF therapy is undoubtedly making a remarkable difference in the lives of thousands of patients with wet AMD. 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 in some countries.

As the first step on the path to developing an action plan for improving the treatment and outcomes for wet AMD, the summit participants were asked what was perhaps the most important question: In their opinion, as leading practitioners in this field who treat patients every day, what would be the desired future state of a patient-centered system that would provide the best outcomes for individuals with wet AMD?

While giving the participants a few moments to ponder this question, the moderator led a brief discussion about the different stages of AMD. Early AMD, which can be detected now using spectral domain Optical Coherence Tomography (SD-OCT), is characterized by the appearance of a larger amount of drusen in both size and number. There is no treatment for early AMD, which is always “dry,” that is, there is no neovascularization or edema. There was discussion about the role of antioxidant supplements in delaying the progression of intermediate dry AMD to wet AMD, although the participants stated that further study is warranted on this topic.

Over time, most cases of early dry AMD progress to late dry AMD, a more advanced form characterized by larger and more plentiful drusen that negatively impact visual acuity and can in severe cases cause blindness by disrupting the retinal pigment layer and the macula. Again, there is no treatment for late dry AMD.

Bringing the discussion back to the question at hand, the moderator went around the table and solicited an answer from each participant. Based on the responses, the perfect future state

would be one in which individuals with AMD are all detected early in the course of their disease, monitored for progression, and at the first signs of wet AMD given a single intervention that would stop the disease in its tracks and permanently reverse any neovascularization that had occurred.

The participants agreed that there was a desired future state that was more within the realm of the possible. The first feature of this 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, and one that would not require dilation, which usually costs an individual an entire day of functioning. Such a treatment would reduce the burden on patients and caregivers associated with having to make monthly visits to retinal specialists, would decrease the discomfort associated with intraocular injections, 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 retinal specialists are experiencing in trying to meet the demands of repeatedly treating and monitoring a growing number of patients with wet AMD and increase the value of the patient-physician relationship. Taken together, these improvements would lead to better overall compliance with therapy and outcomes. The participants also noted that the desired state would include cell replacement and regenerative therapies for individuals who have lost significant vision or who do not respond to therapy.

The second feature of the desired future state would be a better-educated general public and non-retinal specialist physician community that would increase the number of individuals coming in for screening at the earliest signs of vision loss and being referred to retinal specialists for therapy while wet AMD is most treatable. One participant suggested promoting the idea that the signs of AMD are akin to an eye attack in the same way that the cardiology community has raised awareness of the symptoms of stroke through its “Brain Attack” campaign. Another suggested the idea of getting everyone to routinely check their vision by covering each eye and making sure that a straight line isn’t wavy.



While this idea seems simple, several countries have in fact developed successful programs that have dramatically increased awareness of AMD among the target populations, both affected and ones that are getting patients into the care system. For example:

- The Australian Macular Degeneration Foundation, a patient advocacy group, has spearheaded an aggressive, high profile public relations campaign featuring billboard and bus advertising to reach large segments of the population. Cigarette packs now sport the warning that smoking increases the risk of blindness.
- Colombia, for example, 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. The country is also using social media to reach young people and encourage them to talk to their parents and grandparents about AMD. The Colombian Ophthalmological Society has a program for training primary care physicians and optometrists, and has worked with the pharmaceutical industry to educate cardiologists and gerontologists about AMD.
- Swiss media regularly mentions AMD and encourages self-testing, with the result that both the general public and physicians are well aware of the disease.
- Singapore has a national AMD awareness week and is developing telemedicine approaches to increasing awareness.

Capitalizing on a better educated public, the third feature of the desired future state would be the availability of technologies that would make it easier to diagnose AMD and 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. One approach, being developed in Singapore, would use a robotic SD-OCT system/fundus camera, coupled with automated interpretation, to conduct initial screening across the larger physician community.

Perhaps the most useful approach, though also the most scientifically challenging, would be one based on a panel of biomarkers that would:

- Identify the 15 percent of the population over 50 who have early AMD the two percent who will go on to develop the disease.
- Predict response to therapy and identify subsets of patients who will have durable responses with less frequent or no ongoing therapy.

The development of biomarkers dovetails with the fourth feature of the desired future state – a more complete understanding of the biology of AMD in general and wet AMD in particular. 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 diseases 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.

Finally, the desired state would feature a care system that is better organized around the needs of the patient and that can handle the ever-increasing number of individuals who need treatment. In addition to the features listed above, which would markedly improve an individual's experience, and therefore their likelihood continuing to seek and receive care, the medical system must do a better job of coordinating care across the many physicians that many older patients see. Such a system would perhaps split the tasks of monitoring patients and performing injections, and it would certainly ensure that patients be able to receive treatment on a regular schedule as dictated by the course of their disease and response to therapy.

## Barriers and Prioritization

With the desired future state defined, the moderator then asked each participant to list one barrier that is standing in the way of reaching this desired state. The identified barriers included:

### Barriers Related to Treatment

- Incomplete knowledge of the pathology
- Priority for treating AMD when co-morbid conditions exist
- There are no clear guidelines on when to stop treatment
- Co-morbidity with anti-coagulant drugs and other medications
- The lack of treatment for dry AMD - what good does it do to deploy cameras if there's no treatment?
- Poor prognostic indicators
- Lack of effectiveness data: do early screening programs work?
- All current treatments are short-acting

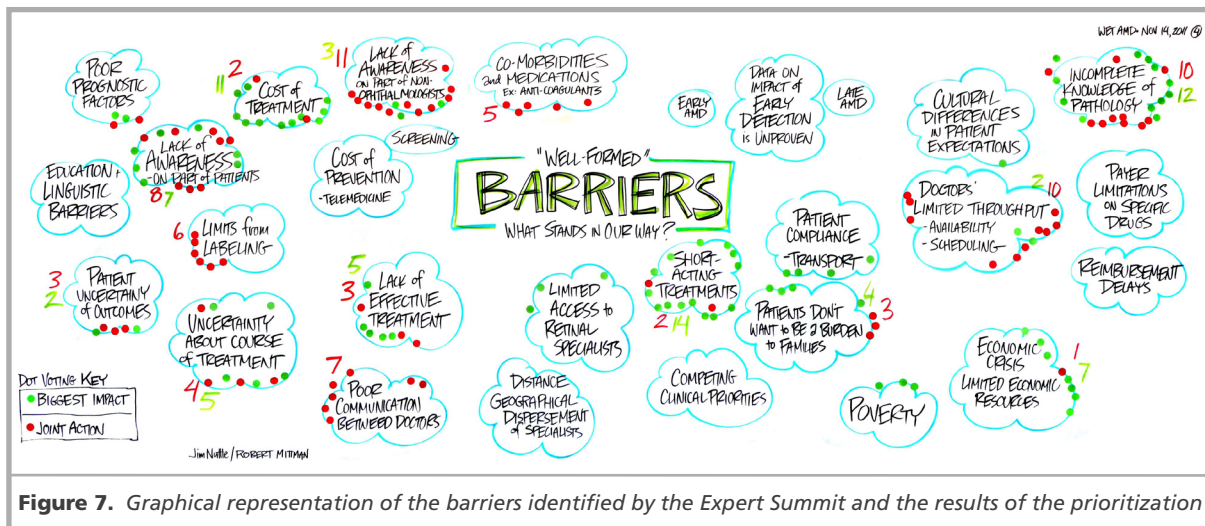
### Barriers Related to Patients

- Lack of awareness about AMD among the general public
- Patient compliance is made difficult because patients do not want to be a burden on their families given the difficulties of securing transportation to appointments for treatments
- Patient understanding and uncertainty of outcome of treatment reduces compliance
- The current worldwide economic crisis is limiting resources
- Cultural differences in patient expectations
- Poverty

## Barriers Related to the Healthcare System

- The cost to the healthcare system of deploying screening equipment could be high
- Limited access to retinal specialists
- Geographic dispersal of retinal centers
- The organization of care system makes doctors unavailable and limits throughput
- Cost of the treatment is prohibitive over the long-term
- Lack of communication among doctors treating patients with comorbidities
- Lack insurance reimbursement and poor organization of reimbursement makes it difficult in many cases to provide optimal care
- Lack of awareness among non-ophthalmologists
- Regulatory label limits treatment options

The participants were then asked to prioritize these barriers according to two different criteria: Which barriers, if surmounted, would produce the biggest impact on the field, and which barriers are most addressable through joint action by the assembled participants and their colleagues. Each participant was allowed to cast several votes according to each of the two criteria. The results are shown graphically in Figure 7.



**Figure 7.** Graphical representation of the barriers identified by the Expert Summit and the results of the prioritization

**In terms of impact, the most important barriers were ranked as follows:**

- All current therapies are short-acting
- Incomplete knowledge of the pathology of disease
- Cost of treatment is prohibitive over the long-term
- Lack of awareness about AMD among the general public
- Patients do not want to be a burden on their families/Patient transport issues
- The current worldwide economic crisis is limiting resources
- The lack of an effective treatment for dry AMD
- Uncertainty about the course of treatment
- Lack of awareness on the part of non-ophthalmologists
- The organization of care system makes doctors unavailable and limits throughput

**In terms of joint action addressable through joint action by the participants, the most important barriers were ranked as follows:**

- Lack of awareness on the part of non-ophthalmologists
- Incomplete knowledge of the pathology of disease
- The organization of care system makes doctors unavailable and limits throughput
- Lack of awareness about AMD among the general public
- Lack of communication across treating doctor groups in patients with co-morbidities
- Co-morbidity with anti-coagulant drugs and other medications
- Lack of an effective treatment for dry AMD
- Uncertainty of outcome of treatment and patient understanding of outcome reduces compliance
- Patients do not want to be a burden on their families/Patient transport issues
- Treatment cost

# Developing Solutions

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With the barriers defined and prioritized, the summit participants engaged in a discussion about their findings. They agreed that three barriers in particular met both criteria in terms of the ability to do something about them and their potential impact.

## Getting Patients Into the System: Improving Awareness and Early Detection

Early diagnosis and prompt and aggressive treatment of wet AMD, within the first year of disease, are essential for improving visual outcomes for patients<sup>10,11</sup>. The majority of patients with wet AMD, however, are not receiving the optimal care that is needed to maintain vision and prevent progressive vision loss. A number of factors are at play. The number of injections a patient can receive that is covered by payers is limited in some countries. In Italy, for example, one eye can receive limited treatments, but once this is completed, the other eye is not eligible for injections that are covered by the health system. Co-payments may be required of patients in order to receive anti-VEGF therapies or to be regularly monitored with OCT. Such payments can present financial hardships to some and or are prohibitively expensive for others, leading to their inability to be treated and monitored in line with best medical practices.

The most addressable barrier, the group agreed, was lack of awareness on the part of patients and physicians other than retinal specialists. Getting patients into the clinic for treatment at the earliest appearance of wet AMD and keeping them in treatment will keep the majority of individuals from losing vision.

The participants agreed that the successful outreach efforts developed in countries such as Australia, Colombia, and Switzerland could serve as exportable models for raising public awareness. Such efforts will likely have the corollary effect of increasing political support for expanding capacity to meet the growing demands for treatment. They also agreed that such campaigns would work best with

simple strategies. One idea suggested was to promote an eye self-exam in the same way that the cancer community promoted breast self-examinations as a means of spotting breast cancer as early as possible. Another would be to associate the early symptoms, of wet AMD, such as blurred central vision, with an emergency situation much like those of a stroke or heart attack. In Australia, a robust public AMD awareness campaign used posters on the backs of buses showing the wavy lines and black spots characteristic of early AMD.

The question was raised; if such campaigns raised the number of false referrals, would that overwhelm the system? The unanimous response was “no” – increasing awareness among the public is a good idea because it will increase the number of patients seeking treatment early in the course of their disease, and that will save many people from losing vision. The participants also noted that such efforts are also likely to increase early detection of other eye diseases as well.

In Germany, where the general public and physician communities are generally well informed about AMD, most patients are seen at the earliest stages of wet AMD and when treatment is most likely to be successful. In Australia, individuals receive treatment for wet AMD within four weeks of coming in to see a physician, though this response has come at the expense of individuals with diabetic retinopathy who now have to wait longer for appointments. Colombia's Day of Vision has an objective of getting patients into the health system early, with wet AMD designated as a “priority condition.” The general agreement among the participants from countries with well-informed citizens was that a growing number of patients are being spared losing their vision because they are getting treatment early in the course of the disease.

These cases show the power of having a well-informed public and physician community. In Italy where AMD has only recently popped up on the public's radar, patients are not getting treatment early enough and in many cases, individuals do not seek help until they begin losing vision in their second eye. This is a particular problem in Italy because patients there are only allowed to receive treatment in one eye. Often, patients are aware that they are



having vision problems, but they do not realize how serious the problem may become, or their physician may underdiagnose the condition, finding they have cataracts, but overlook the concomitant presence of wet AMD. So, the problem in the back of the eye is actually overlooked. There is a new service in Italy, SOS Macula, in which private-pay individuals can access via a toll-free number to get treatment within 48 hours.

In Spain, the physician community is generally well-aware of the urgency of getting their patients into the treatment system early, but the current economic situation there has led the government to cut back on approvals for emergency treatment. In most cases, physicians stop pushing for such an emergency designation, delaying care and leading to vision loss in some individuals.

In fact, the medical care systems in many parts of Europe are so overwhelmed with patients that care is being compromised. Part of the reason that the medical system is overwhelmed is that retinal specialists make up just a small percentage of ophthalmologists; until the advent of anti-angiogenesis therapy, this just was not typically a medical specialty that required large numbers of practitioners. There are a few exceptions, and in those regions where the number of retinal specialists per capita is above average, such as Switzerland, patients are receiving timely care.

Summit participants were largely in agreement, though, that poorly organized medical systems, coupled with the demands that come from having to do monthly injections, OCT scans, and assessments, are making a challenging situation worse. The main culprit here is that retinal clinics were ill-prepared to handle the sudden influx of patients that have come with the paradigm shift in therapy and the need to treat each of these patients with additional injections, perhaps for the rest of their lives, all while new patients continue to come in for treatment. And with some retinal specialists already doing as many as 100 intraocular injections a day, there is little excess capacity in the system to care for both existing patients and ever-increasing number who are expected to enter the system as the population ages.

Several of the participants, though not all, suggested that the system needs reengineering,

perhaps in a way that creates centers for both screening and evaluation that then assist in scheduling individuals to receive injections from retinal specialists. Another option would be to create injection centers staffed by trained technicians or nurses that would allow larger volumes of treatment to occur without relying upon a small number of retinal specialists. Electronic medical records may be of some help, particularly when it comes to coordinating care across many medical subspecialties, but also when it comes to scheduling appointments.

The participants agreed that systems such as Spain's SOS Macula that get patients who need immediate treatment can greatly improve outcomes for the most serious cases of wet AMD. However, SOS Macula is only available for private-pay individuals, which brings up the point that treatment in many countries is class-based. Those patients who can afford private insurance can secure immediate appointments and rapid access to therapy, while those who depend on state providers have to wait for an appointment or have no access at all, or access only to the unlicensed therapy via Avastin.

It was also suggested that monthly evaluations may not be necessary for many patients, and by changing the evaluation schedule it would create time for new patients. The European label for Lucentis to treat wet AMD currently states that after the first 3 months, the retinal specialist will monitor vision on a monthly basis and use worsening vision to determine when to administer Lucentis again. It was noted that such frequent monitoring occupies capacity in the clinician's schedule that could otherwise be used to assess new patients. If the proposed European package insert for Eyelea mirrors that in the U.S., monthly monitoring would not be part of the recommended dosing instructions. One participant noted that there is a machine available for rental that allows patients receiving treatment to monitor their vision at home. In Switzerland, SD-OCT machines are being deployed outside of retinal clinics. With the mention of OCT, the moderator asked the participants if this technology was being used widely in their countries. Every participant said that the use of SD-OCT has become routine and part of the standard of care, though there is country-by-country variation into how imaging is reimbursed. For example, the procedure is an out-of-pocket expense for patients in Colombia,

Singapore, and Australia, though in Australia the Veterans Administration does pay for OCT. In Germany, Switzerland, Italy, Spain, and the United States, coverage is routine when associated with therapy. In Spain, OCT is an out-of-pocket expense for private-pay patients.

The general agreement was that as is the case with anti-VEGF therapy, the field is still learning how to best use SD-OCT given that the technique is still being improved. The participants voiced some concern that without the development of training and even certification programs, the dissemination of SD-OCT into general ophthalmology and primary care settings is likely to lead to overtreatment. The group agreed, however, that the use of SD-OCT should be incorporated into ophthalmology training.

## **Understanding the Disease: A Route to Improved Interventions**

The second important addressable barrier the summit participants focused on was the incomplete knowledge about the pathology of AMD. Though practicing retinal specialists by and large are not engaged in the basic research needed to address many of the important questions about AMD pathology, they can play a larger role in research that aims to identify genetic and lifestyle risk factors, biomarkers for disease progression and response to therapy, and optimal approaches to therapy for specific subsets of patients.

One activity retinal specialists can undertake is the creation of patient registries for research. Registries that capture treatment outcomes could provide a wealth of data that could be used to compare the effectiveness of different drugs or treatment regimens. One of the major intervention issues today is deciding which patients need monthly treatment to continue after an initial three-month regimen and which patients can switch to variable dosing regimens. No trial has yet addressed the issue of whether there are markers for progression to wet AMD in the second eye if a patient has wet AMD already in the one eye, and registries could be useful for addressing this question. The participants agreed that only through the use of large

datasets of the type that registries can provide will researchers be able to identify disease and patient characteristics that may predict which subset of patients need monthly injections to maintain visual outcome. Registries, combined with appropriately collected biospecimens, could also speed the discovery of prognostic biomarkers and genetic markers.

Some countries do have registries in some form. Italy, for example, has a national registry and requires treating ophthalmologists to enter patient data, including imaging data, into the registry in order to receive reimbursement. Currently, however, the Italian registry is not being used for research. Registries exist in Germany, but current regulations do not permit data aggregation into large databases. Switzerland's national registry does allow physicians to extract outcome data that they can use to compare the average results for that physician's patients to the national average. The Swiss registry does not include images, however, contains only qualitative information, and does not define patient subgroups.

There are no national registries in Spain, the United States, or Colombia (or anywhere else in Latin America). Australia's Medicare system has a registry, though unlike in Italy, Germany or Switzerland, participation is voluntary. In some countries, such as Singapore, local hospitals are starting their own registries for research purposes. The Singapore National Eye Centre has a registry containing a predominantly Chinese population and associated blood samples for genotyping.

In recounting the treatment practices in their home countries, the participants made it clear that gold standard for therapy are the approved drug(s) accompanied by SD-OCT. All participants agreed that long-term efficacy data are still lacking due to the newness of the current treatments. Avastin is not considered a gold standard because it is not indicated for wet AMD by health authorities in any country, and because the safety of its use as a pharmacy-reformulated cancer drug has yet to be established. However, the high cost of ongoing monthly Lucentis therapy for every wet AMD patient, coupled with the time demands that monthly therapy puts on patients, is driving the field to use PRN therapy despite the absence of long-term data that such an approach will maintain vision gains. The approval of Eylea, which only requires bimonthly injections, may

alleviate the time demand issue. Regulatory review of Eylea is pending in the EU, Australia and Japan.

The development of new drugs or sustained release formulations that require less-frequent intraocular injections, or extended release devices, would represent tremendous advances, as would a topically applied or orally available anti-VEGF therapy for wet AMD. The participants agreed that pharmaceutical companies are interested in developing this next generation of products, but need the active support of the ophthalmologists who will test these drugs and develop guidelines. The participants agree that the community of retinal specialists needs to do a better job expressing its support for such efforts and to take a more active role in the development of clinical trials and guidelines. Along those lines, the participants agreed that the field would benefit from the formation of a strong professional organization for retinal specialists, something that is lacking today.

In the meantime, the participants were of one mind when it came to developing and participating in trials that would generate data on the long-term efficacy of monthly and variable dosing treatment and that would look more closely at so-called non-responders and durable responders. There was also strong support for the idea of convening a body that could generate practice guidelines analogous to the guidelines that have been issued for the use of anti-VEGF therapies in cancer care. Such guidelines would not only serve the needs of retinal specialists, but also help influence reimbursement practices. As one participant noted, reimbursement is what really guides therapy.

## **The Value Analysis and Drive to Reduce Costs**

The cost of therapy was the third barrier that the participants felt was addressable and important. While the community of retinal specialists has little control over the cost of Lucentis or Eylea, the community can advocate for comparative effectiveness clinical trials for Avastin, as has occurred with the CATT study. Several of the participants pointed out that such comparative

trials are unlikely to be undertaken in support of a label expansion, which can only be applied for by the drug manufacturer in many parts of the world. The molecules used to formulate both Lucentis and Avastin are manufactured by the same company. This company has focused its clinical development of Avastin exclusively on oncology.

In the countries represented at the summit, Lucentis is approved for use and is reimbursed to some extent, though often with limits. Avastin is used, but in most cases patients must pay for it out-of-pocket. Some countries, such as Italy and Spain, limit the amount of Lucentis that is available and patients are then left to choose whether to receive Avastin, often at their own expense. In Australia, Lucentis is fully reimbursed – it is now the third most costly drug to the healthcare system there – while Avastin is not, leading to a situation where Avastin's cost to society is lower, but its cost to patients is higher. In Colombia, Avastin was banned for two years following the approval of Lucentis, but that ban has now been lifted. Recently, Colombia cut the amount it will pay for Lucentis by 30 percent. In the U.K., Lucentis is approved for reimbursement, but the manufacturer pays for all drug costs after the 14<sup>th</sup> injection. In the U.S., there is no universal reimbursement policy for either drug.

While the financial cost of wet AMD treatment is certainly a concern, monetary cost is not the only consideration when thinking about the value proposition for anti-VEGF therapy. Patient-centered outcomes are clearly valuable. From the patient's perspective, the ability to continue reading, driving, recognizing faces, and maintaining independence is incalculable. For society, there is undoubtedly a concrete economic savings associated with preventing blindness, but there are less tangible benefits as well. In the United Kingdom, for example, the cost of blindness is estimated to be about GBP£18,000 per quality-adjusted life year<sup>2</sup>. Not all countries, however, place such a high value on preventing vision loss in older individuals. Italy, for example, put that value at GBP £60 based on the retirement benefit supplement given to blind individuals.

With respect to therapy taken as a whole,

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<sup>2</sup> Quality-adjusted life year (QALY) accounts for both the quantity and quality of life generated by healthcare interventions and is used to assess the value of a medical intervention relative to its monetary cost.

patients also place high value on a consistent supportive environment that includes reliable evaluation and a clear perspective about the future given by a loyal therapist. Value for the patient also increases when their care provider takes time to explain the importance of receiving consistent treatment, the benefits of and differences between approved treatments, the potential safety issues involved with both on-label and off-label therapy, and the importance of keeping appointments in terms of saving vision. It is critical that providers convey to patients the impact that losing their vision would have on daily living and their quality of life. This is especially important given that the time burden of monthly therapy is substantial to patients and their caregivers, and often leads to problems with patient compliance. After the first few injections, patients can begin to lose their fear of going blind and they start becoming more sensitive to the time and often the financial burden associated with consistent monthly therapy. The fear of pain associated with regular injections can also become an issue for some patients if treatments are not explained properly.

The value proposition for anti-angiogenesis therapy also includes physician-related factors. An ophthalmologist who has received fellowship-level training in retinal diseases to become a retinal specialist can provide personalized care and care guidelines that impact the value proposition for patients. However, the sudden increased demand for the services of retinal specialists to treat patients with wet AMD has led an increasing number of general ophthalmologists to offer anti-VEGF treatments without additional training. This situation may not always be good for patients, but the field will have to figure out a way to boost capacity if it is going to meet the needs of a growing number of patients.

Retinal specialists are also coming under pressure from their national healthcare systems due to the sudden rise in expenditures that come with the availability of new treatments for wet AMD. As the gatekeepers of care, retinal specialists are being put into a position of balancing efficacy and safety, particularly concerning the off-label use of Avastin, with cost.

# Setting a Research Agenda

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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 area of basic understanding of disease, translational science, and the delivery of health services.

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 addressing underlying factors, such as angiogenesis, are critical. A better understanding of how the pathological changes relate to functional changes remains to be elucidated. While 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 of the pathogenesis of AMD is driven by genetic factors, 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. The connection between changes in visual acuity and the pathology of disease needs to be clarified, for example. 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), and HGF (hepatocyte growth

factor) — play in neovascularization and identify the molecular pathways that trigger fibrosis. Already, a drug is under development to reverse retinal fibrosis, which currently has no medical treatment. 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 non-responders 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.

The summit participants also noted that the development of functional imaging could provide an important tool for understanding the pathology of disease. New technologies could enable researchers to test single photoreceptor function, for example.

In the area of translational science, the summit participants stressed the need to develop 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. A gene therapy approach is being tested in Australia as a way of producing longer-lasting blockades of angiogenesis. Support should also be given to efforts to develop automated robotic screening instruments that could be used effectively by general practitioners, ophthalmologists, and optometrists.

Finally, research is needed to develop efficient and cost-effective methods of delivery of diagnostic, treatment, and monitoring services to an aging population. Such efforts are underway in some places. Singapore, for example, has been studying the value of screening and shown that it is not cost effective to use ophthalmologists for large-scale screening programs. Australia is now conducting a study on the pharmacoeconomics of anti-VEGF therapy.



# Recommended Actions

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Based on the discussions by the assembled experts, the summit developed the following set of actions that the Angiogenesis Foundation could promote in collaboration with stakeholders in the field.

## **1. Improve the early detection of wet AMD:**

- Enact public awareness campaigns to increase the general public's knowledge about the early signs of AMD.
- Work with primary care physicians and general ophthalmologists to improve early detection of AMD and increase referrals to retinal specialists for follow-up exams and treatment.
- Develop comprehensive programs for SD-OCT training that may be amenable to a wider range of physicians beyond ophthalmologists specializing in retinal diseases.

## **2. Improve effective intervention for preventable vision loss:**

- Ensure that health authorities adopt approved wet AMD treatments on formulary and make them available for prompt intervention and chronic management of the disease, accompanied by appropriate monitoring.
- Develop better practice and care models that will retain more patients with wet AMD in the medical system so that they receive optimal treatment and avoid losing their vision.
- Create national and international registries that will enable long-term follow-up of therapeutic outcomes and facilitate research on the etiology and subtypes of AMD.
- Convene a consensus conference to define the disease state and its persistence, response to and failure rate of treatment.
- Establish a systematic approach to evaluating the risks of reformulated Avastin used off label.

# Recommended Actions

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## **3. Improve value for stakeholders:**

- The benefits and risks of licensed and unlicensed medications should be openly discussed between retinal specialists and their patients, since their drug formulation and delivery may differ substantially from licensed medications and have safety implications.
- Ensure that new practice models are patient-centric, that is, they work to minimize the burden to the patient while maximizing therapeutic outcome.
- Develop the knowledge base to determine the cost-effectiveness of different treatment options.

## **4. Advance translational research:**

- Identify key factors and pathways beyond VEGF in wet AMD that may be attractive targets for therapy development.
- Promote research to elucidate the pathogenesis of AMD and its progression from dry to wet forms.
- Determine biomarkers distinguishing between responders and non-responders to wet AMD therapy.
- Foster research to improve the drug delivery and pharmacokinetic properties of wet AMD therapy so that more effective but less frequent treatments are needed.

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# Acknowledgements

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The Angiogenesis Foundation wishes to express gratitude to the following individuals who contributed in various ways to the preparation of this report:

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This report was made possible by the support of the Miller Family Foundation, the AJA Charitable Fund, and Bayer Healthcare Pharmaceuticals.







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