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

A report based on the
Australian Wet Age-Related Macular Degeneration Coalition
Expert Summit convened in Sydney, Australia, July 2012

The Angiogenesis Foundation

KEY POINTS

1. Age-related macular degeneration (AMD) is the industrialised world's leading cause of vision loss and blindness in adults over the age of 65.

2. In 2010, one in seven Australians over the age of 50, or 1.023 million people, had some evidence of AMD. That number is expected to climb to 1.77 million by 2030 as the Australian population ages.

3. During the past decade, new therapies and diagnostic techniques, in the form of 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 AMD, the most serious form of the disease. Patients now have effective treatment options that can help keep them from going blind.

4. Australia is a global leader in providing affordable and accessible care to people with wet AMD. However, there are still gaps in access to care, so that not all Australians are receiving the optimal care that is needed to maintain vision and prevent progressive vision loss. It should be stressed that the treatment window for wet AMD is relatively short. Any delay can mean the difference between retaining vision and developing blindness.

5. The barriers in Australia to receiving timely and optimal care include:

   - Inefficiencies and delays in the referral process
   - Uneven geographical distribution of retinal specialists
   - Fragmented and inconsistent diagnostic and treatment practices
   - High treatment costs in the private sector and limited treatment options in the public sector
   - Lack of Medicare funding for OCT scans
   - Lack of effective treatments available for dry AMD, the precursor of the wet (neovascular) form of the disease
   - Lack of awareness among the public and non-retinal healthcare providers about the disease
   - Poor awareness, referral and, hence, utilisation of rehabilitation in people who do lose vision
   - Significant variation in cost and quality of AMD-related care, from diagnosis through treatment to vision rehabilitation services

6. As a result of the many barriers, many patients:

   - do not seek treatment at all
   - delay seeking diagnosis and treatment
   - skip treatment sessions or stop the treatment prematurely
   - have difficulty locating and accessing care, particularly in Australia's rural areas

7. All these factors increase the likelihood of potentially catastrophic outcomes for patients with wet AMD. Overcoming these current challenges to the early diagnosis and effective treatment of wet AMD will require the concerted efforts of all Australian stakeholders, including patients, caregivers, patient support organisations, physicians, researchers, scientists, industry leaders, regulators, policymakers, funders, the media and society at large.

TABLE OF CONTENTS

Introduction

What Is AMD?

Age-related macular degeneration (AMD) is a disease associated with ageing that gradually destroys sharp, central vision needed to read, recognise faces, drive, and in general, to see most things 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 main types of AMD: early (with no or minimal vision loss) and late (with vision loss). Late can be further split into dry, or atrophic, AMD (also known as geographic atrophy) and wet AMD. Both the dry and wet forms can occur in one or both eyes, although the development of AMD in one eye appears to increase the risk that AMD will develop in the second eye. Neither form of AMD is painful. As a result, the disease may not be diagnosed until it produces marked loss in vision. When AMD affects one eye, it often goes undetected because the brain uses visual information from the second eye to compensate for any loss of vision in the first eye.

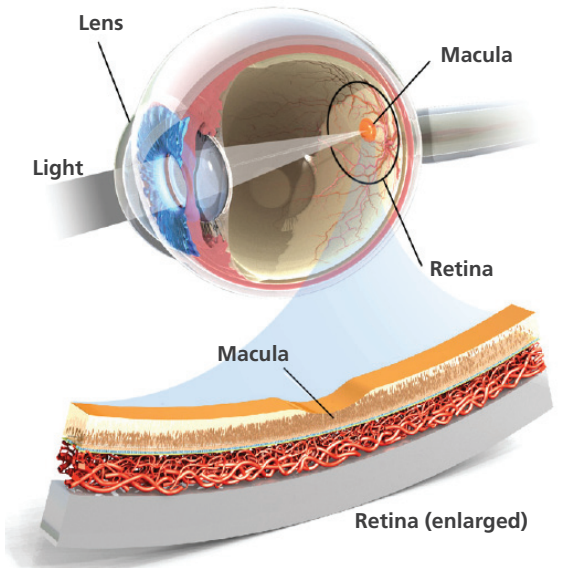

Figure 1. *Anatomy of the eye*

Early AMD, the more common form of macular degeneration, is characterised 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. Early AMD generally develops slowly, but can progress to late-stage dry AMD, which can impose significant vision loss.

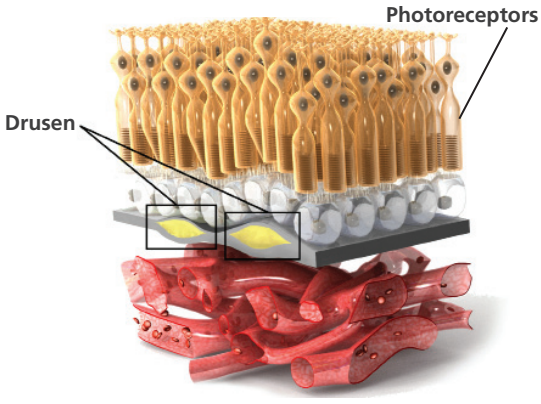

Figure 2. *Drusen deposits in the macula result in distortions in vision*

Wet AMD is the more serious form of the disease. For reasons that are as of yet unclear, 10% to 15% of adults with early or dry AMD will suddenly progress to wet AMD and experience abnormal blood vessel growth under the macula. The growth of new blood vessels, known as angiogenesis or neovascularisation, 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.[1] An example of an early symptom of wet AMD would be straight lines appearing wavy.

In most parts of the world, AMD is a relatively unappreciated disease, yet among industrialised countries 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% of all blindness and 50% of blindness in industrialised countries.[2] The WHO projects that these numbers will double by 2020 as the population of industrialised countries ages.

In Australia, one in seven residents over the age of 50 in 2010, or an estimated 1.023 million people, had some evidence of AMD in at least one eye.[3] Of these, an estimated 856,000 had early AMD (drusen and/or pigment changes), 55,000 had late dry AMD (geographic atrophy), and 112,000 had wet AMD in at least one eye. In the absence of prevention or treatment programs, these numbers would increase to 1.77 million by 2030, of which 207,500 individuals would have wet AMD.[3]

Macular degeneration is the most common cause of legal blindness in Australia, and is responsible for about half of the country's cases of blindness.[3]

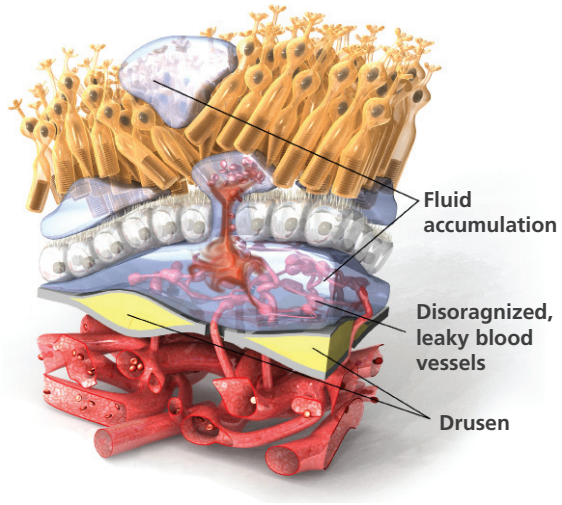

Figure 3. *New blood vessel growth leads to blood and fluid leakage that can scar the macula*

Paradigm Change

Anti-angiogenesis focused research, which began in the early 1970s, made dramatic advances in the late 1990s. Those advances culminated in the identification of specific antiangiogenic-related approaches to treating a variety of diseases, ranging from cancer to skin disease to blinding disorders, such as wet AMD. Presently, more than 10,000 laboratories around the world are involved in angiogenesis research, and over US$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 treatable with early, appropriate care.

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

Anti-Angiogenesis Therapies

In December 2004, the U.S. Food and Drug Administration (FDA) approved pegaptanib (intravitreal injection), 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.[4] This antiangiogenic therapy, aimed at halting abnormal blood vessel growth, became recognised as an entirely new class of disease treatment.

An even more effective drug, ranibizumab, was approved for the treatment of wet AMD in the U.S. in late 2006, and in Australia in early 2007. Ranibizumab, as well as pegaptanib, interferes with a small protein known as vascular endothelial growth factor (VEGF). This growth factor stimulates the angiogenesis that lies at the heart of wet AMD. Clinical trials demonstrated that 95% of patients treated with a once-monthly intravitreal injection of ranibizumab into the eye maintained their vision as long as the injections continued over the course of the trial.[5,6] "Maintaining vision" meant that their ability to read a vision chart declined by no more than 15 letters, or three lines. In addition, up to 40% of those treated with monthly ranibizumab for a year experienced an improvement of 15 or more letters (3 lines) in visual acuity.

For the first time, physicians could offer their patients the opportunity to save vision, and even reverse lost vision in some individuals. The major drawback to this new therapy, however, was the price, about US$2,000 per injection, and the burden that receiving a monthly injection places on the patient and caregivers.

Before ranibizumab was approved, retinal specialists began experimenting with another anti-VEGF agent, bevacizumab. It had been used since 2004 for the treatment of colorectal cancer in many countries, including Australia, and was later also approved for the treatment of other cancers. Bevacizumab is a larger molecule, known as a monoclonal antibody, from which ranibizumab, a smaller drug, is derived.

Bevacizumab is not indicated for eye diseases, and has not been approved by any regulatory authority for use in the eye. It has been shown, nonetheless, to be clinically effective for the treatment of wet AMD, and is used off label for this purpose at a cost of about US$50 per intravitreal injection.[6] (Off-label drugs are ones that are prescribed for use that is 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

quantities needed for treating the eye. Numerous documented cases of infection from bevacizumab's use in the eye have been reported. Some of these cases are likely due to poor pharmacy practice when dividing the product, not the molecule itself, while others may be caused by differences in production specifications for an intravitreal injection versus an IV infusion, for which bevacizumab is produced. Clinical trials comparing ranibizumab with bevacizumab have suggested, however, that both drugs are similarly effective at stopping disease progression and restoring visual acuity, at least when dosed monthly during the first two years of treatment. [6,7]

On November 18, 2011, a third anti-VEGF drug, aflibercept, received U.S. FDA approval for the treatment of wet AMD.[8] Based on a novel drug technology that fuses proteins together to neutralise VEGF and block angiogenesis, aflibercept is designed to be administered by intravitreal injection, every other month, following three initial monthly injections. In March 2012, Australia became the second country to approve aflibercept for AMD treatment. It also received a recommendation for approval in the European Union, in Switzerland, Brazil, Colombia, and in Japan in 2012.

Current Status of AMD Therapies in Australia

Ranibizumab is the standard wet AMD treatment for most patients in Australia. It has been listed on the Pharmaceutical Benefits Scheme (PBS) since August 2007. Ranibizumab has also been registered in Australia for the treatment of vision loss due to diabetic macular edema and macular edema secondary to retinal vein occlusion, and the drug's manufacturer has applied for reimbursement for these indications. Australians who are under the age of 50 or who have non-AMD neovascular lesions cannot generally receive reimbursement for ranibizumab; they are typically given bevacizumab instead, which usually costs about AU$50 per dose.

The PBS reimbursement for ranibizumab applies to all Australian citizens and permanent residents. In 2012, pensioners paid only AU$5.80 per dose for the drug, while non-pensioners paid AU$35.40 per dose. The remainder of the drug's cost is subsidised by the taxpayer.[9] Since its introduction, the use of ranibizumab has grown significantly in Australia, from 7,054 injections in 2007 to 152,292 injections in 2011. The number of bevacizumab injections given in Australia each year for AMD is unknown.

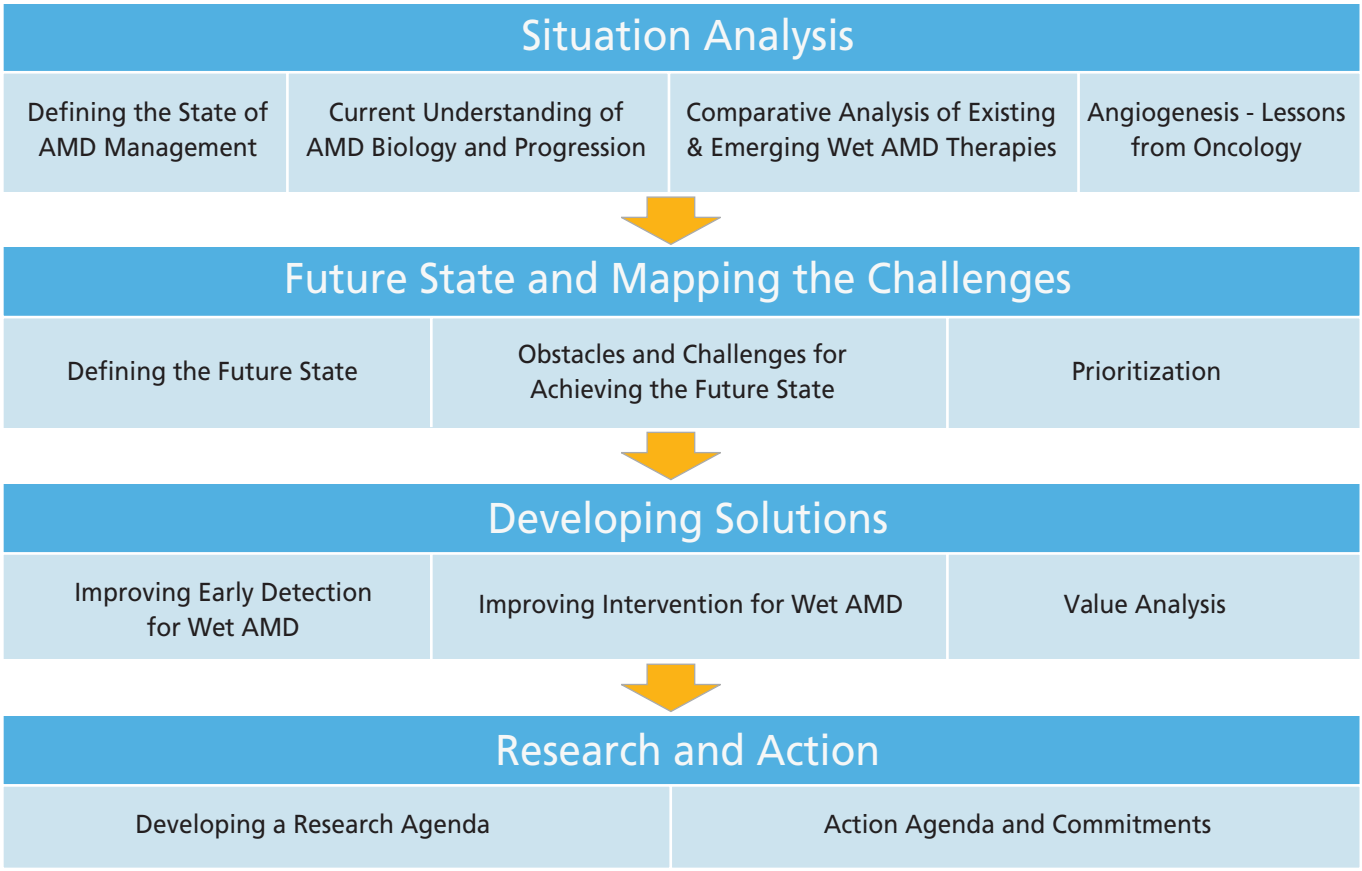

Figure 5. *Schematic Flow of the International Expert Summit*

Optical coherence tomography (OCT) scans are not a listed Medicare Australia item, and, therefore, are not reimbursable. The average charge for an SD-OCT scan is about AU$70, although in some areas it can be as high as AU$100. Some ophthalmologists reduce or waive the charge for pensioners. Medicare does provide partial reimbursement for most other AMD treatment-related costs, including angiograms and the doctors' consultation and injection fees. Doctors, however, are free to set their own fees, so the amount that patients pay for services related to AMD treatments varies. Medicare rebates 75% of the scheduled fee for in-hospital treatment and 85% for in-office treatment. When the procedure is performed in-office, Medicare also rebates 80% of out-of-pocket costs when those costs reach a certain threshold in any calendar year, under the Extended Medicare Safety Net (EMSN). In 2012, that threshold was AU$598.80 for pensioners and AU$1,198 for non-pensioners. Out-of-pocket costs, therefore, vary from patient to patient. The benefits payable under the EMSN were previously uncapped, but from November 1, 2012, these will be capped at the standard rebate, plus 80% of the schedule fee.

The Need for Improvement

The globally expanding use of anti-VEGF therapies is dramatically improving the quality of life for countless numbers of individuals with wet AMD in Australia and around the world. Many more people are now able to retain their vision and, consequently, their independence. However, even in countries like Australia, where AMD-related drug costs are relatively low due to reimbursement and accessibility is relatively high, room for improvement remains in several areas. Innovative research and enhancements to existing healthcare systems are needed in order to ensure that AMD is diagnosed and treated early enough to save the sight of thousands of Australians.

The Australian Wet AMD Coalition Expert Summit

Given the changes that have come with the advent of multiple effective therapies, and the fact that these therapies have revolutionised the field of ophthalmology, the Angiogenesis Foundation determined in 2009 that it was an opportune time for the AMD stakeholder community to take a step back and review the progress it had made, the challenges it faced, and the questions that needed to be answered to best meet the needs of those with wet AMD.

As a scientific nonprofit organisation whose mission is to conquer disease through the control of neovascularisation, the Angiogenesis Foundation recognised that it was well positioned to play the role of a neutral facilitator of such a review. The Angiogenesis Foundation immersed itself in the field of macular

Figure 6. *Expert Summit, Australia, July 12, 2012*

degeneration and began looking at how it could apply the lessons it learned from its interactions within the oncology and wound healing communities to this new area of clinical opportunity.
As its first major global step, it decided to assemble an interdisciplinary group of international leaders in AMD treatment and translational science. The International Expert Summit for Age-Related Macular Degeneration was convened in Berlin, Germany, on November 14-15, 2011. Its success led to a second event, the Latin American Wet AMD Coalition Expert Summit, which was held in Bogotá, Colombia, on March 10, 2012, in partnership with the Pan-American Retina & Vitreous Society. Experts at both these meetings identified, discussed, and achieved agreement on the rationale for antiangiogenic therapy to treat wet AMD: the role of early intervention in preventing wet AMD-associated blindness; the safety of repeated, long-term therapy; and the role of chronic suppressive antiangiogenic therapy for wet AMD. Each meeting resulted in a white paper that provided an overview of the group's discussions and presented key steps needed to advance the treatment of wet AMD using anti-VEGF therapies to impact the greatest number of individuals possible.

Building on the success of those earlier meetings, the Angiogenesis Foundation, in partnership with the Macular Degeneration Foundation of Australia, convened the Australian Wet AMD Expert Summit in Sydney on July 12, 2012. The Australian summit, like the two earlier ones, 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 event opened with two short presentations. One recapped the current status of wet AMD prevention, diagnosis and treatment in Australia. The other offered angiogenesis lessons from the field of oncology. 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. A graphic recorder 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. Working off of the foundation laid by these discussions, the experts then developed a research agenda specific to Australia that could move the field toward the desired future state of AMD prevention, diagnosis and treatment. The meeting ended with the identification of a specific action agenda. This white paper provides an overview of the group's discussions.

The Role of the Angiogenesis Foundation

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

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

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

The Angiogenesis Foundation recognises the challenges of optimising patient care and outcomes with such paradigm-shifting discoveries as angiogenesis-based treatments for retinal diseases. It also deeply understands that the complex needs of all the stakeholder groups involved, including patients, caregivers, patient-support organisations, physicians, researchers, scientists, industry leaders, regulators, policymakers and funders, must be aligned and met in order to meet the goal of improving global health through angiogenesis-based medicine.

The Angiogenesis Foundation is committed to helping those groups work together to ensure that all people benefit from current and future advances in angiogenesis-based medicine.

The Macular Degeneration Foundation has been instrumental in significantly improving awareness of macular degeneration within the Australian general population. In 2011, four years after the organisation launched a comprehensive public informational campaign, awareness of MD among people aged 50 years and older (the campaign's primary target audience) had increased from 58% to 92%.[10]

The Role of the Macular Degeneration Foundation

The Macular Degeneration Foundation is a national organisation founded in 2001 to meet the needs of Australia's macular degeneration (MD) community. Its vision is to reduce the incidence and impact of macular degeneration in Australia through the provision of education, awareness programs and client services. It undertakes research and funds research programs along with a strong advocacy role in representing the interests of the MD community to government and policy makers.

The organisation serves all Australians affected by MD, including the families and caregivers, and all those at risk of the disease. It also supports all health care professionals who are involved with the diagnosis, treatment and rehabilitation for AMD.

In 2010, it was estimated that one in seven Australians over the age of 50 (or 1.023 million people) had some evidence of MD and that without effective prevention or treatment measures, this number would increase by 70%, or 1.77 million people, by 2030.[3]

Figure 7. *Moderated discussion at Expert Summit, Australia, July 12, 2012*

To open the Australian summit, two experts gave 15-minute presentations as background for the subsequent roundtable discussions. Dr. Paul Mitchell, a professor of clinical ophthalmology and eye health at the University of Sydney, described the current status of the prevention, diagnosis, and treatment of AMD in Australia, including areas where more improvements need to be made. Dr. William Li, president and medical director of the Angiogenesis Foundation, then gave an overview of how angiogenesis research is transforming the field of oncology and the lessons that this transformation offers AMD researchers, patients and healthcare professionals.

The State of AMD in Australia

Prevalence and Incidence

The prevalence of early AMD (defined as the presence of large drusen and retinal pigmentary changes[11]) is currently estimated to be about 13% among Australians aged 50 and older. As might be expected, the percentage varies greatly according to age, from about 6% for people aged 50-59 years to about 35% for those aged 90 years and older. The prevalence of neovascular disease is currently estimated at 1.38% and that of geographic atrophy at 0.65% among Australians aged 50 and older. In 2010, an estimated 107,617 Australians had neovascular AMD in one or both eyes. That number is projected to increase up to 207,543 by 2030.[12,13]

Since 2004, early treatment with anti-VEGF therapies (pegaptanib, ranibizumab, bevacizumab, and aflibercept) has made it possible to limit or reduce the size of the neovascular lesion, thereby preserving or even improving visual acuity.[5,14] This development is having a remarkable effect on reducing the number of people who go blind as a result of AMD. In Denmark, for example, the incidence of AMD-related legal blindness plummeted between 2000 and 2010, from 52.2 to 25.7 per 100,000 people aged 50 years or older.[15] In absolute numbers, that equates to about 400 people per year whose blindness is now avoided in Denmark.

Statistical modeling suggests something similar is happening in Australia. The incidence of choroidal neovascularisation (the major cause of severe vision loss in patients with AMD) in Australia was about 20,000 in 2010, of which about 10,000 were individuals 80 or older. Without anti-VEGF treatment, an estimated 2,200 of those patients would be expected to go blind in both eyes within two years of diagnosis. With treatment, however, the incidence of blindness drops by 68%. In absolute numbers, that means 1,600 Australians avoid losing their vision each year (95% CI; 357 to 1,031) as a result of anti-VEGF therapies.[16] (Similar modeling applied to a U.S. population has estimated that anti-VEGF therapies reduce the number of AMD cases progressing to legal blindness by 72%.[17])

Needs and Gaps

The Pharmaceutical Benefits Scheme (PBS) subsidises all Australian citizens and permanent residents with wet AMD for most wet AMD-related diagnosis and treatment, including anti-VEGF therapies. However, major needs and gaps in AMD treatment exist in Australia, especially related to access to care. Certain socio-economic and demographic populations in Australia are at a distinct disadvantage when it comes to accessing AMD-related care. Factors involved in this inequity include:

- Transportation issues (both cost and distance), particularly in rural areas
- No funding for spectral domain optical coherence tomography (SD-OCT) screening, or for older time-domain OCT screening, which is still used by some practitioners
- Variations in the cost of intravitreal injections
- Variable and inconsistent access to public hospital services for diagnosis and treatment
- A lack of caregiver assistance for many patients, including a lack of caregivers who can transport patients to their anti-VEGF treatments
- An uneven geographic distribution of trained retinal specialists.

In addition, PBS funding for anti-VEGF therapy is currently only available for sub-foveal age-related macular degeneration. PBS subsidies are not available for people with other macular dystrophies, extra- or juxtafoveal lesions, diabetic macular edema, retinal vein occlusions, or other neovascular lesions.

As a result, some AMD patients receive suboptimal care, even though Australia is, in many respects, a world leader in the diagnosis and treatment of AMD. In addition, the number of Australians receiving anti-VEGF therapies is actually lower than had been predicted based on incidence statistics. This finding suggests that a number of people who need anti-VEGF treatment are not receiving it.

Statewide differences in reimbursement for the anti-VEGF drug ranibizumab (Lucentis) appear to reinforce this observation. In 2010-2011, the rate of

reimbursement for ranibizumab was more than twice as high in New South Wales (44.4/1,000 persons aged 61+) than in Victoria (21.7/1,000 persons aged 61+).[18] Closer examination of this data has revealed that these statistics aren't explained by state-to-state differences in the number of anti-VEGF injections people are receiving, but by differences in the number of people for whom treatment is initiated.

Recent research suggests that people with symptoms of AMD may benefit from receiving treatment early in the disease's progression.[19,20] It's not clear yet whether earlier treatment would translate into fewer injections, but early treatment does delay or reverse vision loss. Thus, there is a need to raise the awareness of the Australian public and first-line referrers (such as optometrists and general practitioners) about key early symptoms of the disease. The Macular Degeneration Foundation has already undertaken an impressive educational effort, but additional work in this area is needed. Improvements are also needed in healthcare processes so that all patients with early symptoms receive rapid care from an ophthalmologist.

Other AMD-related "gaps" that need to be addressed in Australia include the following:

- Premature discontinuation of therapy. Some people stop treatment for wet AMD because of issues related to the cost of treatment, transportation problems, or a misunderstanding about the importance of the treatment. Injection anxiety and/or fatigue (not wanting to return so frequently for injections) can also be a factor. For certain patients, it may be possible to administer the latest anti-VEGF drug, aflibercept, less frequently than previous drugs.
- Treatment failure. The scope of this problem is unknown. Data suggests that switching to a different drug therapy may be beneficial to some non-responders for other retinal diseases.[21]
- Non-uniform approaches to treatment. Recent government data indicates marked variability in AMD-related treatment across Australia.[22] This finding suggests a strong need for updated treatment guidelines and improved training of providers. Government data does show, however, that the frequency of intravitreal injections is increasing in Australia, a trend that suggests providers are recognising the importance of monitoring and treating more aggressively.[23]
- Limited audit of outcomes. More and larger studies on the long-term effectiveness and safety of anti-VEGF therapies are needed. To help with such research, there is a need for further work on simple computer software that will enable ophthalmologists and retinal specialists to record patient treatment outcomes, including quality-of-life outcomes.

Angiogenesis: Lessons from Oncology

An important aspect of angiogenesis is microcirculation (the transportation of blood within an organ's tissue by small blood vessels). Microcirculation is remarkably adaptive and varies according to the organ involved. As a result, angiogenesis in the colon is very different than in, say, the breast or the brain. Microcirculation varies at different times in a person's life cycle, and even from organ to organ within the same person. Scientists do not currently understand what drives these differences. Some answers may emerge from the Human Vascular Mapping Project, which is currently underway at the University of Texas MD Anderson Cancer Center in Houston, Texas.[24] For that project, researchers are subjecting endothelial cells harvested from diseased cancer tissue to genomics and proteomics studies and examining the results for context-specific differences between healthy and diseased tissue.

Many of the factors involved with the progression of wet AMD are also commonly seen in cancer. As in wet AMD, VEGF helps drive tumor angiogenesis and leads to disease progression. Many other characteristics of the progression of wet AMD, such as fibrosis, scarring, and inflammation are also seen with tumor angiogenesis. In tumors, as in the eye, VEGF induces vascular permeability,[25] and studies have shown that treating tumors with anti-VEGF therapies can markedly decrease interstitial fluid leakage[26]—again, as it does in the eye.

Since 2004, more than a dozen anti-VEGF therapies have been approved for the treatment of a variety of cancers, including those involving the colon, lung, breast, brain, kidney, pancreas, and liver. This compares with three anti-angiogenesis drugs (pegaptanib, ranibizumab, and aflibercept) approved in ophthalmology. Oncologists have begun to expand their focus, however, to other angiogenesis targets. More than 30 additional targets have already been identified, and each has become the subject of developmental therapeutics by bio-pharmaceutical companies. Where we are today with anti-VEGF cancer therapy may soon be eclipsed by these other drugs. Some may find uses in ophthalmology as well.

The research to date in oncology offers five broad take-away lessons about anti-VEGF therapies:

1. Different anti-VEGF agents have different effects.

As comparative-effectiveness testing in animal models has shown,[27] different anti-VEGF therapies target different members of the VEGF family of growth factors. Ranibizumab, for example, blocks only VEGF-A, while aflibercept has a broader mechanism of action, targeting VEGF-A, VEGF-B and PlGF (placental growth factor). Neither drug, however, blocks other members of the VEGF family (VEGF-C, VEGF-D, and VEGF-E).[28]

2. Ongoing maintenance therapy is important.

After anti-VEGF treatment is initiated, the blood vessels of a tumor that has rapidly vascularised can regress quite dramatically. When the treatment is stopped, however, the blood vessels grow right back—and in the same empty sleeves of the basement membranes (the thin sheet of fibers that underlie the epithelium) of the vessels that had regressed.[29] Thus, the chemotherapy treatment model of "drug holidays" does not seem to be beneficial with anti-VEGF therapies. How to influence those "ghost vessels" so they do not grow back after halting anti-VEGF therapy is currently under study.

3. Escape occurs via upregulation of other factors.

Anti-VEGF cancer therapies eventually result in changes in local gene expression, which causes an upregulation of other, non-targeted growth factors in order to sustain the original neovascularisation response of the tumor.[30] These escape pathways are being studied, and they suggest that combination therapy may be more effective than monotherapy.[31] Indeed, a 2012 phase II clinical trial reported that combining an anti-PDGF (platelet-derived growth factor) drug (aptamer) with an anti-VEGF one (ranibizumab) was more effective than anti-VEGF therapy alone in the treatment of AMD.[32] Another consequence of the gene expression that results from anti-VEGF

therapy is that genes for defensive antiangiogenic molecules become down regulated. Research has shown that when the anti-VEGF-A drug bevacizumab is used to treat colon cancer, a rise in the expression of VEGF-C occurs right before the disease progresses.[33] There may be a similar escape biomarker or progression marker for AMD.

4. Responses to anti-VEGF therapies are not homogeneous.

Not everybody responds the same way to the same anti-VEGF drug. Anti-VEGF therapy has, for example, transformed the treatment of kidney cancer, but patient response to anti-VEGF treatment differs significantly. There are good responders, non-responders and poor (intermediate) responders. Even among patients who are good responders, their response can vary over time. Some respond quickly, but then their disease recurs and progresses quickly, while others respond more slowly and for a longer period of time. Differences in responses are also seen in patients with AMD. Treatment outcomes need to be captured and studied to better understand these response differences—and to develop more effective therapies.

5. Sequential therapy can improve disease control.

Sequential anti-VEGF therapy (sunitinib followed by sorafenib) has been shown to improve disease control in kidney-cancer patients.[34] Research also suggests that some patients with kidney cancer respond to a later re-challenge by their initial anti-VEGF therapy.[35,36] Sequential anti-VEGF therapy may also prove beneficial for AMD patients who are non- or poor-responders to the initial anti-VEGF drug with which they are treated.[37]

Anti-VEGF therapy is undoubtedly making a remarkable difference in the lives of people with wet AMD, including those in Australia. Unlike in many other areas of the world, Australian patients aged 50 and older with wet AMD receive almost complete reimbursement for ranibizumab treatments via the PBS. The PBS began providing reimbursement for aflibercept on December 1, 2012. The agency provides reimbursement when a patient switches from one PBS-listed anti-VEGF drug to another because of a poor or non-response to the first treatment. Both the Macular Degeneration Foundation and the Angiogenesis Foundation advocated for switching reimbursement by the Pharmaceutical Benefits Advisory Committee (PBAC).

Australia's Medicare also provides partial reimbursement for most non-drug costs related to AMD treatment. In addition, awareness of the disease is much higher in Australia than in other countries, in large part because of the wide-ranging awareness and educational efforts of the Macular Degeneration Foundation.

Still, as participants in the Australian Wet AMD Expert Summit acknowledged, there is room for improvement in terms of how patients are brought into the Australian AMD treatment system and how they are cared for once their condition is diagnosed.

The Desired Future State of Wet AMD in Australia

The moderator opened this segment of the summit by asking participants to discuss a key question: As leading practitioners in this field who treat or interact with AMD patients every day, what would a patient-centred system of AMD treatment and care look like in Australia if that system could become completely successful?

From the Perspective of the Patient

The participants agreed that the most desired patient-centred outcome would be the maintenance of normal vision so that patients could fully enjoy a high quality of life. In addition, participants envisioned a care system that puts the focus on the overall health of patients, a system that treats not just the eye, but also the whole body. In such a system, patients would become knowledgeable about their individual risk profile for AMD and would embrace healthy behaviours to improve that profile. In addition, all family members of patients with AMD would be counseled about their genetic risk.

Summit participants agreed that a completely successful AMD care system would also include easier access to diagnostic, treatment, and rehabilitation services. Patients would know not just when to seek diagnosis and treatment, but also where, and systems would be in place to make sure both diagnosis and treatment occur quickly and efficiently. In addition, prompt, high-quality care and rehabilitation, for those who have lost vision, would be available in all regions of the country. Out-of-pocket treatment costs would be lower as well (or, ideally, free). Furthermore, there would be new treatments that require less frequent visits to the doctor. Gaps in treatment would also be eliminated, and patients would experience "a seamless pathway" of care.

From the Perspective of the Patient's Family and Caregivers

A completely successful AMD care system would also reduce the social, emotional, and physical burden on the patient's family and caregivers. Treatments that require less frequent doctor visits, for example, would ease some of the time and transportation demands placed on family members and other caregivers. Better education of families and caregivers about the progression of the disease would also be provided. Because AMD has a genetic component, the relatives of people with AMD carry the emotional burden of worrying if AMD is going to affect them or other members of their family. Thus, a successful AMD care system would provide resources to help relatives understand and manage their own risks.

From the Perspective of Healthcare Professionals and Institutions

The summit participants then discussed what a successful AMD care system would look like from the point of view of healthcare professionals and institutions. They agreed that optometrists should have better diagnostic capacity so that the progression of appropriate patients into treatment could occur more quickly. Currently, only a minority of optometrists have OCTs. While they may be able to determine an abnormality, timely referral of appropriate cases does not always happen. Summit participants also agreed that in a successful AMD care system, general practitioners (GPs) would receive better training about the key indicators for AMD so they could act more quickly to get patients to

optometrists and/or eye specialists. GPs would also automatically ask patients aged 50 and older if they had visited an optometrist within the previous 24 months and, if the answer were negative, would make sure the patient sets up an appointment. (A recent project conducted by the Macular Degeneration Foundation found that general practitioners' knowledge about AMD was low. Some summit participants pointed out, however, that fewer AMD patients are presenting to eye specialists with blindness in one eye, a factor that suggests that both general practitioners and optometrists are referring patients to specialists earlier than in the past.)

Summit participants also agreed that a successful AMD care system would have more retinal specialists than presently exist in Australia and those specialists would be spread more evenly across Australia's various states and regions. Currently, about 150 of Australia's 700 practicing ophthalmologists are believed to have sub-specialty retinal training. In addition, general ophthalmologists would receive "up-skilling" so that they could provide specialised AMD-related care. Follow-up care for AMD patients would be shared with other types of physicians, including general practitioners, using telemedicine and electronic records systems. Physician assistants would also be enlisted to help with ongoing patient care regarding concurrent medical conditions. To provide a "seamless pathway" of care, a single flowchart of care would be distributed to all of the patient's healthcare professionals.

In regard to healthcare institutions, the summit participants agreed that in a successful AMD care system the quality of treatment received by AMD patients would be the same in both public and private medical facilities. The public system would be properly funded to enable AMD patients who receive their care through public medical institutions to receive timely and seamless treatment. In addition, no patient would receive lesser care due to language, economic, regional or functional barriers.

Key Components of the Desired Future State

In summary, the ideal future state of a patient-centred AMD care system in Australia would have the following features:

- Effective treatments for wet AMD that require fewer office visits
- Effective treatments for early AMD, which would also prevent progression to wet AMD
- Consistent treatment standards that reflect the accepted evidence base for best practice
- An emphasis on treating the whole body, not just the eye
- Easy and affordable patient access to diagnostic, treatment and vision rehabilitation services
- A "seamless pathway of care" that includes coordination among all of the patient's healthcare providers
- Full access to counseling and educational resources regarding AMD risk factors and prevention for family members as well as for the AMD patient
- Greater utilisation of AMD screening technology and improved training for "first-line" diagnostic clinicians, including optometrists, general practitioners and general ophthalmologists
- More retinal specialists and a more even geographic distribution of their services
- An equalising of the quality and availability of treatment received by patients in the public sector, as compared to the private, provided at minimal or no cost
- Equal access to and affordability of care regardless of income, language, location or circumstance

Existing Barriers

With the desired future state of AMD in Australia defined, the moderator asked participants to list barriers that stand in the way of the nation attaining it. Here are the key barriers that were identified:

Barriers Related to Patients and Their Families/Caregivers

- Public awareness of the disease and especially of the need for early diagnosis and treatment
- The differing health messages regarding diet and nutrition across various disease states, which can be confusing
- Poor incentives for behavioural changes that would help prevent the disease and improve treatment outcomes
- Transportation costs, patient isolation, and a lack of social support to help patients access treatment
- High out-of-pocket treatment costs (primarily consultations, injection fees, and scans)
- The burden of current treatments (an ongoing series of injections)
- Unrealistic patient expectations of treatment outcomes
- A lack of patient awareness of the benefits of vision rehabilitation

Barriers Related to Healthcare Professionals and Institutions

- Fragmented and inconsistent diagnostic and treatment practices
- Inefficiencies and delays in the referral process
- Inability to effectively treat early or dry AMD
- A lack of retinal specialists and an uneven geographical distribution of existing specialists
- The disconnect between diagnosis, treatment and rehabilitation with a lack of clinician awareness of the benefits of vision rehabilitation
- A lack of effectiveness data for diagnostic screening and treatment
- The rising number of people who need care (due to an ageing population), and the strain this puts on existing resources
- Inefficient utilisation of existing AMD-related resources, including vision rehabilitation services
- Inability to predict treatment response or outcomes
- The speed of the disease's progression, which requires quick referrals and treatment onset
- Incomplete scientific knowledge of the pathology and underlying causes of the disease
- The widespread use of non-standard therapy

Barriers Related to Government Policies and Services

- A lack of awareness from state and federal government agencies to make macular degeneration a medical priority, consistent with its prevalence and impact
- A proposed government-funded disability system that does not consider blindness a severe disability for people aged 65 and older
- Lack of reimbursement for OCT scans
- A lack of quality low-vision services
- Finite healthcare and research fund

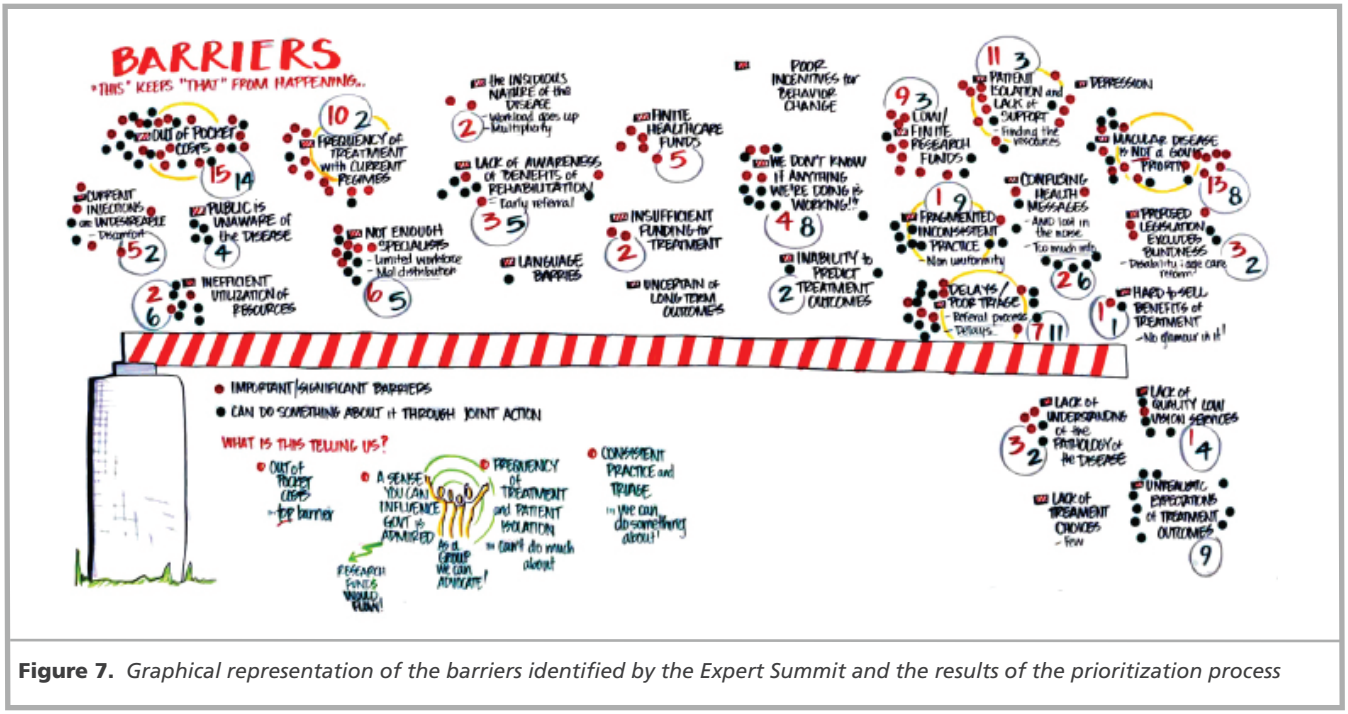

Figure 7. *Graphical representation of the barriers identified by the Expert Summit and the results of the prioritization process*

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 detection and treatment of wet AMD, with a special emphasis on speeding up access to treatment. 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 Early Detection of Wet AMD

Summit participants focused their discussion about improving early detection on two key areas: 1) the recognition of early symptoms by patients and first-line clinicians (optometrists, general practitioners and general ophthalmologists), and 2) the actual detection of the disease by optometrists followed by accurate and timely referral.

Early Symptom Recognition

The summit participants agreed that a major barrier to improving early detection of wet AMD is a lack of symptom recognition among people who have developed the disease. Although an ongoing campaign by the Macular Degeneration Foundation has raised the awareness of the disease among people aged 50 and older from 58% to 92% between 2007 and present, people are still ignoring early symptoms and waiting too long to have their eyes checked for macular damage. The Macular Degeneration Foundation has launched a new campaign that focuses on symptom recognition; it will be closely monitored for effectiveness. The Foundation is also considering developing a smartphone app that could help individuals identify symptoms.

Summit participants agreed that simple messages are usually the most effective. One key message that needs to be emphasised with the Australian public is that early AMD symptoms are monocular (occurring in one eye), so people may not realise they have the symptoms unless they cover one eye while checking an Amsler grid, trying to read or perform some other visual task.

Summit participants also discussed the possibility of encouraging the government to couple the eye exam that accompanies driver's license renewals with a screening test for AMD. In addition, participants agreed that a greater educational effort is needed to encourage AMD's target demographic (people aged 50+ years) to receive regular eye exams. The grown children of individuals in this demographic should be targeted as well, for they can help persuade their parents about the need for such exams. This is especially true of families in which older members are immigrants with a language barrier, which may have impeded their ability to understand public health messages about the importance of eye exams.

The Role of Optometrists and Other "First Referrers"

Optometrists, which number approximately 3,000 in Australia, play a central role in referring appropriate patients with AMD symptoms to ophthalmologists, particularly in Australia's rural areas. That role, however, could be made even more effective, according to summit participants. An estimated 30% of optometry practices have OCT equipment, but that technology is advancing quickly, and some optometrists are unsure of how to interpret the technology's results. Improved training would help, as would national screening guidelines. Fortunately, optometrists in Australia are generally eager to acquire more information and training regarding AMD.

Many general practitioners, who do not receive sufficient ophthalmology training in medical school (about four days, on average), are also unaware of early symptoms. More AMD-related training for this group—and for general ophthalmologists, as well—is needed. Again, national practice guidelines for AMD-related screening and treatment would help speed up and improve care.

Future Action Steps

Summit participants then discussed what specific shared actions could be taken to improve the early detection of wet AMD in Australia. They developed the following list:

- Develop AMD-related national guidelines for all healthcare practitioners
- Continue to monitor the outcomes of current symptom-recognition public-awareness programs to determine what is most effective
- Require AMD eye exams as part of regular medical checkups for people aged 50 and older
- Develop AMD-related awareness/training programs for "first referrers" (optometrists, general practitioners, and general ophthalmologists), working in collaboration with Medicare Locals
- Engage in research to track efforts to improve early detection by "first referrers"

Improving Access to Effective Interventions for Wet AMD

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. Despite government reimbursement for AMD-related treatment, gaps in access to effective interventions still exist. In this segment of the summit, the experts discussed the interventions that need to be expanded or added to the Australian healthcare system to improve access to AMD-related care.

Greater Affordability

The high cost of OCT scanning is a major problem, summit participants agreed. Currently, OCT scans are not listed as a Medicare item, and thus are not reimbursable. Healthcare providers charge varying amounts for this exam; as a result, some Australians pay as much as AUS$100 for OCT scanning, although some physicians reduce or waive the charge for pensioners. Retinal specialists also charge varying amounts for AMD-related treatments, and any non-reimbursable portion of those charges can be burdensome to the patient. Add to this the out-of-pocket expense of securing transportation to and from a clinic or hospital for monthly treatments, it becomes clear why some patients fail either to undergo screening or to start timely treatment, and why they stop treatment early. This problem is particularly acute in rural areas where patients have limited access to retinal specialists and where transportation is a significant barrier.

Some patients are reluctant to tell a doctor that they can't afford treatment; instead, they may simply stop coming for their anti-VEGF injections. Private healthcare providers, therefore, need to be cognizant of this reluctance to discuss financial matters and to be alert to the difficulties faced by patients with cost of treatment. If the specialist is unable to provide financial relief, they have a professional and ethical obligation to 1) explain to financially challenged patients that other providers may offer the treatment at a lower fee and 2) facilitate referral.

Efforts to better educate patients about their options regarding costs are also needed. This includes better informing patients about the Extended Medicare Safety Net and the need for the patient to check that he/she is registered for its use (required for couples, automatic for singles). In addition, patients should understand that stopping treatment is generally not a viable option, as it will put their vision at risk.

Another major concern regarding affordability that was repeatedly discussed at the summit is the "no-switching" policy by the PBS. Thanks to the actions of the medical community and the Macular Degeneration Foundation this policy has been amended, and switching between anti-VEGF agents is now permitted. Research has suggested that switching patients unresponsive to intravitreal ranibizumab to intravitreal bevacizumab can be effective in some cases.[37]

Greater Accessibility

Relatively few Australian ophthalmologists have received retinal sub-specialty training (approximately 150/700), so there is a shortage of appropriately qualified clinicians providing anti-VEGF injections. The shortage is particularly acute in non-urban areas of the country. In addition, there is currently very limited availability of free treatment in public hospitals for those in need. This factor further limits patients' accessibility to treatment. Summit participants talked about the need to expand public treatment and the need to provide more ophthalmologists with specialty training so they can treat AMD patients.

More efficient systems for delivering AMD-related care—ones, for example, that enable clinicians to increase the number of injections they administer daily—would also improve patient accessibility to treatment. Some of these practice efficiencies are already in place, particularly in medical facilities in large cities, but more needs to be done. A referral website could also help with accessibility; not only would such a website enable patients to find an ophthalmologist who can treat them, it would also help ensure that they receive treatment as soon as possible after diagnosis. Potential sources of funding for such a website include the government, pharmaceutical companies, and, perhaps, non-governmental organisations.

Summit participants also discussed the need for AMD patients to have improved access to lifestyle and behavioural interventions, such as programs that encourage smoking cessation and better nutrition. A 2005 review of 17 studies found that smoking was associated with a two- to three-fold increased risk of AMD.[38]

Research has suggested that a diet rich in antioxidants, particularly the carotenoids lutein and zeaxanthin, which are found in green and yellow fruits and vegetables, might also decrease the incidence and slow the progression of AMD.[39] In addition, a 2001 randomised trial found that a particular formulation of high-dose supplements of antioxidants and zinc may slow the progression to late-stage AMD by 20% to 25% in high-

risk patients over a six-year period,[40] although the long-term safety of taking such high dose supplements is unknown.

Antioxidant supplements are currently not funded by the Australian government for the management of AMD [strictly speaking, supplements are not treatments]. Some participants at the summit proposed implementing advocacy efforts to encourage such funding. The participants agreed that public health messages about these complementary treatments must be clear, uncomplicated and consistent. They must also be evidence-based.

Improved access to quality low-vision services is also needed. In addition, Australians over the age of 65 should have the same access to disability services as younger people under the National Disability Insurance Scheme (NDIS). AMD patients with significant vision loss typically need episodic rather than continuous disability services, which the proposed aged care and disability schemes do not manage well.

The Need for Standardised Practice Guidelines

A repeated issue discussed throughout the entire summit was the need for standardised diagnostic and treatment guidelines. Such guidelines, the experts agreed, would help close many of the existing gaps in AMD care. The guidelines must be evidence-based, however, and reflect a seamless continuum of care, from diagnosis through treatment to vision rehabilitation services. The Australian government has a tradition of funding medical practice guidelines, and most of those guidelines have been well received. It has not yet authorised the creation of guidelines for the treatment of AMD, however. The Macular Degeneration Foundation had applied for government funding for AMD practice guidelines in 2011, but was turned down. The Foundation is currently exploring several possible avenues of funding.

Future Action Steps

Summit participants then discussed what specific shared actions could be taken to improve interventions for wet AMD in Australia. They developed the following list:

- Advocate for improved funding and access to treatment, including a reversal of the PBS' "no-switching" policy. (A post-meeting note: The PBAC has now approved switching between PBS-listed anti-VEGF treatments)
- Advocate to expand vision disability services to include those over the age of 65
- Expand access to quality lifestyle/behavioural treatment interventions
- Develop more efficient systems for ensuring early diagnosis and referral and for delivering AMD-related care
- Investigate the development of an up-to-date and easy-to-use "referral" website
- Develop standardised AMD diagnostic and treatment guidelines

Value Analysis: Defining Successful Outcomes

After discussing possible solutions for improving the early detection 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 desired patient-centred outcomes for wet AMD treatment, and how are they measured? The subsequent discussion focused on quality-of-life endpoints.

Quality-of-Life Endpoints

The primary endpoint of the effectiveness of anti-VEGF treatment is improvement in visual acuity, which is measured by the familiar eye chart with its 11 lines of block letters ("optotype"). Visual acuity may not, however, reflect the true vision of patients. Patients who are receiving treatment for their wet AMD value more "real-life" functional endpoints—the ability to remain mobile, self-sufficient, and engaged in their usual activities. Summit participants discussed the existing tools available for measuring health-related quality-of-life endpoints, including the generic SF-36 (36-Item Short Form Health Survey), the EQ-5D (EuroQol-5D) and the visually oriented NEI-VFQ-25 (National Eye Institute 25-Item Visual Function Questionnaire and Macular Disease Quality of Life Scale). They agreed that quality-of-life measurement tools are important for assessing AMD treatment outcomes and measuring success from the patient's perspective. Having a patient fill out such a questionnaire before treatment would also provide useful quantitative baseline data with which to assess treatment progress. The data could also be used to create a national registry of treatment outcomes. However, current quality-of-life measurement tools are either too long and/or not sensitive to vision complaints. Thus, the tools are often not practical for ophthalmologists to use with AMD patients. Indeed, few ophthalmologists incorporate them into their

practices. Work needs to be done on developing shorter questionnaires and encouraging ophthalmologists to use them.

Mental Health Endpoints

Quality-of-life measurements are particularly important given the high rate of emotional distress[41] and depression[42] associated with AMD. Summit participants agreed that collecting data on depression among AMD patients would be useful. Ophthalmologists can fail to recognise depression in their AMD patients, partly because they are not asking the right questions. In cases where depression is suspected, retinal specialists refer the patient back to his or her general practitioner, who then makes a referral to a psychologist or psychiatrist. But often, the summit experts acknowledged, nothing can happen, and the patient fails to receive treatment for the depression. The development of some kind of follow-up system to ensure that AMD patients receive care for depression or anxiety is needed. Summit participants also discussed the need to better educate and possibly accredit psychologists and psychiatrists about the effects of vision loss on mental health. That is where more data collection would be very useful.

Developing a Strong Research Agenda

One of the themes voiced throughout the summit was the need for more data collection and research. As a final item of business, the summit participants listed AMD-related knowledge gaps and research priorities, particularly as they relate to improving outcomes for Australians with the disease.

- Basic research: A more detailed understanding of the pathogenesis of AMD is needed. Given that the development of AMD may be strongly driven by genetic factors, there should be greater investment in the study of genotype and phenotype correlations. Basic research into the molecular biology of AMD should also lead to the development of better animal models for both the dry and wet forms of the disease and perhaps to the identification of intraocular and circulating biomarkers. Such biomarkers could then be used to determine an individual's risk profile for AMD and, if the individual goes on to develop the disease, which therapies might be most effective. Another priority should be research into prevention. Why, for example, do some ageing individuals never develop drusen or other changes in the retina?

- Treatment-effectiveness research: More research is needed on how current anti-VEGF treatments work in the "real world." Better tools for measuring treatment outcomes would help—as would a national registry for collecting and assessing that outcome data. One such registry project is underway (Fight Retinal Blindness!). Initial uptake was slow, but its use is steadily increasing.

- Research into the safety and effectiveness of "switching" anti-VEGF medications must also be a top priority. In addition, the safety and effectiveness of behavioural and dietary interventions, such as the use of antioxidant supplements, demands much more study.

- Translational research: Advances in fields such as nanotechnology and cell biology need to be brought to bear on the delivery of drugs into the eye. Funding support should also be given to efforts to develop new and less expensive screening instruments that could be used effectively by a greater numbers of clinicians in Australia.

- Delivery-of-services research: Demographic data on Australians who are failing to receive timely or adequate diagnosis or treatment for AMD need to be collected and assessed. The barriers that are keeping people from accessing treatment also need to be more systematically identified. In addition, an evaluation needs to be made on how many retinal specialists the country will require to keep up with Australia's ageing population and the resulting demand for AMD treatment. Research also needs to be undertaken on the quality, effectiveness, and geographic distribution of vision rehabilitation services for patients with the disease.

Research Gaps Requiring Action

Summit participants then composed a summary list of the knowledge/research issues that need addressing to achieve the desired patient-centred outcomes for wet AMD treatment in Australia:

- A greater investment in basic AMD-related research is needed.
- A systematic collection of data to correlate outcomes and treatment is needed. The establishment of a central national registry could help in this effort.
- Outcome data must include quality-of-life endpoints. Collecting that data will require more efficient measurement tools.
- Research into the safety and effectiveness of switching a non-responding patient to a second anti-VEGF drug is needed.
- Research into modifiable risk factors, including behavioural changes, should be expanded.
- More research into biomarkers is needed, both to help develop risk profiles and to better tailor treatments to individual patients.
- More data about the effectiveness of vision rehabilitation services should be collected, and ways to help more people access such services need to be identified.

The summit participants agreed that resolving these and other AMD-related knowledge gaps would require a unified effort of all interested stakeholders.

Summary of Future Action Steps

Over the course of the day-long 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 Australians who will be diagnosed with wet AMD in the coming years.

1. Improve awareness and early detection

- Support the Macular Degeneration Foundation in enacting public awareness campaigns to increase the general public's knowledge about the early signs of wet AMD.
- Work with optometrists, general practitioners and general ophthalmologists to improve early detection of wet AMD, and increase referrals to suitably qualified eye specialists for follow-up exams and treatment.
- Make AMD eye exams part of regular medical checkups for people aged 50 and older.
- Develop comprehensive programs for diagnostic training that will reach a wider range of clinicians beyond ophthalmologists specialising in retinal diseases.
- Increase access to diagnostic technologies for all patients throughout Australia.
- Advocate for government reimbursement of patients' OCT scanning costs.
- Encourage state and federal government agencies to commit to making macular degeneration a medical priority.
- Promote research efforts to develop new and less expensive screening technology.

2. Improve access to effective interventions

- Develop healthcare systems that provide a "seamless pathway" of AMD-related care, from diagnosis through vision rehabilitation services.
- Develop standardised AMD practice guidelines to ensure that all Australians receive the same efficient, effective and high quality care.
- Investigate the development of an easy-to-use "referral" website.
- Improve the co-ordination of healthcare clinicians to better manage co-morbidities associated with wet AMD.
- Encourage physicians to discuss all treatment costs and options with their patients, including the option of seeking care from another physician.
- Educate patients about their options regarding treatment costs.
- Increase the number of retinal specialists, particularly in less-populated areas of the country, and provide specialised training to general ophthalmologists so that they can also provide specialised AMD-related care.
- Increase the quality, availability and accessibility of free treatment via the public hospital system.
- Expand the PBS listing of anti-VEGF treatments to include extra- and juxta-foveal lesions, and other neovascular conditions of the retina.
- Encourage greater clinician participation in a national registry for collecting and assessing outcome data.

3. Improve outcome value for stakeholders.

- Develop AMD-related treatment practices that put the focus on the overall health of patients—a system that treats not just the eye, but also the whole body.
- Provide counseling and other resources that would help individuals both understand their AMD risk profile and manage those risks.
- Advocate for the development of more efficient and vision-oriented quality-of-life measurement tools.
- Improve the education of patients, families and caregivers about the progression of the disease and about expectations regarding treatment outcomes.
- Improve clinician awareness of the benefits of vision rehabilitation.
- Improve patient access to evidence-based lifestyle and behavioural interventions.
- Improve patient access to quality low-vision rehabilitation services.
- Advocate the expansion of government-sponsored vision disability services to include AMD patients over the age of 65.
- Develop better healthcare systems for ensuring that AMD patients with depression receive prompt psychological treatment for the depression.
- Encourage the development of better tools for measuring treatment outcomes.
- Promote research on the effectiveness of vision rehabilitation services.

4. Improve translational research.

- Promote research efforts to develop less invasive and less frequent treatments.
- Promote research on how current anti-VEGF therapies work in the "real world."
- Promote research that elucidates the pathogenesis of AMD and its progression from dry to wet forms.
- Promote research on AMD-related biomarkers.
- Encourage the development of better animal models for the study of wet AMD.
- Promote research on lifestyle and behavioural prevention and interventions.

References

1. Wong T, Chakravarthy U, Klein R, et al. "The natural history of prognosis of neovascular age-related macular degeneration." Ophthalmology. 2008;115(9):1524.

2. World Health Organization (WHO). Vision 2010: The Right to Sight. Geneva, Switzerland: WHO. 2007.

3. Macular Degeneration Foundation. Eyes on the Future: A Clear Outlook on Age-Related Macular Degeneration. Deloitte Access Economics. 2011.

4. Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR, for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. New England Journal of Medicine. 2004;351(27):2805-2806.

5. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine. 2006;355(14):1419-1431.

6. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GL, for the CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine. 2011;364(20):1897-1908.

7. Martin DF, Maguire MG, Fine SL, et al., for the CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388-1398.

8. U.S. Food & Drug Administration. FDA approves Aflibercept for eye disorder in older people. Silver Spring, MD: FDA; Nov. 18, 2011.

9. About the PBS. Department of Health and Ageing website. http://www.pbs.gov.au/info/about-the-pbs. Accessed October 16, 2012.

10. Heraghty J, Cummins R. A layered approach to raising public awareness of macular degeneration in Australia. American Journal of Public Health. 2012;102(9):1655-1659.

11. Wang JJ, Foran S, Smith W, Mitchell P. Risk of age-related macular degeneration in eyes with macular drusen or hyperpigmentation: the Blue Mountains Eye Study cohort. Archives of Ophthalmology. 2003;121(5):658-663.

12. BMES data based on Mitchell et al, 1995, and later.

13. Mitchell P, Smith W, Attebo K, Wang, JJ. Prevalence of age-related maculopathy in Australia: The Blue Mountains Eye Study. Ophthalmology 1995;102 (10):1450-1460.

14. Brown DM, Michels M, Daiser PK, Heier JS, Sy JP, Ianchulev T, for the ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology. 2009;116(1):57-65.

15. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark:
year 2000 to 2010. American Journal of Ophthalmology. 2012;153(2):209-213.

16. Mitchell P. Ranibizumab may significantly reduce AMD-associated blindness in Australia. Data presented at Australian Wet AMD Expert Summit; July 12, 2012; Sydney, Australia.

17. Bressler NM, Doan QV, Varma R, et al. Estimated cases of legal blindness and visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. Archives of Ophthalmology. 2011;129(6):709-717.

18. Mitchell P. PBS/RPBS reimbursement of Lucentis, 2010-11. Data presented at Australian Wet AMD Expert Summit; July 12, 2012; Sydney, Australia.

19. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. American Journal of Ophthalmology. 2008;145(2):239-248.

20. Arias L, Armada F, Donate J, et al. Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. Eye. 2009;23(2):326-333.

21. Labriola LT, Sadda SR. Rapid resolution of macular edema associated with central retinal vein occlusion using ranibizumab after failure with multiple bevacizumab injections. Seminars in Ophthalmology. 2011;26(6):387-391.

22. Pharmaceutical benefits schedule item reports. Medicare Australia website. https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml. Accessed October 16, 2012.

23. Mitchell P. Medicare Australia supplied prescription data, accessed November 2011. Presented at Australian Wet AMD Expert Summit; July 12, 2012; Sydney, Australia.

24. Arap W, Pasqualini R. The human vascular mapping project. Selection and utilization of molecules for tumor endothelial targeting. Haemostasis. 2001;31(Suppl 1):30-31.

25. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. Journal of Clinical Oncology. 2002:20(21):4368-4380.

26. Willett CG, Boucher Y, de Tomaso E, et a. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nature Medicine. 2004;10(2):145-147.

27. Kim ES, Seuru A, Huang J, et al. Potent VEGF blockade causes regression of coopted vessels in a model of neuroblastoma. PNAS. 2022;99(17):11399-11404.

28. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, Pyles EA, Yancopoulos GD, Stahl N, Wiegand SJ. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012; Feb. 3 [Epub ahead of print].

29. Mancuso MR, Davis R, Norberg SM, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Journal of Clinical Investigation. 2006;116(10):2610-2621.

30. Jubb AM, Oates AJ, Holden S, Koeppen H. Predicting benefit from anti-angiogenic agents in malignancy. Nature Reviews. Cancer. 2006;6(8):626-635.

31. Dorrell MI, Aguilar E, Scheppke L, Barnett FH, Friedlander M. Combination angiostatic therapy completely inhibits ocular and tumor angiogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(3):967-972.

32. Combining anti-PDGF with anti-VEGF may improve visual acuity, reduce AMD treatment burden. OSN Retina. July 2012.

33. Fan F, Samuel S, Gaur P, et al. Chronic exposure of colorectal cancer cells to bevacizumab promotes compensatory pathways that mediate tumour cell migration. British Journal of Cancer. 2011;104(8):1270-1277.

34. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer. 2010; 116(23):5383-5390.

35. Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer. 2010;116(23):5400-5406.

36. Tournigand C, Samson B, Scheithauer W, et al. Bevacizumab (Bev) with or without erlotinib as maintenance therapy, following induction first-line chemotherapy plus Bev, in patients with metastatic colorectal cancer (mCRC):

Efficacy and safety results of the international GERCOR DREAM phase III trial. In: Journal of Clinical Oncology (meeting abstracts). 2012;30(15): suppl LBA3500.

37. Almony A, Mansouri A, Shah GK, Blinder KJ. Efficacy of intravitreal bevacizumab after unresponsive treatment with intravitreal ranibizumab. Canadian Journal of Ophthalmology. 2011;46(2):182-185.

38. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye. 2005;19:935-944.

39. Ma L, Dou HL, Wu YQ, Huang YM, Huang YB, Xu XR, Zou ZY, Lin XM. Lutein and zeaxanthin intake and the risk of age-related macular degeneration: a systematic review and meta-analysis. The British Journal of Nutrition. 2012;107(3):350-359.

40. Age-related Eye Disease Study Research Group (AREDS). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Archives of Ophthalmology. 2001;119(10):1417-36.

41. Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. The psychosocial impact of macular degeneration. Archives of Ophthalmology. 1998;116(4):514-520.

42. Augustin A, Sahel JA, Bandello F, Dardennes R, Maurel F, Negrini C, Hieke K, Berdeaux G. Anxiety and depression prevalence rates in age-related macular degeneration. Investigative Ophthalmology and Visual Science. 2007;48(4):1498-1503.

Acknowledgements

Summit Participants

Paul Beaumont, FRANZCO, FRACS
Sydney Retina & Vitreous Centre
Sydney, NSW

Rob Cummins, BSc, GDM
Macular Degeneration Foundation
Sydney, NSW

Samantha Fraser-Bell, BSc (Med), MBBS, MMA, MPh, PhD, FRANZCO
The University of Sydney
Sydney Eye Hospital
Sydney, NSW

Mark Gillies, MBBS, PhD, FRANZCO
The University of Sydney
Sydney Eye Hospital
Sydney, NSW

Bamini Gopinath, PhD, Btech (Hons)
The University of Sydney
Westmead Hospital
Westmead, NSW

Julie Heraghty, BA, DipEd
Macular Degeneration Foundation
Sydney, NSW

Wilson Heriot, MBBS, FRACO, FRACS
University of Melbourne, RVEEH,
Gisborne St, East Melbourne.

David Hilford, MBBS (Hons), FRANZCO B.Ed
Queensland Eye Hospital
Spring Hill, QLD

Alex Hunyor, MBBS, FRANZCO, FRACS
Retina Associates
Chatswood, NSW

Anthony Kwan, MD, FRANZCO, FRCOphth
Queensland Eye Institute
South Brisbane, QLD

Vincent Li, MD, MBA
The Angiogenesis Foundation
Cambridge, MA, USA

William Li, MD
The Angiogenesis Foundation
Cambridge, MA, USA

Paul Mitchell, MBBS (Hons), MD, PhD, FRANZCO, FRACS, FRCOphth, FAFPHM
The University of Sydney
Westmead Hospital
Westmead, NSW

Jim Runciman, MBChB, FRACS, FRACO, FRANZCO
Adelaide Eye and Retina Centre
Adelaide, SA

Weiyong Shen, MD, PhD
The University of Sydney
Save Sight Institute
Sydney, NSW

Suellen Tapsall, BA, MA
Macular Degeneration Foundation
Sydney, NSW

Nitin Verma, MD, FRANZCO, MMed
Hobart Eye Surgeons
North Hobart, TAS

Dimitri Yellachich, MBBS, BMedSci, FRANZCO
Fremantle Hospital
Fremantle, WA

Other Contributors

Lisa Arora
Justin Leahey
Robert Mittman
Susan Perry
Diana Saville
Michelle Sylvanowicz
Katya Margolin
Gayatri Gaekwad
The Angiogenesis Foundation

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

The Angiogenesis Foundation

One Broadway, 14th Floor, Cambridge, Massachusetts 02142 USA
617.401.2779 | amdreport@angio.org | www.scienceofamd.org