The Journey to See
A Model for Success

A report on Australia's world leading outcomes for the treatment of age-related macular degeneration

Macular Disease Foundation AUSTRALIA™

Our focus is your vision

This report was prepared by Macular Disease Foundation Australia

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Science For A Better Life

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Foreword

As an ophthalmologist, I have seen first hand the devastating impact of losing vision. We've come a long way in our ability to help people keep their vision over the last few decades. I could never have imagined we would be able to save sight like we can now.

Until the early 2000s relatively little was known about macular degeneration. Thousands of people were losing their sight because people couldn't recognise the early warning signs, were unaware of steps that can reduce the risk of disease progression and treatments were largely ineffective. Late diagnoses were all too frequent and the impact of losing sight had a ripple effect through families and communities.

The ability to offer treatment options for patients is a monumental achievement for everyone working in ophthalmology. The progress made is helped by the united commitment from representatives and organisations across the healthcare sector including the remarkable patient organisation, Macular Disease Foundation Australia, along with industry, government and the health professional community of which I am a proud member.

Macular Disease Foundation Australia has shifted the Australian community's understanding of eye disease, how to detect early symptoms and the importance of regular eye checks through their powerful campaigns. The Foundation has also become a hub for those in need of ongoing support and information.

Simultaneously, industry recognised the need to invest in research for the development of a treatment that would ease the burden of the leading cause of vision loss in the western world, wet AMD. This led to the discovery that anti-VEGF antibodies, used to treat cancer, could also treat neovascular eye conditions including wet AMD and diabetic retinopathy.

This was rapidly recognised by the Australian Government, which responded quickly through the registration and reimbursement process to ensure patients had access to these treatments.

In parallel, the professional community were preparing for access to these treatments through education and knowledge sharing programs, upskilling ophthalmologists to ensure patients were being provided with the highest level of care. In support of those, industry's investment in compassionate access programs and patient familiarisation schemes accelerated this further.

The culmination of all of these initiatives across the sector created a monumental shift – from wet AMD being one of the leading causes of vision loss in the world to a disease that could now be managed.

Our work does not stop here. We should all be very proud of the collaborative healthcare framework we have created for wet AMD and similar eye conditions such as diabetic retinopathy and retinal vein occlusions allowing thousands of Australians access to the education, support and treatments they need to enable the best possible outcomes for saving sight. It is a model I hope will become embedded in our health system - not only to tackle dry AMD, the next frontier in eye disease, as soon as new treatments become available, but in demonstrating how this collaborative model can effectively combat many other diseases.

Professor Paul Mitchell AO, MBBS, MD, PhD, FRANZCO, FRACS, FRCOphth, FAFPHM

National Research Advisor
Macular Disease Foundation Australia

1. Executive summary

A little over a decade ago, most people living with wet age-related macular degeneration (wet AMD) lost vision, and often became legally blind. Now, Australia has become a world-leader in the management of wet AMD, arguably delivering the world's best outcomes.[1,2]

Over the past ten years, key stakeholders from across the health sector united in a unique collaboration to help change the lives of thousands of Australians.

The Journey to See: A Model for Success, outlines how a collaboration between government, healthcare professionals, research agencies, the pharmaceutical industry and the Macular Disease Foundation Australia has delivered a continuum of care for Australians – from awareness and prevention to management and support of those living with AMD.

Whether working together in partnership, in parallel or simply with a common goal of improving the eye health of Australians, these outcomes highlight the power that collaboration, together with trust and independence, can bring to a health priority area in order to impact the individual, community and the country as a whole.

Key achievements have included:

- The creation of a **national voice and dedicated patient advocate** to speak on behalf of those at risk or diagnosed with AMD and provide ongoing support for those in need
- An **increase in national awareness and education** across all age groups of the need for regular eye tests, and recognising the symptoms of wet AMD. This includes a 40 per cent increase in those over 50 years of age understanding the importance of completing regular eye tests[3]
- The **development of anti-VEGF treatments** for the treatment of wet AMD
- The registration and **swift reimbursement of anti-VEGF treatments** to enable access for thousands of Australians at risk of blindness
- Fostering of a **highly skilled and adaptable health professional community** enabling world-leading care for those living with disease.

Despite the impressive results to date achieved through this multi-faceted collaboration, further work is needed to develop new treatments and ensure the ongoing prevention, early detection and timely treatment that is required to continue to lead the world in the management of this disease.

In particular, we need to look to addressing the areas of unmet medical need including a treatment for dry AMD and improved diagnostics to better predict those who are at greatest risk of disease progression.

It is only through a continued collaboration, with a focus on equity and sustainability, that we can reduce and ideally prevent the economic, social and emotional cost of vision loss and blindness from age-related macular degeneration in Australia.

1 Rofhaga S et al, Ophthalmology 2013;120:2292-9
2 UK EMR Users Group, Ophthalmology 2014;121:1092
3 Heraghty J et al, Am J Public Health 2012;109:1655-9

Looking to the future

The Macular Disease Foundation Australia believes there are several critical areas that need to be addressed to maintain our world leading position and, importantly, deliver the very best outcomes for Australians.

To achieve this we see four key priority actions:

1. **Elevate macular disease to a national health priority** to shift policy focus to ensure the appropriate attention and resources are allocated to this significant health issue

2. **Invest in education, awareness and support programs** to prevent disease development and reduce progression, ensure early intervention and long-term treatment compliance as well as increase support for people with vision loss and blindness to maintain independence and quality of life

3. **Push the frontier of knowledge with greater investment in research** with the ultimate goal of a cure. In addition, develop improved diagnostic technologies and treatments to fill unmet needs in disease prevention, treatment and rehabilitation

4. **Prioritise the access and use of quality healthcare data** to inform research, improve strategic planning, outcomes measurement and reporting

2. About age-related macular degeneration

Age-related macular degeneration (AMD) is the most common cause of legal blindness and serious vision loss in the developed world. In Australia, estimates from two major population based studies (Blue Mountains Eye Study - BMES; Melbourne Vision Impairment Project - MVIP) indicate that AMD is responsible for 50% of all blindness. In the 2016 National Eye Health Survey (NEHS), AMD was found to be responsible for 70% of blindness in non-Indigenous Australians.

AMD is a disease of the macula, the tiny central section of the retina at the back of the eye. The macula and its even smaller central spot, the fovea, provide the fine, detailed central vision that is required for the ability to read, drive, see faces clearly and a range of other activities. It also provides most of our colour vision. AMD does not lead to total or 'black' blindness as peripheral or side vision typically remains intact. However, the impact on one's independence and quality of life can be substantial and the disease can also have a much wider 'ripple effect' on family, friends and carers.

AMD is categorised as either early stage, typically with little or no impact on vision, or late stage disease where vision may be significantly affected. Late stage disease is further sub-divided into atrophic (dry) or neovascular (wet) disease. Dry AMD tends to progress over many years or decades, whereas wet AMD can appear suddenly, such as overnight. The wet form is invariably preceded by the early form.

In 2017, approximately one in seven people over the age of 50, or 1.25 million Australians, had some evidence of the disease. About 15% of those with AMD had late stage disease with a significant risk of vision loss or blindness. The risk of disease increases dramatically with increasing age. Despite this, AMD should not be considered an inevitable consequence of ageing, but a serious chronic disease.

AMD is the result of a complex interplay between various environmental and genetic factors. A number of simple dietary and lifestyle measures, especially cessation of smoking, can reduce the risk of the disease developing or progressing. For certain people with diagnosed AMD, the use of a particular formulation of vitamins and antioxidants may help to reduce the risk of progression to late stage disease. On the other hand, a direct family history may significantly increase one's risk. For example, first degree relatives of someone with late AMD have a 50% chance of getting the disease.

At the time of this report, treatment is only available for the wet form of AMD using regular injections of an anti-VEGF drug into the eye. The registration and PBS listing of the first anti-VEGF treatment in 2007 (Lucentis®) and a second registered treatment in 2012 (Eylea®) has revolutionised the management of this disease and has significantly reduced the rate of blindness.

Anti-VEGF treatment is highly effective in preserving and, in some cases, improving vision, providing it is initiated quickly after wet AMD develops and is maintained at the appropriate frequency.

Gerald Buttrose

After nine years and about 100 injections for wet macular degeneration in his left eye, Gerald Buttrose, uncle to Macular Disease Foundation Australia's Patron, Ita Buttrose, is thankful for the simple pleasure of reading the morning newspaper.

It's a pleasure Gerald doesn't take for granted, given that he lost the vision in his right eye in 2002. This was prior to effective treatment for macular degeneration.

Gerald describes wet macular degeneration as a 'thief in the night', which can come on quickly and without warning.

"It was 2008 and I was driving with my wife Colleen when I noticed the white lines on the middle of the road starting to waver. That was the first inkling I had that there was something wrong with my sight," said Gerald.

Gerald is one of seven siblings. Four have had macular degeneration, with Ita's Dad and two other siblings losing their vision to the disease. When Ita heard of her uncle's symptoms she arranged for him to see an eye specialist in Sydney the next day.

"Within 24 hours I was in a doctor's office, Ita made sure of that. I was diagnosed with wet macular degeneration and had my first injection. That was nine years ago," said Gerald.

Ita's timely intervention saved her uncle's sight. Gerald, who lives in Sydney comes every six weeks to see his diagnosing specialist and has had more than 100 injections. His vision is better than when he began the treatment.

Reflecting on macular degeneration and its treatment, Gerald says, "You don't get much warning with macular degeneration, so any sign of the symptoms, go to the doctor. If saving my sight means having 100 injections, I've been happy to do that. I'll take 200 if I can keep my eyesight. It's worthwhile because your vision is so important."

"If saving my sight means having 100 injections, I've been happy to do that. I'll take 200 if I can keep my eyesight. It's worthwhile because your vision is so important."

PART A - THE STAKEHOLDERS

3. People with AMD

Age-related macular degeneration is a chronic eye disease that usually develops in people over the age of 50, with the risk of disease increasing dramatically with each decade of life.

While the early signs of the disease may start to appear from the age of 50, people will usually remain free of any symptoms until it has progressed to the intermediate or late stages, which normally occurs in their 70s or later.

Based on extrapolations from the Blue Mountains Eye Study (BMES) and the Melbourne Visual Impairment Project (MVIP), there were an estimated 1.25 million Australians in 2017, or one in seven over the age of 50, with some evidence of AMD.[23]

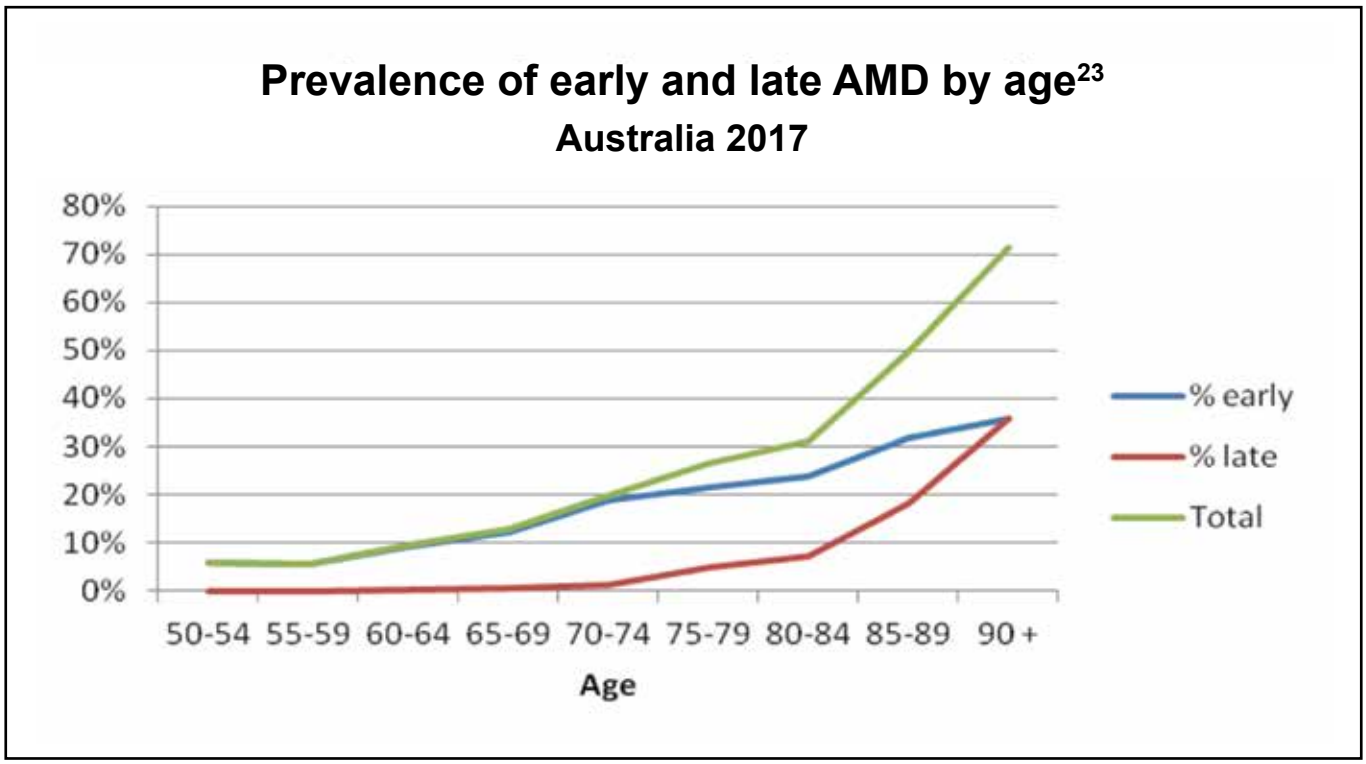
Just over a million of these will have early stage disease, while about 214,000 will have progressed to the late stage, where there is a significant risk of major vision loss.

Almost 12% of people in their 80s have late stage disease, which climbs to more than 30% for people aged 90 or more.

AMD can affect people of any background or socioeconomic group, although certain risk factors can increase the likelihood of being affected. (See Section 9)

As the majority of people with late stage disease are aged in their 70s or beyond, most will be pensioners or self-funded retirees, on limited, fixed incomes. They will also commonly have one or more co-morbidities, such as arthritis and mobility issues, heart conditions, diabetes, dementia, anxiety/depression or other mental health issues or general frailty. Despite this, many will have responsibility as a carer for a partner or sibling, and some may also be providing care for grandchildren. Others will need a carer themselves.

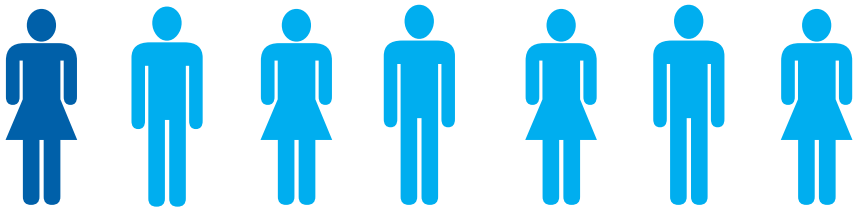
This generation is known to be stoic and generally accepting of their circumstances. Their uptake of technology is variable, though increasing, and their health literacy may be less than ideal. This age group can be vulnerable and often depends on patient organisations for education, support and acting as an advocate in dealing with AMD.



Age-related macular degeneration affects older Australians

Age-related macular degeneration affects central vision and the ability to read, drive and see the faces of family and friends. It impacts quality of life and independence.

1 in 7 Australians over 50 (1.25 million people) show some evidence of age-related macular degeneration.



Age-related macular degeneration is the leading cause of blindness and serious vision loss in Australia.

1.048 million – Early Stage

214,000 - Late Stage

Dry (81,000)

Wet (133,000)

12% of 80 year olds have late stage disease

36% of 90 year olds have late stage disease

AMD can affect people of any background or socioeconomic group

8,000 Australians start anti-VEGF injections each year

40% of people receiving injections at 7 years maintain driving vision.*

Age-related macular degeneration impacts quality of life and independence.

All figures as at 2017

*Gillies M et al, Ophthalmology 2015;122:1837-1845

4. Patient health education organisations Macular Disease Foundation Australia

Vision: To reduce the incidence and impact of macular disease in Australia.

Macular Disease Foundation Australia, a national not-for-profit, patient based organisation began operations in 2001, when it was known as the Macular Degeneration Foundation.

At the end of 2012, the Foundation's name was changed to Macular Disease Foundation Australia to broaden the scope of its activities and help people with all macular diseases, including diabetic retinopathy / diabetic macular oedema, retinal vein occlusions and a range of macular dystrophies. This move was logical given the many similarities between the various macular diseases, the treatments involved, the same or similar healthcare audience and the issues faced by patients and their families. The Foundation was also acknowledged by Government as a peak body.

Fundamental to this vision is the realisation that the risk of developing macular disease in the first instance, or the risk of it progressing to a more serious stage, can normally be modified by undertaking risk reduction behaviours or treatment, when appropriate. Moreover, at all stages, including when vision is impaired or lost, a number of strategies can help to reduce the overall impact of the disease.

When the Foundation began operations, evidence was steadily accumulating that the initial development and progression of macular degeneration could be significantly and favourably impacted by dietary and lifestyle changes.

In addition, the first generation of treatments for wet AMD (especially PDT with Visudyne®) had recently been introduced. These factors highlighted the need to educate the public about the disease, and the ways in which the risk factors could be reduced by behavioural change. While the new treatment (PDT) was not especially effective, in some cases it could play a role if people were treated early, by slowing the progression of major vision loss. In the meantime, there was great promise held for a number of new anti-VEGF treatments that were moving well through phase I and phase II trials.

Why is the Foundation needed?

Macular diseases, especially macular degeneration, are very common, serious but highly complex diseases primarily affecting older Australians. Although there are currently no cures for these diseases, there are several interventions that can reduce risk and delay progression. Critically, there are now highly effective treatments for the most devastating forms of these diseases, but treatment must be provided early to maintain the best possible sight.

All of these factors require a high degree of disease awareness and health literacy. To produce meaningful changes in behaviour, the public needs consistent, relevant and accessible information that is expert, independent and accurate. A dedicated not-for-profit health organisation, totally focused on improving patient outcomes, is arguably in the best position to provide this information, while also being the voice of advocacy for its community.

Benefits:

- provides an immediately accessible source of evidence-based, non-clinical information such as diet and lifestyle interventions which the treating clinician or staff may not have time to deliver
- delivers information that reflects the broader views of the eye healthcare community by virtue of the oversight of a national medical committee
- provides a mechanism for patients and their families or carers to receive independent guidance and advice regarding other aspects of their care and support that falls outside the realm of acute clinical care. These non-clinical areas include transportation, carer support payments, community services and low vision rehabilitation
- avoids the real or perceived bias and conflict of interest with information provided by commercial operations
- ensures the needs of the community are voiced at government level where there are often conflicting priorities and demands on resources

Foundation clients

Clients include those at risk of developing macular disease and people, families and carers who are impacted by disease. The Foundation also serves healthcare professionals, providing them with information and resources. The toll free helpline, website, newsletter and wide range of publications are all part of the continuum of care for the macular disease community.

Foundation structure

a. Board

Oversight of the Foundation's governance and strategic direction is provided by a Board comprising seven people with broad experience in ophthalmology, health, law, finance, education, marketing, the not-for-profit sector and government. All Board members provide their services on a voluntary basis and receive no payment for their time.

b. Committees

A number of committees provide valuable guidance on key areas of activity. Committees include Board members and in some cases, external experts. Committees include:

- **Audit and Risk Committee**: assist the Board with financial and regulatory reporting, internal controls, compliance, investment, risk management and auditing
- **Medical Committee:** 12 of Australia's leading ophthalmologists and retina specialists provide expert advice on medical matters and key messaging reflecting the latest evidence and clinical practice
- **Client Services Committee**: provides input and guidance on the Foundation's client service related activities
- **Research Committee:** provides expertise and guidance related to the Foundation's research activities, especially in relation to the Foundation's Research Grants Program
- **Board Nomination and Evaluation Committee**: advises on Board appointments, performance, induction and continuing development.

c. Staff

A full-time staff of 15 people working from a national head office in Sydney, plus one part-time person in Western Australia provides support for the macular disease community around Australia. Staff deliver programs to regional, rural and interstate locations across Australia.

d. Volunteers

A dedicated group of volunteers, many of whom live with macular disease, provides many hours of help with mailings, education sessions and other areas of the Foundation's work.

e. Collaboration

The Foundation works with a wide range of other not-for-profit organisations, companies and government in the areas of health, aged care and disabilities to ensure the needs of people with macular disease are met.

Funding

The Foundation operates on an annual income of approximately $4.2 million in the financial year 2016-2017 funded by:

- donations and fundraising (27%)
- sponsorship (27%)
- federal and NSW Government grants (18%)
- corporate support (14%)
- income from investments (14%)

Foundation activities

Working under the overarching vision, the Foundation operates within five core areas of activity:

a. Raising disease awareness

One of the key factors contributing to improved health outcomes is a high level of public health literacy and disease awareness with educated consumers interacting with a responsive health care team.[4] For people to benefit from health education, a high level of engagement is required. There is good evidence that interventions to improve self-care, including self-management and lifestyle modification, can improve self-efficacy, patient satisfaction and

coping skills. Significant clinical benefits have been seen with self-management or lifestyle interventions in many other diseases including diabetes, coronary heart disease and rheumatoid arthritis.

Since its inception, increasing community awareness of macular degeneration has been a major focus of the Foundation to promote:

- risk reduction behaviour
- regular eye tests
- early diagnosis of those with disease
- early treatment when indicated
- early rehabilitation for people with existing vision loss.

Evidence from numerous trials of anti-VEGF treatment for wet age-related macular degeneration clearly shows that patients maintain the best vision when they commence treatment early, when the leaking lesion is still small. For people to receive a diagnosis and to seek early intervention, regular eye tests to check for any changes or abnormalities and awareness of the disease and symptoms is critical.

In February 2007, when anti-VEGF treatment first became available with reimbursement on the Pharmaceutical Benefits Scheme (PBS - see Section 6), Macular Disease Foundation Australia (then known as the Macular Degeneration Foundation) commissioned a national Galaxy poll to measure awareness levels of the disease.

The results were of great concern with the total population awareness of the term 'macular degeneration' in people aged 16+ being only 47%. In the main at-risk group, it was slightly higher at 58%.

Importantly, only 32% (aged 16+) or 45% (aged 50+) were aware that macular degeneration affected the eyes.

Finally, only 33% of people aged 50+ had knowingly had an eye test, including a macula check, in the preceding two years. A repeat of the poll in December 2007 obtained almost identical results.

These low awareness figures highlighted the need for action in the form of a national public health awareness campaign along with a myriad of awareness activities, which continue to this day.

Over this period, a wide range of activities has been undertaken to increase overall awareness leading to earlier diagnosis, timely diet and lifestyle modifications and early treatment to reduce the likelihood of vision loss. A constant focus of these activities is to reinforce the need for regular eye tests, including a macula check.

The Results

The many activities undertaken by the Foundation have contributed to Australia being a world leader in awareness of age-related macular degeneration resulting in:

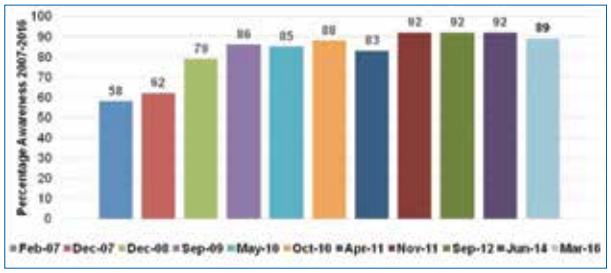
89% Australians aged 50+ are aware of macular degeneration (2007- 58%)

82% of Australians aged 50+ are aware that macular degeneration affects the eyes (2007- 45%)

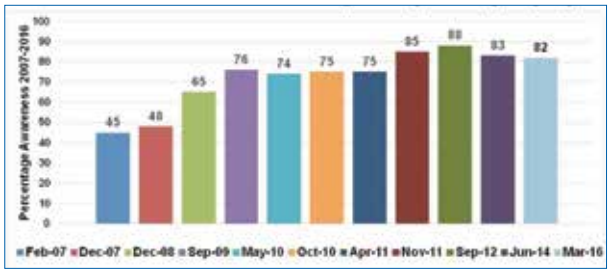
86% of Australians aged 50+ stated that their macula has been checked in the past two years (2007 – 33%)

National Galaxy Research

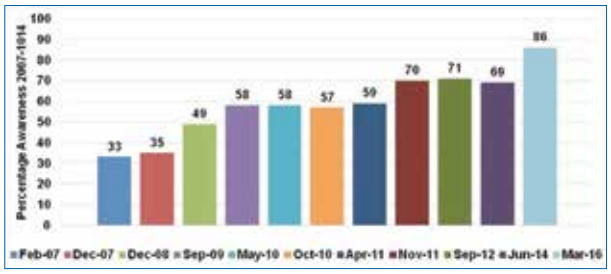
MD Awareness: 50+ population



Awareness: MD = eyes (50+ population)

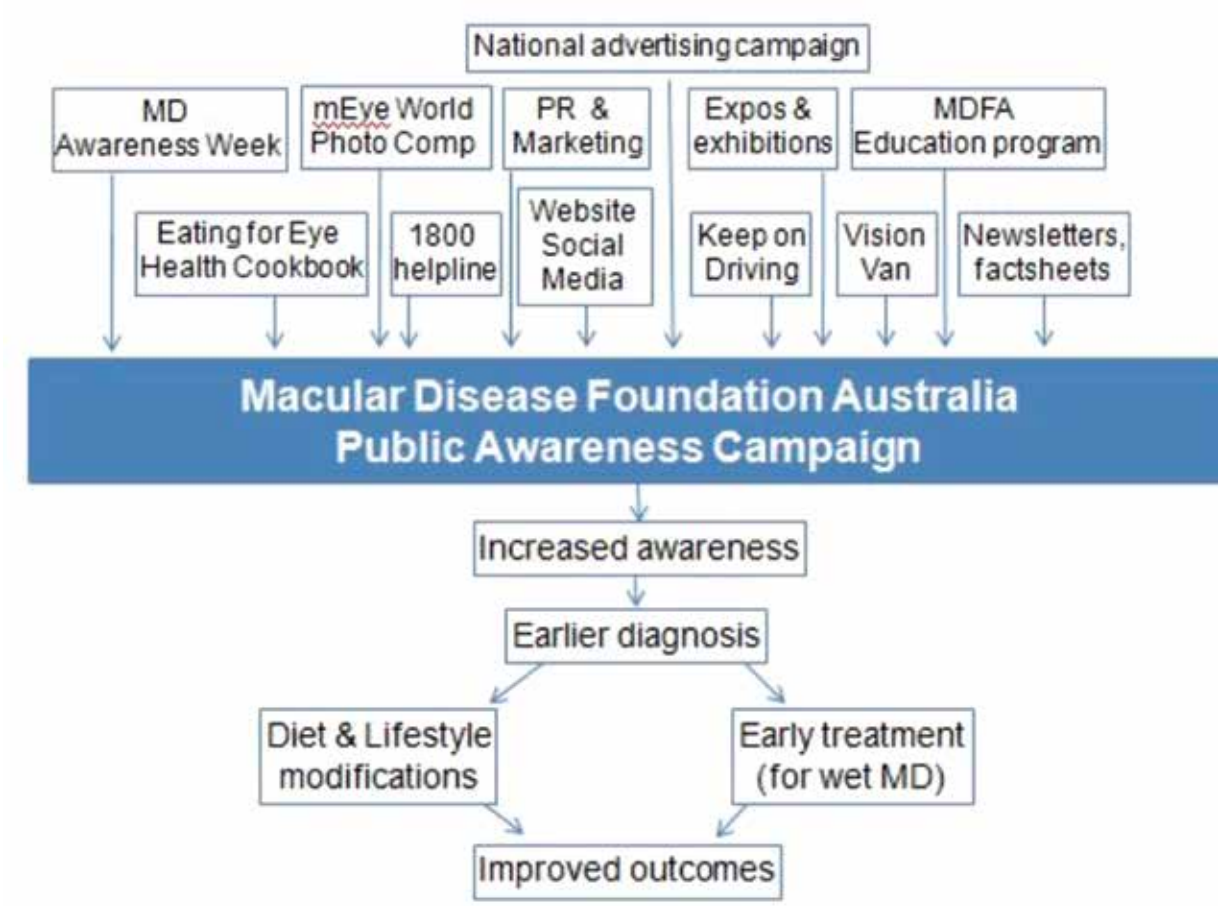


Macula check past two years 50+



Awareness Model

Key Foundation Activities



Macular Degeneration Awareness Week

Macular Degeneration Awareness Week (MDAW) has been a major national annual activity for the Foundation over the past 15 years. MDAW involves a range of activities including media relations, direct mail, community engagement and education and delivering key messages across the community.

Messaging always includes a call to action for everyone in the at-risk category to have an eye test and to ensure the macula is checked.

Media activities typically include interviews with the Foundation's Patron Ita Buttrose, the Chief Executive Officer, the Foundation's ambassadors, friends of the Foundation, community leaders and members of the Foundation's Medical Committee.

Specific campaign materials are developed for use by ophthalmologists, optometrists, orthoptists, pharmacists, libraries, federal and state parliamentarians and community groups, including cultural and linguistically diverse (CALD) groups.

A national direct mail campaign involves the distribution of more than 12,000 information kits to these groups with provision for reordering of additional free resources.

Significant coverage is obtained with community service announcements (CSAs), interviews or stories in mass media (TV, radio and print). The distributed resource kits also facilitate local media coverage by optometrists who wish to reinforce the Foundation's key messages.

Increasing coverage is also obtained through social media, using Facebook, Twitter and YouTube.

Macular Disease Foundation AUSTRALIA
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AWARENESS WEEK

CSA + = Community Service Announcement Potential Audience 8,048,375

Television

4,829,016

Potential viewing audience*
6 pieces of coverage
2 syndicated across a further
62 regional and metro stations

Radio

2,918,936

Estimated radio audience**
236 pieces of coverage including
interviews and prerecorded news grabs

Press

1,582,510

Trade and consumer print
audience / circulation
across 52 articles nationally

CALD TOTAL COVERAGE

133,690

Weekly listening audience^
of the radio stations that aired
interviews and MDFA messages

133,690

Weekly Listening Audience^
of the radio stations that aired
paid adverts in 4 languages

300,487

Print circulations of the papers
that provided editorial coverage

285,487

Print circulation of the papers
where paid adverts appeared

*Estimated potential audience. ** Reported reach from Insentia, Radio Release and Commercial Radio Australia surveys. ^ There could be duplication of audience in these figures. Frequency of message (no. of times heard) has not be taken into account.

Macular Disease Foundation AUSTRALIA

Our focus is your vision

CAMPAIGN SUMMARY

Online

61,685,420 Online editorial views* across 79 websites

462,512
Total impressions no. of people who saw paid online advert

5,946
Total number of people who clicked through from online advert to MDFA website

Social Media

3,362,669 Potential audience on third party social media platforms (no. of likes / followers)

MDFA Facebook Page

113,971 Total reach / no. of people who saw MDFA campaign posts

68,442
Reach / no. of people who saw (organic) campaign posts

11,134
Total Engagement†

Facebook Paid Advertising

84,187
Total impressions / no. of people who saw paid advert

756
New "likes" on the MDFA Facebook Page generated from the paid adverts

MDFA Facebook Boosts

44,529
Reach / no. of people who saw (paid) posts

58,310
Total Impressions / no. of people who saw (paid) posts

13,294
Total Actions & Engagement of (paid) posts††

MDFA Twitter

10,100
Impressions / no. of people who saw MDFA 'tweets'

157
Total Engagement‡‡

†Engagement includes comments, reactions, shares, post clicks and video views. ‡‡Engagement includes replies, clicks, retweets, likes & link clicks. * Standard industry measure is no. of viewers on a website across 1 month. Figures are assumed to be unique, however there could be duplication. ** Engagement includes clicks, page likes, post likes, shares, comments and video views.

MACULAR DEGENERATION AWARENESS WEEK 2017

National TV and radio awareness campaign

Following the first national Galaxy polls in 2007 which revealed low community awareness, a pilot TV disease awareness campaign was developed and aired in April-May 2008. Favourable results from this led to a national TV, print and radio campaign at the end of 2008, with subsequent campaigns once or twice per year until 2012, and again in 2014.

The initial campaigns presented a simple message to raise the awareness of the disease and its impact, and highlight the importance of regular eye testing. When awareness in the at-risk group had been raised to more than 90% in 2011, a complementary campaign was developed in 2012 to increase recognition of the key symptoms. The overarching theme throughout the campaigns was “How’s your macula?” - with matching imagery used in printed materials for other activities. Substantial additional coverage was obtained with free community service announcements (CSAs).

Serial national Galaxy polls using identical methodology tracked the awareness levels and uptake of eye tests over the course of the campaign. In 2014, awareness had climbed steadily to 82% overall and 92% in the 50+ at-risk group. Awareness that macular degeneration affected the eyes increased to 75% (aged 16+) and 88% (aged 50+). Of those aged 50+, 71% stated that they had had an eye test and macula check in the past two years.

“How’s your macula?” imagery used throughout the advertising campaign.

Part of 2012 symptom recognition advertisement

mEye World Photo Competition

The mEYE World Photographic Competition was established in 2011 to encourage awareness of macular degeneration and to develop links with those in the “at risk” group, as well as the wider community, through media and stakeholder engagement.

In the competition's first year, more than 400 entries were received in four categories, Macular Degeneration Community, Open, Healthcare Professionals and Junior, for a range prizes donated by various sponsors. In the ensuing six years, the competition has grown steadily and now receives more than 2,000 entries each year.

Of great importance, however, is that the competition provides additional opportunities for engagement with the public, including many younger people, in which key messages can be delivered. While the initial competition coincided with MDAW, subsequent competitions have been held later in the year to provide additional media coverage.

Key outcomes of the **mEye World Photo Competition** 2016:

- national CSA campaign across 146 radio stations and 10 television stations achieving a potential audience of **25 million people** across metro and regional Australia
- over six weeks period an online banner ad was presented to more than **1.5 million people**, with more than 9,500 clicks through to the specially created website landing page
- 30% increase in "likes" on the Foundation's Facebook page over the duration of the campaign (from 4,681 followers up to 6,093)
- radio coverage included interviews with Foundation's CEO Julie Heraghty and Foundation Patron and competition judge Ita Buttrose interviewed on four stations each
- television coverage included a Sky News interview with Ita Buttrose and Julie Heraghty
- competition results of 2,424 entries

Competition judges Rex Dupain, Ita Buttrose and Alan Pryke

The Vision Van

In 2008 and 2009, a collaboration between the Foundation, industry, Optometry Australia and the Royal Australian & New Zealand College of Ophthalmologists (RANZCO) resulted in an Australian-first mobile eye screening unit to provide free tests for macular degeneration in rural and regional centres.

The Vision Van initiative had the dual role of testing people for AMD as well as raising awareness of the disease. The widespread media coverage reached thousands of Australians with the message to have their eyes tested and macula checked. The Foundation supported the media campaign and conducted a series of education sessions in many of the locations where the Vision Van visited. The project generated worldwide interest and media attention.

Vision Van mobile screening unit

Outcomes

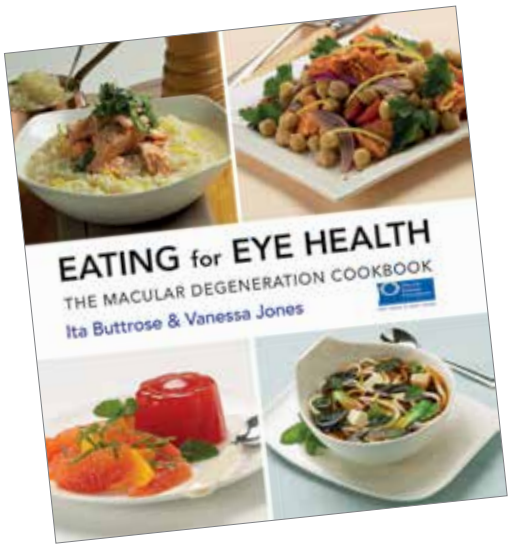
During three tours that reached all states and territories, the Vision Van screened 3,607 people over 270 days. Signs of AMD were detected in one in eight people, closely reflecting the findings of the renowned Blue Mountains Eye Study which showed one in seven Australians over the age of 50 has some evidence of the disease. The project resulted in substantial regional media coverage highlighting the importance of regular eye tests.

Eating for Eye Health - The Macular Degeneration Cookbook

In March 2009, the Foundation launched the Eating for Eye Health cookbook, written by Sydney chef, Vanessa Jones, and Foundation Patron, Ita Buttrose. The launch received extensive media coverage, promoting awareness of macular degeneration, the importance of nutrition, and having eye tests. The cook book has provided a major platform for the promotion of key health messages through diet and lifestyle (nutrition, exercise, healthy living and anti-smoking).

The book has proven to be very popular, and is now into its second (revised) edition and fourth print run.

Macular Degeneration Cookbook – 2nd edition released by co-author and Foundation Patron, Ita Buttrose in 2014



Keep on driving - safely campaign

In January 2009, the NSW Minister for Roads launched the Keep on driving - safely campaign for the Foundation.

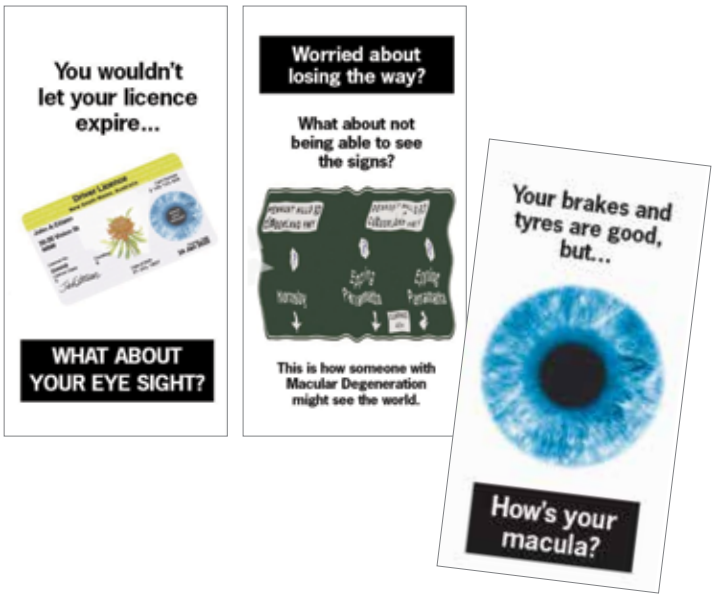
The project involved a Foundation flyer being inserted into more than 1 million driver's licence renewals per year for five years - totalling 5 million insertions. The flyer encourages an eye test and macula check and provides a tear-off response card to request a Foundation information kit. The NSW project was completed in December 2014.

Outcomes

More than 18,000 information kits have been requested and provided since January 2009 in response to the Keep on Driving program. The Foundation is aware of many recipients who have obtained eye tests in response to this program and have subsequently been diagnosed with macular degeneration or other eye conditions.

Subsequent projects

A similar Keep on Driving project began in the ACT in July 2014, involving 65,000 inserts per year. Additional programs started in 2016 in WA (654,000 inserts to all drivers) and SA (94,000 inserts per year to drivers over 50).



b. Education

General public

The Foundation delivers face-to-face education sessions on macular degeneration and other macular diseases to the Australian public. Sessions are either initiated by the Foundation ("public talks") or via requests from community groups such as Rotary, Lions and Probus clubs, Computer Pals, retirement villages and low vision groups ("community talks").

Education sessions may be conducted by Foundation education staff, with or without a guest presentation from an ophthalmologist. Numerous 'low vision days' are also held each year at which presentations are given on macular degeneration as well as presentations and demonstrations of aids and technologies by one or more of the low vision agencies or suppliers.

The local ophthalmologist(s), optometrist(s) and libraries are advised in advance of all public talks, and additional promotion is achieved via local papers.

Foundation education staff regularly attend relevant conferences and exhibitions targeted towards older Australians, such as retirement and lifestyle expos, where they give talks and run information booths, handing out information kits, Amsler grids and tips on low vision aids and technology.

Key messages include risk reduction measures (diet, lifestyle, smoking cessation), regular eye testing, including self testing with an Amsler grid, awareness of family history, early treatment when indicated and the importance of early low vision support and rehabilitation when vision starts to deteriorate.

Education sessions are also conducted with translation services to Culturally and Linguistically Diverse (CALD) communities.

Attendees are asked to complete an evaluation of the session, and results are analysed each year to ensure standards are maintained and clients' needs are being addressed.

Outcomes

Since 2006, the Foundation has conducted more than 1,900 education sessions to the public, speaking to almost 90,000 people.

Attendees' ratings of the quality of education sessions remain consistently very high with more than 95% rating the sessions as good or excellent. In addition, almost all attendees state that they have learnt a great deal during the talk and those who had not had a recent eye test invariably state that they will now do so.

Education of eye health and related professionals

The Foundation has consistently been involved in education of all sectors of the eye health professional community and related healthcare workers, including ophthalmologists, optometrists, orthoptists, practice nurses and managers, ophthalmic theatre staff, general practitioners, pharmacists, psychologists and residential aged care facility staff.

Examples of professional education have included:

- the Eye Health Care Partnership initiative - a comprehensive Continuing Professional Development (CPD) program, accredited by the Royal Australian College of General Practice (RACGP) at the highest level, for general practitioners. This was accompanied

by distribution of an educational CD and Amsler grid to all Australian GPs via the Drivetime Radio Medical Initiative, and distribution of patient support resources via the GP “SamplesPlus” program.

- presentations to orthoptists, ophthalmic nurses and practice managers at the RANZCO annual congress
- lectures to GPs, pharmacists and optometrists at scientific symposiums and evening sessions in collaboration with Medicare Locals/Primary Health Networks
- presentations to ophthalmic nurses and associated staff from around Australia at Sydney Eye Hospital retina courses
- presentations on macular disease and low vision as part of the Masters in Orthoptics course at the University of Technology Sydney
- presentations to students at UNSW School of Optometry and Vision Science
- development of fully accredited continuing practice development (CPD) training programs for GPs and psychologists
- debinars to various groups such as the Australian Association of Smoking Cessation Professionals, and psychologists
- development of core curriculums and slide packs on macular degeneration and diabetic retinopathy for use by RANZCO members when they are educating other health professionals
- publication of peer-reviewed articles on macular degeneration and diabetic retinopathy clinical practice and research in industry publications such as mivision, Insight and Medical Observer.

c. Support services

The Foundation provides a wide range of free services to help support people with disease, their families and carers, and the eye health profession.

Examples of these services include:

National toll-free telephone hotline, through which Foundation staff answer questions and provide non-clinical advice on issues such as:

- disease risk and risk reduction including dietary modification and smoking cessation
- the appropriate indications for vitamin supplementation
- family history
- the need for eye tests
- the correct use of the Amsler grid
- treatment costs and reimbursement
- accessing government entitlements
- community transport
- access to aged care and disability supports
- compliance with treatment
- hints on living with low vision
- the use of low vision aids and technology including referral for assessment
- balanced, evidence-based responses to media stories on new research
- finding optometrists and ophthalmologists
- non-clinical aspects of treatment
- where required, foreign language support is available through the national Translating and Interpreting Service

Publications and reports

The Foundation provides a comprehensive suite of publications and factsheets on a wide range of macular diseases, as well as general information on living well with low vision. All publications are available in printed and electronic form and many are on CD for people who are unable to read. Many publications are also available in translated form. All publications are provided free of charge to the public and to healthcare professionals for supply to their patients. Prior to publication or any significant update, all resources are reviewed by the Foundation's Medical Committee for accuracy, relevance and currency to ensure they reflect the latest evidence and clinical practice.

Publications include:

Booklets on:

- Macular degeneration
- Diabetic eye disease
- Slips, trips and falls – A guide
- Family, friend and carer – A guide
- Low vision – A guide
- Low vision aids and technology – A guide

Leaflets or factsheets on:

- Annual research update (for the public)
- Cataract and macular degeneration
- Charles Bonnet Syndrome (CBS)
- Epiretinal membrane (macular pucker)
- Injection treatment costs and reimbursements
- Macular hole
- Macular telangiectasia (MacTel)
- Myopic MD
- Nutrition and supplementation for AMD
- Posterior vitreous detachment
- Retinal detachment
- Retinal vein occlusion
- Retinitis pigmentosa
- Stargardt's disease
- Vitelliform macular dystrophy (Best's disease)
- What to ask your eye care professional

Many publications are also available in:

- Simplified Chinese
- Vietnamese
- Arabic
- Italian
- Greek
- Spanish
- Portuguese
- Audio CD (English)

Reports

The Foundation has written, commissioned or contributed to a variety of major reports to support education and advocacy efforts.

These include:

- **Eyes on the Future – A clear outlook on age-related macular degeneration (2011)**
  This was a comprehensive review of the description, pathogenesis, epidemiology, risk factors, economics, treatment, barriers to treatment and rehabilitation of age-related macular degeneration in Australia. This document provided a comprehensive reference for educational messaging, advocacy and research.

- **Age-related macular degeneration across Australia 2012-2030 (2012)**
  A detailed projection of the geographic distribution of AMD by state and federal electorate, which has been invaluable for local/regional advocacy and media efforts

- **Advocating for Improved Treatment and Outcomes for Wet Age-Related Macular Degeneration (2012)**
  A report based on an expert summit co-convened between the Foundation and the Angiogenesis Foundation

- **The Economic Impact of Diabetic Macular Oedema in Australia (2015)**
  Provided significant input into a Bayer report which was used for education, media and advocacy efforts in the management of diabetic macular oedema

- **Low vision, quality of life and independence – A review of the evidence on aids and technologies (2017)**
  In addition to providing a comprehensive literature review of the evidence supporting low vision aids and numerous case studies highlighting their benefit, this report also detailed the complex history of policy and inaction on the provision of subsidies to support people with vision loss. The report provides suggestions to guide future policy development.

d. Representation and advocacy

As most people with macular degeneration and other macular diseases are elderly and/or face multiple health challenges, the Foundation acts as the voice of the macular disease community and advocates for their best interests to federal, state and local governments. Some of the areas of advocacy include:

- rapid entry onto PBS and MBS of new drugs and treatments
- changes to PBS rules to improve accessibility and flexibility
- maintaining affordability of treatment including limiting of cost shifting onto patients
- improved access to public treatment for people who are unable to obtain or afford private care
- improved services in rural and remote communities
- removal of discriminatory access to support services for people who acquire a major disability such as blindness after the age of 65. These people are excluded from the National Disability Insurance Scheme and are not provided equivalent support through the aged care system.
- nationally consistent funding and access to low vision aids and technologies
- improved funding by private health insurers for low vision technology.

The Foundation is recognised by the Australian Government as a national peak body, which carries various responsibilities relating to advocacy, education and governance.

Examples of key advocacy programs

Drug reimbursement

Following discussion with the Foundation's Medical Committee, whenever a registered treatment for AMD or another macular disease is to be considered for reimbursement by the Pharmaceutical Benefits Advisory Committee (PBAC), MDFA lodges a submission on behalf of patients explaining why reimbursement is important. Comments may also be given on proposed restrictions or rules that may impact access to treatment.

Safety net capping

In 2009, the federal government proposed to limit the rebate payable to people receiving injections for wet AMD by placing an $80 cap on the extended Medicare Safety Net (see Section 6) for the procedure. This had the potential to significantly increase the out-of-pocket costs of those receiving injections with the risk that some patients would refuse treatment or exit treatment prematurely. Armed with a comprehensive submission including detailed modelling, meetings were held with the Government, opposition and cross benchers to explain the potential consequences of the proposed change. The government ultimately reversed the decision and acknowledged the key role the Foundation played in securing the reversal.

In mid-2012, the Department of Health and Ageing advised the Foundation of its revised plans to introduce a cap on the Extended Medicare Safety Net payments for eye injections at the end of 2012 in an attempt to limit excessive fees from a small number of doctors. While the 2009 proposal would have resulted in higher fees for most people, the revised 2012 proposal was more realistic and would affect only a small number of people, while helping to maintain the sustainability of funding. The Foundation accepted the proposal and helped the department develop and disseminate educational resources to explain the changes.

Optical Coherence Tomography (OCT)

Since the introduction of anti-VEGF treatment for neovascular eye conditions, ophthalmologists have routinely been using OCT imaging to help confirm the initial diagnosis, in conjunction with retinal photography and angiography (See Section 15). More importantly, however, OCT has enabled accurate monitoring of the response to treatment and facilitated the use of the "treat and extend" dosing regimen, which for most people, enables fewer treatments and visits while maintaining comparable outcomes to the use of fixed monthly (Lucentis) or bimonthly (Eylea) injections[i]. Indeed, OCT is recognised globally as standard of care to monitor the response to treatment, allowing individualised dosing. Without the use of OCT imaging, ophthalmologists would have to continue monthly treatment with Lucentis or bi-monthly with Eylea, strictly according to the product label, even though most people can be effectively treated with less than this.

As OCT is considered to be standard of care, the Foundation has been advocating for Medicare reimbursement for more than a decade as the majority of ophthalmologists charge a fee for its use, increasing out-of-pocket costs for the patient. Medicare has stated that it requires randomised, controlled trials to prove the value of the technology, but it would be unethical to conduct these trials as it would require withholding the technology in some people.

At the end of 2016, Medicare agreed to fund one OCT per year, but only for the initial diagnosis of neovascular conditions to demonstrate qualification for PBS listed drug treatment. OCT imaging for ongoing monitoring is still not funded, even though its use saves the taxpayer millions of dollars each year by reducing the number of injections given. The Foundation will continue its advocacy efforts until an appropriate reimbursement is provided.

Public hospital capacity

After being informed by patients and ophthalmologists of several issues in the South Australian public system, an advocacy campaign was launched by the Foundation in March 2014 to help address a capacity crisis at three public hospitals in Adelaide, which was causing serious delays in administering sight saving treatments. The Foundation collaborated closely with patients and ophthalmologists and met with the SA government to find a sensible, practical and workable outcome, including the addition of seven funded public clinics per month to address shortages.

In addition, wherever appropriate, the Foundation advocates for greater access to public treatment for those people who are unable to afford private care.

Switching campaign

As discussed in Section 14, in June 2012, following the registration of Eylea, but prior to its formal PBS listing, the PBAC indicated that it would reimburse anti-VEGF treatment (either Lucentis or Eylea) only for 'treatment naive' patients. That is, reimbursement would not be allowed for existing patients who were switched from one treatment to the other. This was ostensibly because there were no data demonstrating the efficacy of either drug when the patient was switched between drugs.

Given the very high success rate with both Lucentis and Eylea, there was no reason to believe that there would be any clinically relevant difference in response rates between the two treatments. The treating ophthalmologist should have the option to choose which treatment to use.

In early August 2012, the Foundation wrote to its clients seeking their support for an advocacy campaign requesting the PBAC reconsider its restriction on switching between drugs. Within 10 days, more than 6,000 letters of support were received from Foundation clients, including many detailed letters from people stating that the ophthalmologist should be allowed to switch patients from either drug to the other if considered appropriate. These letters were presented to the Chair of the PBAC on 27 August 2012 in addition to a detailed written submission summarising the rationale for a change.

By mid-October 2012 the PBAC announced that switching would be allowed.

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i These are the fixed dosing intervals originally approved for Lucentis and Eylea based on the pivotal registration trials. As stated in Section 15 the routine use of OCT scans enables 'treat and extend' dosing with reduced treatment frequency in most people.

In addition, when Eylea was PBS listed, several restrictions were imposed that would limit dosing flexibility and the clinician's ability to use the treat and extend approach (see Section 14).

The Foundation therefore engaged in further discussions with the PBS group in Canberra to explain that it was in the patients' best interests that clinicians maintained the ability to treat patients with a treat and extend approach with Eylea as they do with Lucentis, thus allowing the flexibility to treat more or less aggressively, depending on individual response.

Shortly after the PBS listing of Eylea on 1 December 2012, doctors were allowed to use monthly dosing when switching, and to progressively move patients onto less frequent dosing regimens, rather than moving them straight to eight-weekly.

Low vision aids

For people who have already lost vision, there is clear evidence that low vision interventions, including suitably timed low vision assessment and the provision of low vision aids, technologies and assistive technologies, appropriate to an individual's unique needs, can enhance visual performance and assist in maintaining quality of life and independence. Low vision aids can provide the opportunity to read essential communications, participate in paid work and/or volunteering, for social interaction, hobbies and sport and to engage in everyday activities such as housework, cooking and gardening. Such interventions provide a greater sense of self-worth, reduce anxiety and depression, and enable people to function independently while reducing the need for in-home or residential care. Low vision services can also include orientation and mobility training.

Best practice models of low vision care are multi-disciplinary, extending beyond the involvement of eye health practitioners and bringing together relevant support services including low vision specialists, counselling, occupational therapy, and orientation and mobility training.

Despite these benefits, services in Australia for people with vision loss are highly fragmented, with poor referral pathways, and grossly inadequate and inequitable funding. Some states provide some financial support for aids and technologies, while others provide nothing. People who acquire a significant and permanent disability such as blindness under the age of 65 can access funded support services, aids and technologies, as an entitlement for life, through the new National Disability Insurance Scheme (NDIS). However, anyone who loses vision after the age of 65, which includes most people who lose vision from AMD, cannot access the NDIS. These people are expected to obtain supports and services through the aged care system, which is neither funded nor equipped to provide the kinds of specialised supports that can make a meaningful difference for people with vision loss.

To help prosecute the case for a significant overhaul of the low vision support area, and after many years of advocacy, Macular Disease Foundation Australia published a major report in January 2017 entitled "Low vision, quality of life and independence"[5]. Key recommendations included:

- increased investment in research to quantify the impact of low vision aids and technologies
- the establishment of a nationally funded, accessible and consistent low vision aids and equipment program to replace the current unsatisfactory state and territory programs
- financial support from private health insurance policies for aids that have been demonstrated to improve quality of life for people with vision loss.

e. Research

The Foundation has become increasingly involved in research over the past 10 years. This includes research conducted by the Foundation itself, commissioned research and, since 2011, the awarding of significant grants to world-class Australian clinicians and scientists to conduct research that is consistent with the Foundation's vision of reducing the incidence and impact of macular disease.

Research conducted by the Foundation includes:

- barriers to the treatment for wet age-related macular degeneration
- costs of treatment and patient understanding of the Australian reimbursement system
- the reasons for variations in treatment uptake around Australia[27]
- issues facing people with wet AMD and their carers ("The ripple effect of vision loss")[93,94]
- assessing the impact of a cognitive behavioural training program to assist the carers of people with late stage AMD - ongoing NHMRC Partnership project with the University of Sydney and Carers NSW[6]
- improving the support of people with eye disease living in residential aged care facilities - ongoing (sponsored by the Australian Department of Social Services)

Macular Disease Foundation Australia Research Grants Program

In 2011, the Foundation launched its research grants program to support world-class Australian researchers. Funding for these grants is provided from donations and bequests received from the public specifically for research, as well as surplus funds from general operations. The Foundation has a policy that 100% of funds donated for research are quarantined for grants. The nominal costs of administering the grants process are funded from the Foundation's general operating expenses.

The Foundation has committed $3.6 million to Australian researchers since the program began. To date, 18 separate projects have been funded with grants between $30,000 and $400,000 for projects lasting from one to three years.

The Foundation's major research grants are offered every two years. Applications are received on a standard application template and are subjected to a robust international peer review process, whereby two or three global experts in the particular field of the application provide a detailed commentary on the proposed project using standard criteria based on those of the NHMRC.

Key assessment criteria include:

- scientific quality
- significance and/or innovation
- track record

In addition, other factors that are considered favourably include:

- applications that provide training opportunities for promising younger researchers under the supervision of an experienced mentor(s)
- applications with a significant financial or in-kind co-contribution from the institution or from partner institutions, as this increases the return on our donors' investments.

Following peer review, applications are evaluated by the Foundation's evaluation panel comprising several leading ophthalmologists, other academics involved in the research process, some members of the Foundation's Board and the CEO. Particular attention is given to ensure there are no conflicts of interest in the awarding of any grant.

Research projects have covered a range of fields including diet and lifestyle, early diagnosis, disease pathogenesis (causation), cell regeneration, stem cell modelling, treatment registers and translational research to help optometrists in patient management.

More than 40 peer-reviewed publications have resulted from Foundation-funded research and several projects have resulted in new messaging regarding risk factor management, improvements in early detection, additional diagnostic tests to accelerate clinical trial endpoints and the generation of significant pilot study data to enable additional NHMRC funding.

Information on research

As there is a vast amount of new research being conducted around the world on the various macular diseases, the Foundation fulfils an important role to promulgate results to the public and the profession.

The lay media is replete with stories on new research, although this is frequently overstated, misleading or confusing. The Foundation constantly

reviews the global research literature and media to provide the public with balanced, evidenced-based translation of results. This can be:

- reactive, in response to stories in the media, using stories on the Foundation's website and/or in the quarterly newsletter, as well as answering queries on the national helpline, or
- proactive, with the publication of an annual research update for the public in which some of the more interesting projects from around the world are summarised and explained in layman's language.

In addition, the Foundation publishes a free weekly research update for eye health professionals. This is a summary of the global peer-reviewed literature on key macular diseases that has been published in the preceding week as reported in PubMed. It is distributed via an email link using MailChimp to more than 1,000 subscribers around the world.

Key success factors

- strong strategic planning and execution
- a focus on outcomes and impacts, through ongoing measurement
- regular engagement with macular disease community
- good governance
- taking a leadership role on key issues
- an expert Medical Committee to guide and inform on medical matters and key messages
- simple, consistent key messages, delivered over many years
- strong support from healthcare professionals
- collaboration with other key stakeholders to maximise strength and spread of message
- financial sustainability and accountability, with a key focus on maximising efficiency
- strong support from industry partners
- support from government,
- strong leadership, from the Board and senior management
- a dedicated, highly motivated and skilled staff
- volunteers who perform valuable work

Foundation's key communication messages

- have your eyes tested and macula checked
- do not smoke
- keep a healthy lifestyle, control your weight and exercise regularly
- eat fish two to three times a week
- eat dark green leafy vegetables and fresh fruit daily
- choose low glycemic index carbohydrates
- eat a handful of nuts a week
- consider a suitable supplement in consultation with your doctor
- protect your eyes from the sun
- use an Amsler grid for checking for symptoms of macular degeneration
- seek immediate attention from an eye care professional if there are any sudden changes in vision
- tell your family – they should also have a regular eye test
- early treatment can save sight
- Early rehabilitation support for people with vision loss can improve independence and quality of life

Mel Byrnes

Mel Byrnes was diagnosed with wet macular degeneration in 2007 but considers himself fortunate. A retired pharmacist, he is acutely aware that if he hadn't acted quickly upon recognising the symptoms of macular degeneration, he'd be telling a different story.

"I first noticed something was wrong with my vision when I woke one morning and there was a black spot on the ceiling. I tested my vision with my Amsler grid and straight away noticed the lines, once straight, were wavy and blurry. The next day I saw a retina specialist who gave me an injection in the right eye and I've been having regular injections ever since," said Mel.

Those injections have saved Mel's sight. His right eye hasn't deteriorated further, and because wet macular degeneration was picked up in his left eye virtually before he had any symptoms, and he started treatment immediately, he has retained his sight in that eye too.

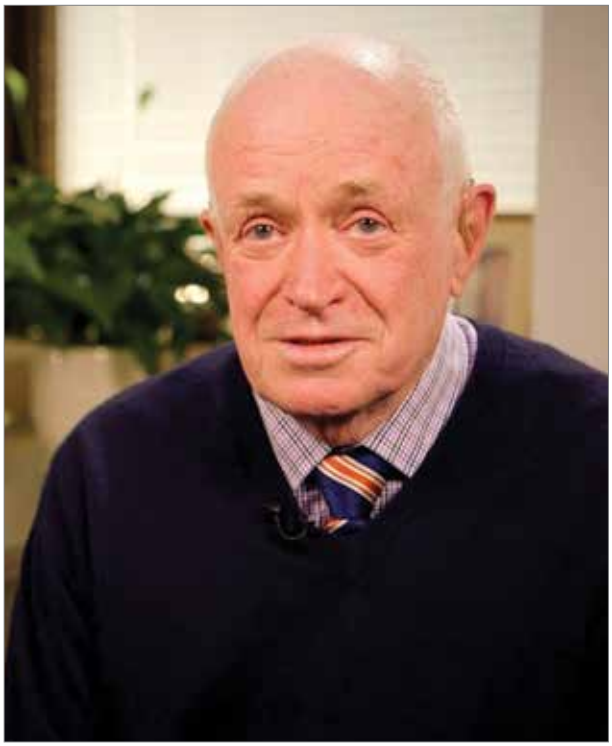
"I am now having injections in both eyes. I count myself fortunate as I can still drive, I can still read, and I can look after my wife Robin who, unfortunately, has frontal temporal dementia. I'd have been a different person now if these injections weren't available."

The strong genetic link associated with macular degeneration means there is a 50% chance of developing the disease if a direct family member has macular degeneration. Looking back Mel realises his father most likely had macular degeneration.

"My father was a soldier and when he came back from the war his eyesight had deteriorated. It was all put down to something that happened in the war, but looking back, I'm sure he must have had macular degeneration."

"My two brothers have also been diagnosed with the same problem, so there is definitely a family correlation," he said.

"I can only stress the importance of making sure that if you have macular degeneration, your immediate family is made aware of the need to have their macula checked regularly," said Mel.



"I am now having injections in both eyes. I count myself fortunate as I can still drive, I can still read, and I can look after my wife Robin who, unfortunately, has frontal temporal dementia. I'd have been a different person now if these injections weren't available."

5. Eye health workforce

In a 2016 report[15] by the Australian Institute of Health and Welfare, using a variety of data sources from between 2011 and 2015, it was estimated that there were almost 11,000 people in the eye heath workforce. As many were working part-time, this was equivalent to almost 10,000 full time equivalent (FTE) positions. This number did not include significant numbers of nursing staff who have specialised in eye health.

The workforce comprises the following (FTEs[ii]):	
optical dispensers	3774
optometrists	3810
ophthalmologists	878
orthoptists	551
optical mechanics	634
orientation/mobility specialists	141
occupational therapists in eye care	74
Total	**9860**

5.1 Ophthalmologists

Ophthalmologists are fully qualified medical doctors with specialty training in diagnosing and treating eye diseases.

Key points in the 2016 AIHW report for ophthalmologists were:

- only 17.4% of ophthalmologists were female
- 78.6% of the workforce worked in major cities, and FTE rates decreased with increasing remoteness
- the average age of ophthalmologists was 53 years, with 56.9% being over 50
- there was no growth in the ophthalmology FTEs per 100,000 population between 2011 and 2014.

In the Health Workforce 2025 Medical Specialties report[200] published in November 2012, shortage in the ophthalmology workforce supply was predicted by 2025, using an estimated growth in workforce demand for ophthalmology of 2% per annum. The report modelled an increase of 20 to 21 new ophthalmology Fellows per year, plus an additional nine permanent skilled migrants per year, for a total of about 30.

In fact, the size of the 65+ age group population, who tend to have much higher eye care needs, is projected to rise by at least 3.2% per annum until at least 2025, suggesting that a larger increase in the workforce will be needed to meet future demand. It is notable that since 2012, the number of new registered Fellows, through the training program and skilled migrants, has averaged 40 per year.

In addition, significant increases in demands on the ophthalmology workforce are expected as a result of the steady growth in intravitreal injections that are now given each year for treating conditions such as wet macular degeneration and diabetic retinopathy.

The number of intravitreal injections are now given each year is 400,000 and this number is expected to keep rising due to more patients being treated, patients staying on treatment longer, and the likely introduction of new intravitreal treatments for currently untreatable conditions, including end-stage dry macular degeneration (geographic atrophy). Offsetting this to a degree is that other therapies now under clinical investigation are likely to have a longer duration of effect, although these are at least several years from introduction.

An additional important issue is that RANZCO has acknowledged a maldistribution of the ophthalmology workforce, with many rural, regional and remote areas being underserviced. While some ophthalmologists also visit rural and remote areas, this may be at a lower frequency than is ideal to provide a patient-centric service.

ii In the AIHW report, an ophthalmology FTE was 40 hours per week, while all other professions were 38 hours per week.

This is because:

a) patients with sudden vision loss, or sudden changes in vision should ideally be seen within a week, especially if treatment is required for a neovascular lesion. Many rural/ regional centres do not have a weekly or even fortnightly service

b) when the interval between patients' intravitreal injections is extended, it is typically done a week or two at a time. This is not possible if the ophthalmologist is only visiting only monthly or less frequently

c) if a patient experiences a complication from an injection, such as endophthalmitis, the ophthalmologist may no longer be in town, leaving diagnosis and management to unqualified local GPs or hospital staff, or else the patient must travel to a major centre

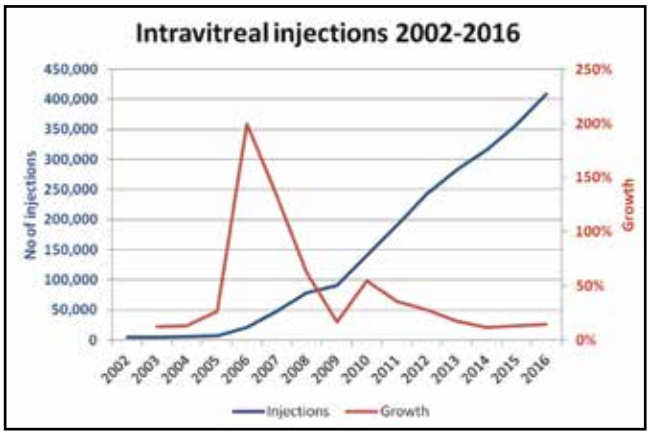
d) most regional and remote services are provided by general ophthalmologists with few retinal specialists visiting these areas.

RANZCO has also acknowledged the lack of public outpatient clinics as a key barrier to patient access to services. Most state capitals have only two or three major teaching hospitals providing public outpatient eye clinics with an intravitreal injection service. Most of these services are working at or close to capacity, and often have lengthy waiting lists. Since early diagnosis and treatment are essential for a good outcome for wet macular degeneration, any wait of more than a week or two can potentially risk sight.

There are very few public injection services in rural and regional Australia, meaning that patients are dependent on private care, assuming it is available. A lack of competition between private providers in regional areas can also result in little incentive to bulk bill and significant out-of-pocket fees being charged.

A 2014 workforce survey conducted by RANZCO stated that up to 90% of urgent cases were treated within one day in the private sector, and 60% of non-urgent cases were seen within six weeks. On the other hand, up to 30% of urgent public outpatients were treated in more than one day, and less than 15% of non-urgent public cases were seen within six weeks. (As stated above, public outpatient treatment for wet macular degeneration is extremely limited.)

Increase in use of intravitreal injections since 2002



Note: The above graph plots Medicare item numbers 42738, 42739 and 42740. Prior to 2012, all intravitreal injections were listed under item 42740. In 2012, item 42740 was reserved for intravitreal injections performed in theatre as part of another surgical procedure. Item 42738 was added for injections* of therapeutic substances, and item 42739 was added for similar injections* requiring an anaesthetist. In 2016, 15,000 of the total injections were performed in theatre as part of another surgical procedure (item 42740). *(including removal of aqueous for diagnostic purposes)*

Registered ophthalmologists (Source: AHPRA Dec 2016, and ABS population data)

	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	NoPPP	Aust
Number of ophthalmologists	15	367	4	165	67	22	247	82	22	991
Number per 100,000 pop'n	4.08	5.08	1.72	3.69	4.08	4.30	4.46	3.48		4.44

It is widely accepted that the standard of training and clinical practice of Australian ophthalmologists is exceptionally high. One measure of this is compliance of ophthalmologists with RANZCO's strict requirements for Continuing Practice Development (CPD). Since 2012, more than 90% of RANZCO Fellows have been compliant at the end of the reporting period, and in excess of 99% were compliant after an extension[7].

5.2 Optometrists

Optometrists are university qualified health practitioners who perform eye examinations and vision tests to determine visual abnormalities and eye diseases. They prescribe corrective lenses and other optical aids to correct visual errors, and can prescribe medications to treat certain eye diseases, usually in collaboration with an ophthalmologist. In the case of macular degeneration, they will frequently provide an initial diagnosis, and monitor patients until they require referral to an ophthalmologist for the management of late stage disease, especially wet AMD. Optometrists are not able to give laser treatment or intravitreal injections.

At 2016, there were 5,134 registered practising optometrists in Australia, with an average age of 42, and approximately 50% of whom are women.

The number of practising optometrists has increased by an average of 4% per year over the past four years. As with ophthalmologists, there is a significant maldistribution of optometrists across the country with 19.0 FTE per 100,000 population in metropolitan areas compared to only 10.7 in outer regional and remote areas. (2014 figures).

Using data from a paper on Australian supply and demand for optometry services by Healy et al[8], Optometry Australia, the peak body representing optometrists stated that there appeared to be sufficient numbers of optometrists to meet community demand.

However, and in marked contrast to ophthalmology, there is likely to be an excess supply of full-time optometrists in the near future.[9] This is likely to be compounded by the recent addition of two new optometry schools, bringing the total to five in Australia. This will double the number of new graduates entering the market.

It is possible that the future surplus of optometrists will see a gradual improvement of services in regional and remote areas, and Optometry Australia suggests that this may already be happening. Optometry Australia is calling for several measures to reduce supply:

a. that public university funding be amended to reflect current and projected supply and demand

b. removal of optometry from the Skilled Occupation List to reduce the numbers of overseas trained optometrists migrating to Australia.

Optometry Australia is also calling for the sector to play a bigger role in growing demand for services, especially through preventative ocular health and vision care by increasing public awareness. In addition, there is an opportunity to address the maldistribution of the workforce by expanding rural and regional services, although a number of barriers continue to limit this goal. It may be partially addressed by providing other health professionals with equivalent incentives to those of general practitioners, as recommended by the National Rural Health Alliance.[10]

The availability of optometry services in rural and remote areas is especially important as they can provide a valuable additional resource for ophthalmologists through close monitoring of at-risk patients with transmission of scans and reports by the internet.

Other than a shortage of optometry services in small outer regional and remote locations, the accessibility and affordability of basic optometry diagnostic services is seldom an issue in Australia, with most optometrists able to see patients at short notice, and most fees being largely covered by Medicare.

Since 2015, optometrists have been allowed to charge above the Medicare schedule fee. In return for this, the federal government has reduced the patient Medicare rebates by 5%. In addition, the previous annual indexation of Medicare rebates has been frozen since 2014. This is placing increasing pressure on optometrists to charge above bulk-billing rate and increase out-of-pocket costs for patients.

To date, active competition within optometry has generally meant that most fees are still bulk-billed or only have a small out of pocket cost, although it is unclear how long optometrists will be able to sustain this. In the May 2017 federal budget, the government announced a relaxation of the Medicare rebate freeze for GPs, and fees for specialists and optometrists will be relaxed over the next three years.

Most optometrists are now able to take retinal photographs and many can perform OCT scans, neither of which attracts a Medicare rebate. Some optometrists will charge a fee for these tests while others will include this as part of their basic fee. There has been some controversy resulting from optometrists charging for OCTs when performed as part of a routine check-up. The 2016 "Choosing wisely" messages issued by RANZCO (the ophthalmologists' college) stated "In the absence of relevant history, symptoms and signs, 'routine' automated visual fields and optical coherence tomography are not indicated." RANZCO's statement was intended to apply to both ophthalmologists and optometrists.

Outcome measurement – frequency of eye tests by age of at-risk groups for AMD

Analysis of 2016 Medicare claims for optometry visits helps inform the proportion of the at-risk population having an eye test, for any reason, in a given year. It should be noted that people aged under 65 are now allowed one Medicare funded comprehensive check per 36 months, while people aged from 65 are allowed one comprehensive check per 12 months.[iii]

Consultations in excess of this would generally be billed to item 10918 (subsequent consultation) which attracts a lower rebate.

Several Medicare item numbers can be used for initial consultations lasting 15 minutes or more. These are 10905, 10907, 10910 (for people aged less than 65), 10911 (for people aged 65+), 10912, 10913 and 10914, with different rules for each.

Item 10915 is used for initial comprehensive assessment of people with diabetes requiring a mydriatic agent, being pupil dilation, to improve visualisation of the retina for retinal photography.

Item 10916 is used for a brief initial consultation.

In summary, for people aged 45-64, who are allowed one comprehensive eye test per 36 months, a little over 10% have a standard, initial, comprehensive consultation in a given year, with a similar number having an "other" initial consultation[iv] per year. It is not clear how many of these consultations are for the same person that received a standard consultation. Regardless, it is likely that 30-50% of people aged 45-64 do not have an eye test within the recommended three year period.

For people aged from 65, in whom one eye test is recommended per year (or more if there are new signs, symptoms or disease progression) only about 30% will have a standard comprehensive consultation in a given year, with about 12% receiving an "other" initial consultation.

Age	Pop'n (mil)	Standard initial consultation <65 (% of cohort) [item 10910]	Standard initial consultation >65 (% of cohort) [item 10911]	Other initial consultations (% of cohort) (Items 10905,10907, 10912, 10913, 10914	Subsequent consultation (% of cohort) [Item 10918]	Initial consultation for diabetes (% of cohort) [Item 10915]	Short initial consultation, less than 15 minutes (% of cohort) [Item 10916]
45-54	3.19	395,030 (12.4%)		296,920 (9.3%)	400,393 (12.6%)	31,579 (1.0%)	173,631 (5.4%)
55-64	2.81	318,334 (11.3%)		400,526 (14.3%)	426,752 (15.2%)	62,786 (2.2%)	150,395 (5.4%)
65-74	2.09	12,184 (0.6%)	636,324 (30.5%)	233,241 (11.2%)	272,260 (13.1%)	65,142 (3.1%)	74,015 (3.5%)
75-84	1.11		370,374 (33.2%)	161,688 (14.8%)	210,294 (18.9%)	37,446 (3.4%)	54,995 (4.9%)
85+	0.49		133,255 (27.4%)	58,281 (12.0%)	71,439 (14.7%)	9,049 (1.9%)	18,816 (3.9%)

iii Note that more than one visit can be claimed for progressive disorders requiring reassessment, or when new signs or symptoms are noticed.

iv These may be referrals from other ophthalmologists, consultations for progressive disorders, or when new signs or symptoms appear.

5.3 Orthoptists

Orthoptists diagnose and manage eye disorders including eye movement issues and low vision. They may work in ophthalmology practices where they conduct many of the diagnostic tests, as well as hospitals, low vision agencies, universities and private practice .

According to the 2016 Eye Health Workforce in Australia report, there were 674 employed orthoptists in Australia in 2011. Of these, 90% are female and almost 90% work in major cities. More recent figures are not available.

Orthoptics Australia reports there is strong demand for orthoptists with new graduates readily gaining employment[11]. This is supported by the University of Technology Sydney, which reported that 100% of graduates of the 2016 Master of Orthoptics course gained employment as orthoptists within two months of completing their course.[12]

5.4 Low vision agencies

Low vision agencies are organisations, typically working in the not-for-profit sector, that provide guidance, training and support for people who are blind or have low vision to help them maintain their independence. Their services include helping people access information using reading technologies or print alternatives, maintain mobility in the home and community and maintain independence with activities of daily living. Some agencies also provide employment services, psychological support, social activities and sports.

Previously, low vision agencies provided all their services through philanthropy and in some cases, block funding from government. With the recent reforms including the introduction of the National Disability Insurance Scheme (for eligible people aged under 65 with significant and permanent disability) and changes in aged care, some of these agencies are increasingly moving towards fee-for service support.

5.5 Changes in workplace practices

The increased awareness of macular degeneration and the ability now to effectively treat the wet form of the disease has not only placed a much greater workload on the eye health workforce, it has also necessitated substantial changes in work practices, models of care, referral pathways, training and investment in new diagnostic technologies and facilities.

5.6 Referral pathways

Unlike the surgical intervention for cataracts where a delay in treatment has little, if any, impact on final visual outcomes, any delay in referring people with the initial signs of wet AMD can have serious consequences. This means that general practitioners and optometrists must now be alert to the possibility of wet AMD and, when suspected, immediately refer the patient to an ophthalmologist, with instructions on how to obtain an early appointment. This has also placed a greater responsibility on ophthalmologists' booking staff to give these patients urgent access, ideally within a week, to ensure the best possible chance for a good outcome if treatment is indicated.

While this is generally well accepted by staff within specialty retinal practices, the Foundation has had to intervene on many occasions to expedite appointments with general ophthalmologists. There is also much work to be done to educate general practitioners on the symptoms of wet AMD and the importance of ensuring a timely specialist review.

5.7 Investment in technology and facilities.

When anti-VEGF treatment first became available, many general ophthalmologists did not feel confident to correctly diagnose or treat the disease, or have the necessary technology to accurately diagnose (e.g. fluorescein angiography) and monitor response to treatment (e.g. OCT). As such, many preferred to refer patients with wet AMD to retina specialists. As a result of their dramatically increased workload, many retina specialists now send well-controlled cases back to the general ophthalmologists for ongoing treatment. In addition, many general ophthalmologists will now initiate and maintain treatment in uncomplicated cases. This has been facilitated by the near universal acquisition of OCTs by ophthalmologists, and the recent change to PBS rules allowing the use of OCT for initial diagnosis of wet AMD and other neovascular conditions, removing the requirement for fluorescein angiography.

The need to provide regular injections to an increasing proportion of ophthalmologists' patients has also required rearrangement of scheduling and clinic structures, with many practices now setting aside several sessions per week dedicated solely to providing injections. Some have restructured their consulting rooms to improve patient flow, which may include one or two dedicated clean rooms to perform injections. Such changes have been necessary to maintain capacity and minimise waiting times for treatment.

In addition, the vast majority of optometrists now have retinal cameras and many also have OCTs which enables more accurate diagnosis and selective referral for neovascular conditions.

5.8 Models of care

The majority of people receiving treatment for wet macular degeneration do so within private ophthalmology practices, which will commonly involve out-of-pocket costs for consultations and treatment if needed. While many ophthalmologists will reduce their fees or bulk bill for people with limited financial means, some patients seek free treatment within the public hospital outpatient system.

It has also been the Foundation's experience that while most people initially prefer the quality of care provided in private practice, some have difficulty with the ongoing costs and may seek public options if they are unable to afford the fees or negotiate cheaper rates privately.

Unfortunately, the public hospital system is neither structured nor funded to provide care in all locations. Indeed, in most states, there are only two or three large teaching hospitals, typically located in state capitals, that are providing public outpatient injection clinics for macular degeneration and similar conditions. This has led to frequently long waiting lists to access treatment (meaning that initially, the patient either has to pay for private care or forgo treatment) and, in some cases, people being treated at less than ideal frequency. In order to minimise waiting lists, it has also been the practice for some hospitals to diagnose and treat people initially (e.g. for two to three months, until stabilised) but then try to move them to private care.

For some people in rural and regional areas, an ophthalmologist may visit on a semi-regular basis, although this will not necessarily be at sufficient frequency to provide a patient-centric, treat and extend approach to management, which may require the ophthalmologist to visit weekly or fortnightly. This also means that if a patient experiences a sudden change in vision in between doctor visits, they have little option but to travel to a major centre for treatment or risk vision loss, assuming they can get an appointment at short notice.

With a handful of notable exceptions, there are typically no public injection clinics in smaller suburban or regional hospitals.

Treatment of people living in remote locations can be especially challenging due to a lack of specialists visiting on a regular basis and the lack of the diagnostic equipment, especially OCT machines, required to diagnose and treat neovascular disease. While Aboriginal and Torres Strait Islander people reportedly have substantially lower rates of age-related macular degeneration than the non-Indigenous population, they do experience very high rates of diabetic retinopathy, including treatable diabetic macular oedema.

The federal government has provided funding to increase the availability of retinal cameras in remote Aboriginal communities to aid in the diagnosis of diabetic retinopathy. However, there is and probably will continue to be a lack of OCT machines in such communities, as it will be impractical and prohibitively expensive to provide a regular injection service. Efforts are underway to increase state government provision of OCTs to state-funded regional hospitals, where ophthalmologists may be able to provide a regular injection service for the treatment of macular degeneration, diabetic retinopathy, retinal vein occlusions and other related conditions for both Indigenous and non-Indigenous people .

5.9 Implementation of anti-VEGF treatment of wet AMD in Australia

The recently reported world-leading outcomes of treatment in Australia[1] are the combined result of a number of inter-related factors, with several sectors working together over many years:

- government
- industry
- eye health care professionals
- not-for-profits

Pre-registration and reimbursement.

1. Several of Australia's key opinion leaders participated in phase 3 (registration) clinical trials of both Lucentis and Eylea. This ensured extensive local experience with the agents including knowledge and management of adverse events. These experts were then able to assist with early, informed education of the wider ophthalmology community as soon as the treatments became available. The experts were also able to provide valuable, informed commentary to regulators during the registration and reimbursement processes.

2. Several opinion leaders also participated on pre- and post-registration advisory boards for industry. Advisory boards play an extremely valuable role in helping the industry to:

    a. understand treatment outcomes and deficiencies

    b. develop appropriate protocols to address real world concerns with proposed treatments, including diagnostic tests, study outcome endpoints and relevant clinical interpretation of outcomes

    c. ensure educational resources reflect the evidence and are time-effective for clinicians.

3. Both Novartis and Bayer enabled ophthalmologists to access their respective drugs prior to registration on compassionate use grounds through the Special Access Scheme (SAS)[v] and, once the drugs were registered but prior to reimbursement, they were made available through patient familiarisation programs (PFPs)[vi] to a selection of specialists. This gave a greater number of clinicians a meaningful, real-world experience with the drug so they could provide unbiased commentary to other ophthalmologists at launch meetings, symposiums etc.

Registration and reimbursement

The registration of Lucentis in Australia by the TGA occurred on 19 February 2007, only 13 months after the first results from ANCHOR were presented. While this was still eight months longer than was achieved in the US under an agreed six month priority review by the US FDA, it was nonetheless an extremely fast approval by Australian standards. Reimbursement via the PBS was also rapid at six months after registration.

Similarly, Eylea was granted registration five months after the USA, and reimbursement took nine months from registration.

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v The SAS scheme enables a doctor to access an unregistered drug for a particular patient. Access requires individual patient approval by the TGA, unless a clinician is granted "Authorised Prescriber" status. The supplier of the drug is allowed to charge a fee for the drug if it chooses.

vi Patient Familiarisation Programs are commonly used to allow some patients to have early access to a treatment after registration but prior to reimbursement. These also give the clinician experience with the drug beforehand. Typically the company agrees to provide the drug at no charge until it is available via the PBS. In contrast to the SAS scheme, supply to a patient does not require individual patient approval by the TGA.

Val Nicholson

When Val was first diagnosed with wet macular degeneration she was frustrated at having to deal with yet another health issue. She felt confronted and wondered "why me". After the initial shock of diagnosis, Val realised she needed to accept that macular degeneration was now part of her life.

Knowing what she does now about macular degeneration, Val regrets not having her eyes checked as soon as she noticed changes in her vision.

"It was a busy time in my life and although I had noticed straight lines appearing wavy, and even a pinkish hue across my vision on waking which disappeared during the day, I delayed making an appointment with my eye specialist," said Val.

"When I finally had my eyes checked I was diagnosed with wet macular degeneration in both eyes and there and then was referred to a retina specialist for immediate treatment."

In the early days, Val's treatment was an injection into the alternate eyes every two weeks. She did this for five years, accepting this was what she had to do to maintain her sight.

"I now go once a month for injections, and have both my eyes treated during the one appointment. It's not for everyone but I prefer to get it done and then get on with my other commitments," said Val.

"We did try and extend the injections longer than a month, but my specialist discovered that my sight deteriorates if I leave it any longer."

Val is aware that her macular degeneration, and its treatment, affects not only her life but her husband's too.

"My husband Doug is tireless in his support, but it can get difficult as he juggles looking after our grandson and driving me to and from my injections. Sometimes following treatment

I am not always able to attend activities planned through our community groups, I just have to fit my life around my injections."

"I am so grateful that there is a treatment available to me. If I had been diagnosed only a few years earlier, before treatment became available, I would have certainly lost my vision," said Val.

"I am so grateful that there is a treatment available to me. If I had been diagnosed only a few years earlier, before treatment became available, I would have certainly lost my vision."

6. The Australian regulatory and reimbursement system

6.1 Drug registration

Australia has one of the more sophisticated regulatory systems globally.

New drugs are reviewed for safety, efficacy and quality by the Therapeutic Goods Administration (TGA), which is part of the Australian Government Department of Health. The TGA is also responsible for regulating the supply, importation, manufacturing and advertising of therapeutic goods in Australia.

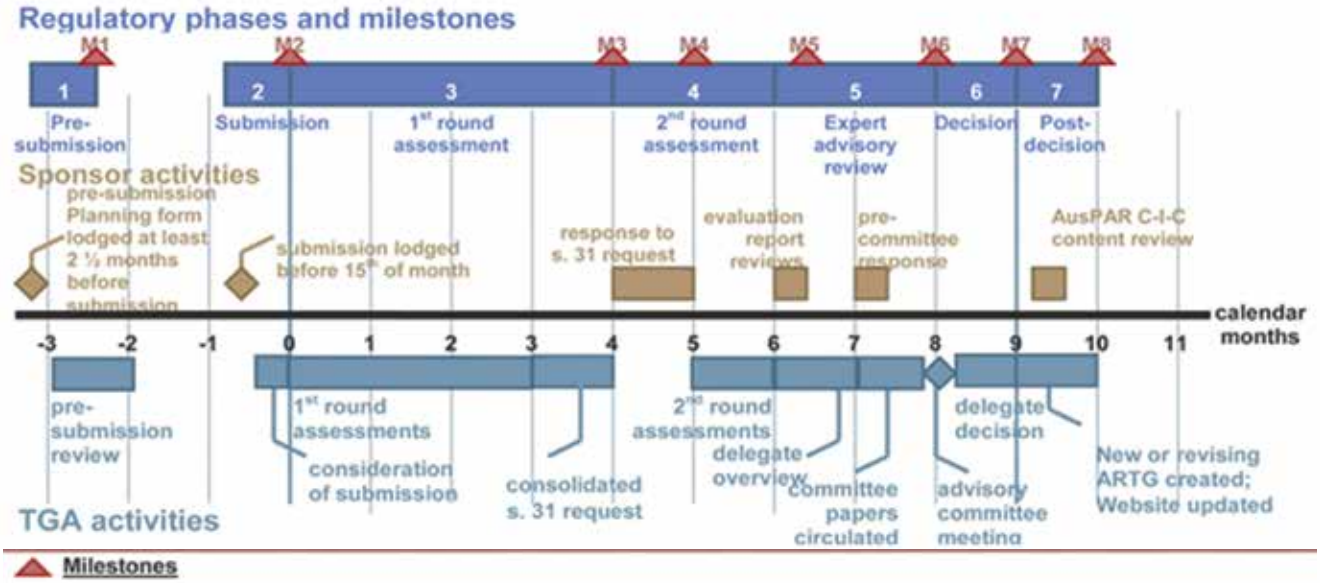
The TGA requires the same standard of evidence for the assessment and approval of a prescription medicine as comparable foreign agencies such as the US Federal Drugs Administration (FDA) or the European Medicines Agency (EMA).

The registration and supply of all therapeutic goods is covered under the Therapeutic Goods Act (1989).

Key aspects of the registration process are:

1. management by milestones
2. registration dossiers are to be prepared in accordance with common technical document (CTD) formatting and certain other TGA regulatory requirements.
3. a pre-submission planning phase where applicants provide details of the proposed application at least nine weeks before lodgement of the dossier. This enables the TGA to identify milestones and plan resource requirements
4. submission of the complete dossier: the TGA provides extensive documents and guidelines to assist applicants. There is no opportunity to deliver new data after the submission date, except as required by the Therapeutic Goods Act (1989). This includes updated safety data, new or updated manufacturing licence details for Australian sites or good manufacturing practice (GMP) clearances for overseas sites.
5. formal requests for information from expert reviewers are consolidated and issued at the end of the initial evaluation round. TGA staff may also ask informal questions to clarify minor issues during the evaluation process.
6. aconsolidated response to the TGA's first round assessment is provided by the applicant within 30 days
7. a second round assessment by TGA staff
8. An expert advisory review of the dossier, assessments and responses is conducted

Australian drug registration timeline



with recommendations made to the delegate, a person who has been given authority by the minister or secretary of the Department of Health and Ageing

9. the delegate decides whether the medicine should be approved, including negotiations regarding product information, consumer medical information

10. final administrative activities to enable entry on the Australian Register of Therapeutic Goods (ARTG).

The TGA commits to a decision by its delegate within 255 working days of the TGA's acceptance of the dossier for evaluation. The registration process is designed to take 330 calendar days (11 months), including the time for applicant activities (responses).

It should be noted that there is no formal priority evaluation system. If an application is considered by the TGA to be a significant therapeutic advance or of critical importance, the TGA will, where possible, work with the applicant in an attempt to facilitate early access.

Registration fees

The TGA operates a user pays system for evaluation of registration dossiers.

Registration of new chemical entities (NCEs) incurs an application fee[vii] of $46,100 and an evaluation fee of $185,100 (2017 figures). Once registered, prescription medicines incur an annual charge of $6,875 (biologicals) or between $3,180 and $3,920 (non-biologicals). Other fees apply for variations, generics etc.

6.2 Drug reimbursement

In order for a registered prescription drug to be widely used in Australia, it generally needs to be added to the Pharmaceutical Benefits Scheme (PBS), a universal[viii] subsidy program whereby the federal government agrees to subsidise the cost of drugs in return for a negotiated price.

In 2017, the subsidy enabled drugs to be purchased by patients for no more than $38.80[ix] per script or $6.30 for people holding concession cards such as aged or disability pensions.

In addition, for people or families with multiple health issues requiring large quantities of medications, additional subsidies are available through the Pharmaceutical Benefits Scheme Safety Net once an annual threshold is reached. When an individual's (or their direct family's) expenditure on PBS drugs exceeds $1494.90 (non-concession card holders) or $378.00 (concession card holders) in a calendar year, the PBS safety net means that all additional PBS scripts for that calendar year will be $6.30 (non-concession card holders) or free (concession card holders). All figures are for 2017 and are subject to change.

The parallel drug registration and reimbursement process

The full process to apply for drug reimbursement via the Pharmaceutical Benefits Scheme is contained in the document *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee,* available from the federal Department of Health website[13].

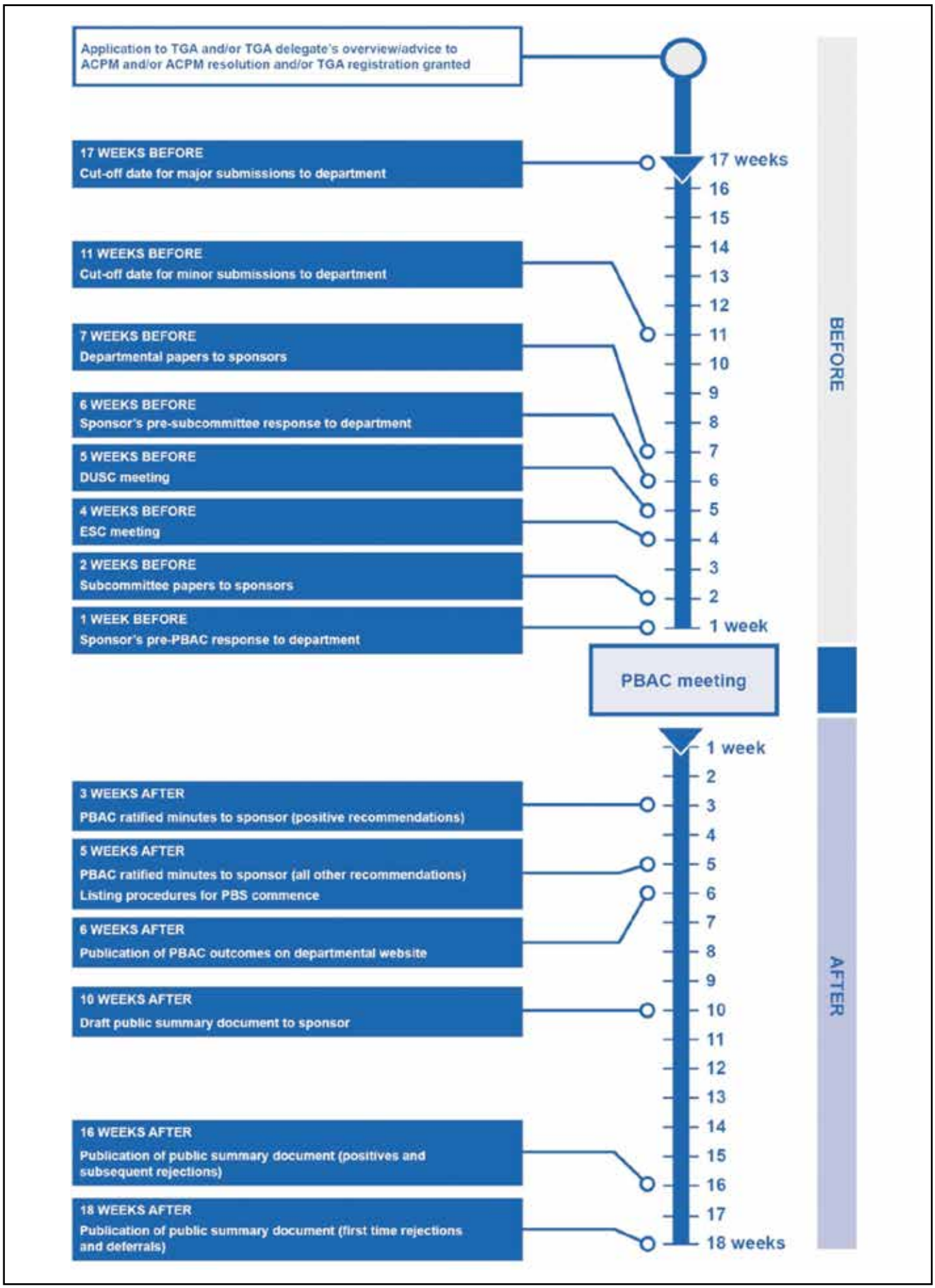
A drug can be submitted for reimbursement at the same time as it is submitted for registration, but reimbursement cannot be approved until the drug is registered. As the four-month process for approval of reimbursement is significantly shorter than registration (minimum nine months), and each process carries significant costs to the sponsor, most sponsors delay submitting reimbursement applications until there is a clear indication that the registration is likely to proceed, such as when a response is provided to the consolidated set of questions from the TGA during the 5th month of the registration process.

vii Fees at July 2017

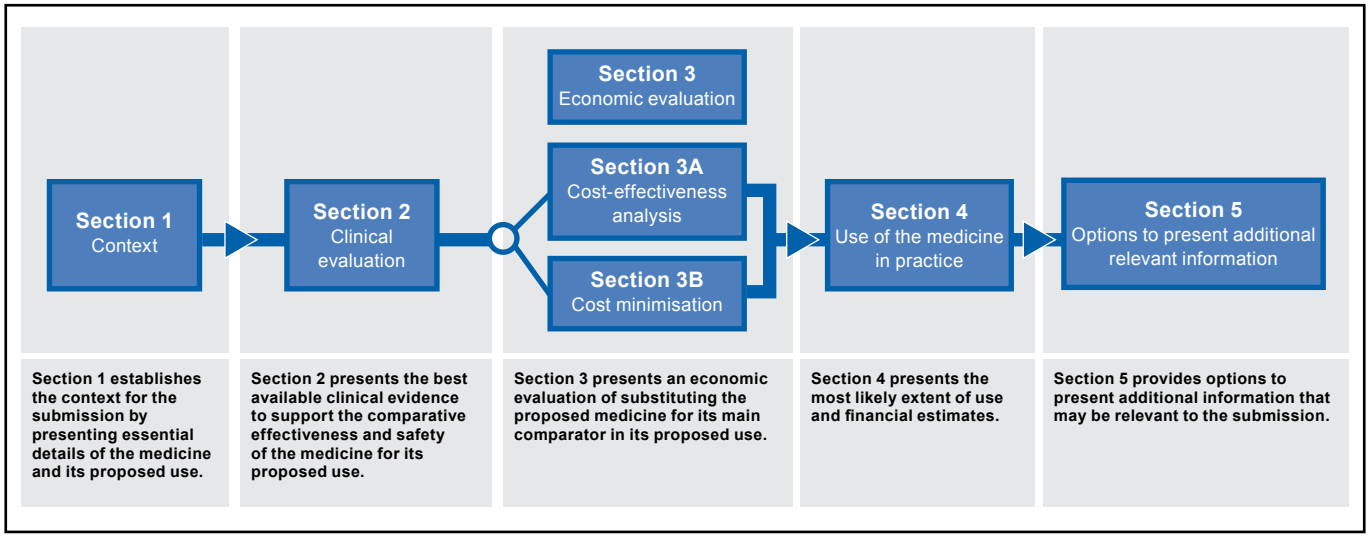
viii PBS subsidies are available to all Australian residents who hold a Medicare card. Visitors from certain countries with which Australia holds reciprocal arrangements can also access the scheme for ill health or injury that occurs while in Australia. This generally does not include pre-existing conditions such as age-related macular degeneration, although new cases should be covered for initial treatment. Countries covered include the UK, Ireland, New Zealand, Malta, Italy, Sweden, the Netherlands, Finland, Norway, Belgium and Slovenia.

ix Note that when a generic drug is available at the PBS price, a manufacturer may choose to charge above the PBS price for a branded product. The patient will also pay the difference between the PBS price and the higher price (known as a brand premium).

Australian drug reimbursement timeline



Structure for major reimbursement submission



PBAC decision making is influenced by five quantitative factors:

- Comparative health gain. Assessed in terms of both the magnitude and clinical importance of effect for both effectiveness and safety
- Comparative cost-effectiveness. Presented as incremental cost-effectiveness ratios or a cost-minimisation approach. Includes a consideration of comparative costs, including the full spectrum of health care resources.
- Patient affordability in the absence of PBS subsidy. Presented as cost per patient per course for acute or self-limited therapy, or cost per patient per year for chronic or continuing therapy
- Predicted use in practice and financial implications for the PBS. Presented as the projected annual net cost to the PBS/RPBS.
- Predicted use in practice and financial implications for the Australian government health budget. Presented as the projected annual net cost per year

Other less readily quantifiable factors that also influence PBAC decision making include:

- overall confidence in the evidence and assumptions relied on in the submission.
- equity implicit equity and ethical assumptions, such as age or socioeconomic and geographical status, may vary for different submissions and need to be re-evaluated case by case
- presence of effective therapeutic alternatives helps to determine the clinical need for the proposed medicine
- severity of the medical condition treated
- ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most. The cost-effectiveness of the proposed medicine may be greatest in patients likely to benefit the most. Claims of benefits that are greater than the average result from an intention-to-treat analysis should be supported by appropriate trial evidence
- public health issues
- any other relevant factor that may affect the suitability of the medicine for listing on the PBS.
- In addition to reviewing clinical and costing data from the drug's sponsor, the PBAC has expressed an increased willingness to obtain feedback from consumers or their representative body, either from written submissions or in-person hearings, to obtain greater understanding of issues faced by patients and of any changes in societal values that may require a shift in PBAC policy.

Drug Utilisation Sub-Committee

A key mechanism within the PBAC is the Drug Utilisation Sub-Committee (DUSC), which conducts estimates of anticipated usage and financial costs to assist with decisions regarding reimbursement for new drugs.

In addition, DUSC conducts periodic analyses of actual (real world) usage following registration and reimbursement. These analyses include input from relevant stakeholders including prescribers, professional colleges and patient organisations. DUSC provides advice to the PBAC regarding anomalies in prescribing patterns that may require attention, and issues public release documents giving the public access to reports that outline how the utilisation of PBS medicines compares to the use as recommended by the PBAC.

Medical procedure reimbursement

In addition to government subsidies for drugs, the federal government provides reimbursement through the Medicare Benefits Scheme (MBS) for a wide range of medical procedures and diagnostic tests performed by registered medical practitioners, including general practitioners, optometrists and medical specialists such as ophthalmologists.

The procedures suitable for reimbursement, the conditions imposed on reimbursement and the amount reimbursed are all determined by the Medical Services Advisory Committee (MSAC) following review of submissions from clinicians, manufacturers or other interested parties. Procedures considered appropriate for reimbursement are given an MBS item number, and a schedule fee is determined and published. While updates to the MBS list are made monthly, passage through the MSAC process is typically very slow, and may take many years.

Patients are reimbursed by Medicare 85% of the schedule fee for procedures performed out of hospital (OOH) - typically in the practitioner's rooms - or 75% if performed in a hospital setting. The difference between the schedule fee and the 85% OOH rebate is known as the "gap amount".

To ensure that people requiring regular or expensive treatments do not experience undue financial hardship, two additional safety nets apply for Medicare items. The Original Medicare Safety Net (OMSN) increases the Medicare rebate from 85% to 100% of the MBS fee once the accrued "gap amount" exceeds an annual (calendar year) threshold. In 2017, this threshold was $453.20 per patient (including any immediate family on the same Medicare card).

Importantly, medical practitioners are permitted to charge in excess of the Medicare Benefits Schedule fee. The difference between what the doctor charges and the Medicare benefit is known as the "out-of-pocket" (OOP) cost. This is different to the "gap amount" above.

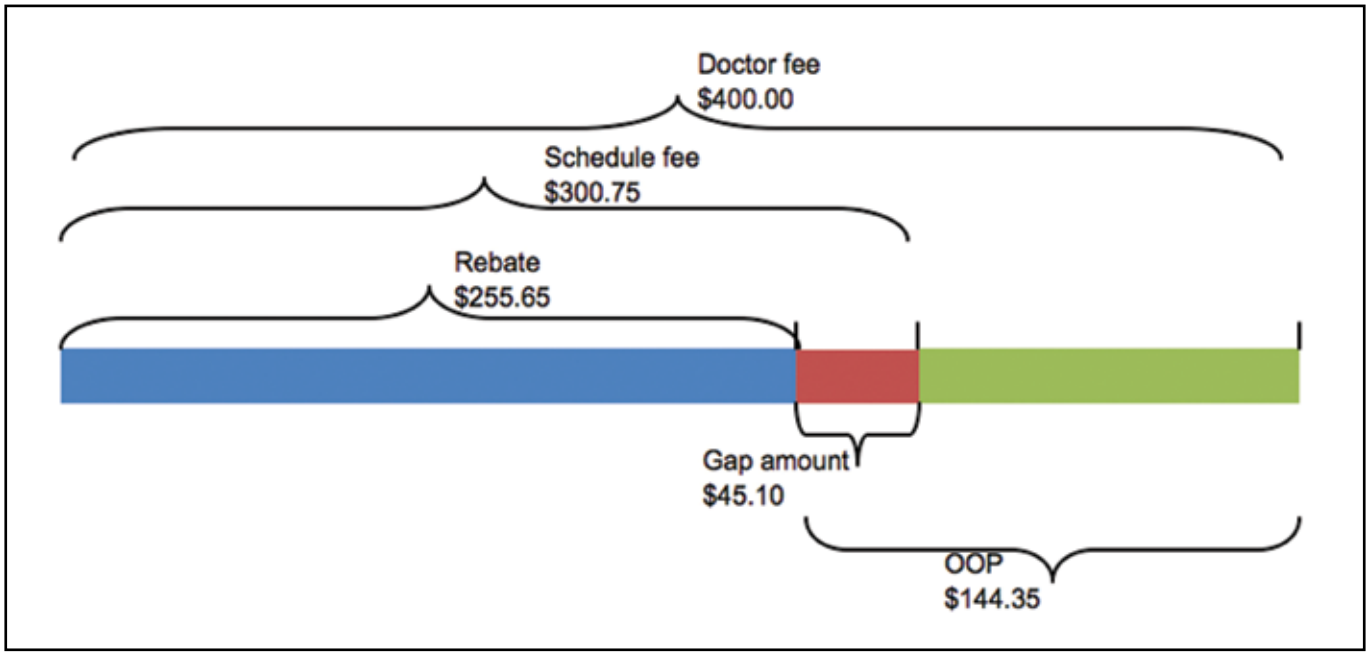
Once the total OOP cost for Medicare items performed out of hospital exceeds another threshold, the Extended Medicare Safety Net (EMSN) reimburses 80% of future out-of-pocket costs, in addition to the applicable Medicare rebate. To limit excessive fees, limits are placed on the EMSN rebates paid for some procedures. In 2017, the EMSN threshold was $656.30 for concession card holders or $2,056.30 for those without a concession card.

Example: A doctor charges $400 for item 42738 which has a schedule fee of $300.75. The Medicare rebate for this procedure is normally 85% of the schedule fee ($300.75 x 85% = $255.65, leaving a gap amount of $45.10 ($300.75- $255.65) and an OOP of $144.35 ($400-$255.65).

Once this person's (or family's) total gap amounts for all out-of-hospital Medicare procedures exceeds $453.20 in a calendar year, the Medicare rebate for this item would be increased to $300.75, leaving an OOP of $99.25 ($400.00 - $300.75)

Once this person's total OOPs for out-of-hospital Medicare items exceeds the EMSN threshold in a calendar year, the EMSN would rebate 80% of the OOP in addition to the applicable Medicare rebate.

Reimbursement definitions for a typical injection (Item 42738)



In April 2015, the federal government announced a major review of MBS items to be conducted over two to three years. The scope of the review included:

- all current MBS items and the services they describe
- increasing the value derived from services
- concerns about safety, clinically unnecessary service provision and compliance with guidelines
- evidence for services, appropriateness, best practice options, levels and frequency of support
- legislation and rules that underpin the MBS

The review is clinician led and there are ostensibly no cost-saving targets within the terms of reference. Optometry and ophthalmology we expected to be reviewed in late 2017 or 2018.

Mavis Weller

Mavis Weller, 92, first experienced difficulties with her sight when she was driving. The normally straight white lines separating the lanes appeared to be zigzagging across the road.

Mavis, who lives in South Australia, was concerned she could be a danger to herself and others and called her doctor straight way. She was told she needed an immediate appointment.

“I was very lucky,” said Mavis, reflecting on the quick action taken to save her sight. “I have wet macular degeneration in my right eye and dry in my left. Just imagine my feelings about that! I had my first injection for wet macular degeneration that very day.”

Now five years on Mavis continues with injections in her right eye. Initially these were every four weeks, then six, eight, and now every nine weeks. The sight in her left eye continues to slowly deteriorate, given that there is no treatment for dry macular degeneration.

“I’m very fortunate that there is a treatment that can save the sight in my right eye,” said Mavis. “I can’t say I enjoy the injections, but I’m getting results. I’m also thankful for my specialist; he’s incredibly gentle with the injections. The first time he treated me I wasn’t sure if he had done the injection or not,” she said.

Mavis has a wonderfully positive outlook on life and is thrilled that she can continue with her hobby of cross-stitching a passion she has had for 25 years.

“I recently had a delightful day doing my cross stitching while listening to an audio book,” said Mavis. “I admit I use easier patterns now, and tend to make lots of mistakes, but that’s just fine, I unpick and start again.”

Mavis is acutely aware of how lucky she was that there was a treatment available when she was diagnosed with wet macular

degeneration. Had it been only a handful of years earlier, she would have lost her sight.

“I tell everyone how fortunate I am. Not that I have macular degeneration, but that I got it when there was a treatment that could save my sight,” said Mavis.

“I tell everyone how fortunate I am. Not that I have macular degeneration, but I got it when there was a treatment that could save my sight.”

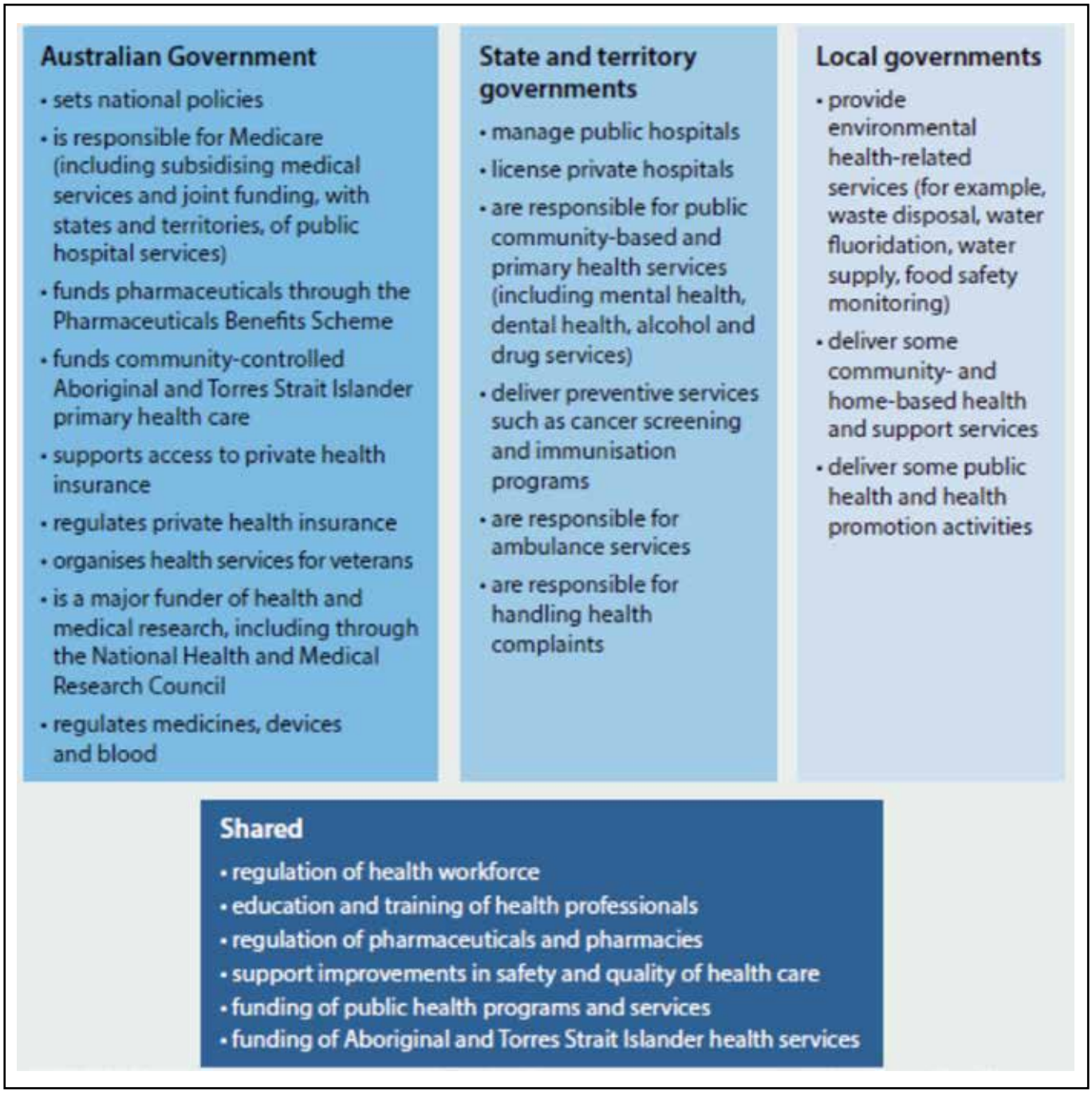
7. Australian health system

The Australian health system is highly fragmented. It is provided through a mix of public and private care with a complex split of federal, state and territory funding, regulation and responsibilities.

Australia has a population of 24.6 million[14] with an advanced economy, and a nationalised, universal health system that delivers some of the best health outcomes globally, at a cost that is below the OECD average. Some key indicators include:

- Total health expenditure in 2013-14 (the most recent compete figures available) was $155 billion, $105 billion (or 68%) of which is paid by state and federal governments.[15]
- The $105 billion of government funding comprised:
  - $63.5 billion - federal government
  - $41 billion - state governments

Main roles of government in Australian health care[15]



- The $155 billion of total funding paid for:
  - hospitals - $59 billion,
  - primary care - $55 billion (including $10.1 billion for the PBS)
  - other health goods and services (including specialists' services) $32 billion
  - capital expenditure $9.1 billion
- The non-government funding of $50 billion comprised:
  - individual payment $27.5 billion
  - private health insurance $13 billion
  - other $9.4 billion (eg workers' compensation, 3rd party insurance)
- In 2016-17, the federal budget allocated A$71.4 billion for the health portfolio, projected to increase to $79.3 billion by 2019-20. This represents 15.9% of federal expenditure in 2016-17. Total health expenditure = 9.4% of GDP (2014).[16] This has remained relatively stable in recent years, increasing from about 8.4% of GDP in the 1990s.[17]
- Physician density = 3.27 per 1,000 population (2011)
- Hospital bed density = 3.9 beds /1,000 population (2010)

7.1 Out-of-hospital care

Overall lead responsibility including policy, funding and regulation for primary care rests with the federal government.

Primary care

Primary care is generally provided by a general practitioner (GP), mostly working in private clinics. Medicare item numbers apply for GP consultations, and the majority of consultations (85%) are charged at the level of the Medicare benefit ("bulk billed"), meaning there is no out-of-pocket cost for the patient.

In figures released in December 2016, only 64.7% of patients had all their GP visits bulk-billed. This is because the bulk-billing rate is inflated by the 10% of chronically ill people who utilise 46% of Medicare services. For patients who are not bulk-billed, the Australian Medical Association recommends a fee of $78 for a standard 20 minute consultation, leaving an out-of-pocket gap of $41.[18]

Eye tests and most services by optometrists are also subsidised by Medicare. Prior to January 2015, all standard eye tests were required to be charged at the schedule fee or bulk-billed, but optometrists are now allowed to charge above this level. Due to competitive pressures, the majority of optometry visits are still bulk-billed.

Asymptomatic people aged under 65 are entitled to one Medicare-funded comprehensive eye exam every three years, or as required if symptomatic. People aged 65 or over are entitled to one Medicare-funded comprehensive eye test per year, or as required if symptomatic.

Primary Health Networks

In July 2015, the federal government established 31 Primary Health Networks (PHNs) around the country. The PHNs link with GPs, hospitals, primary health care workers and the general community to:

a) increase the efficiency and outcomes of medical services, with a particular focus on those at risk of a poor outcome

b) improve the coordination of care including improved referral pathways "to receive the right care in the right place at the right time".

The boundaries of PHNs normally align with those of the Local Hospital Networks (LHNs) or clusters of LHNs. This is to improve collaboration, reduce duplication and improve the management of people with chronic or complex conditions.

Secondary and tertiary level care

Care provided by a specialist follows a referral by a GP, or another relevant health care provider such as an optometrist for a consultation by an ophthalmologist. The majority of specialist consultations are performed in private clinics with Medicare rebates, but a much higher proportion of these visits incur out-of-pocket costs. For ophthalmology, about 17% of consultations were bulk-billed (2014 Medicare figures).

7.2 Hospital care

Public hospitals are jointly funded by federal and state/territory governments, but are essentially managed by the states/territories. This arrangement is formalised through the National Healthcare Agreement and the National Health Reform Agreement.

All Australian citizens regardless of income are entitled to receive free care in a public hospital, either as an inpatient or outpatient. Depending on the care required and the location of the hospital, this may involve varying waiting periods for elective procedures, although critical or emergency cases are required to be treated promptly. Treatment in a public hospital does not allow a choice of doctor.

Not all public hospitals provide a full range of services, with ophthalmology generally being limited to larger metropolitan hospitals, teaching hospitals and some bigger hospitals in regional centres.

Importantly, the provision of free eye injections for conditions such as AMD is generally limited to outpatient clinics in two or three large hospitals in each state capital. Some of these clinics have long waiting lists; others attempt to move people into the private sector once they have been stabilised and some are not accepting new patients. Only a very limited number of public outpatient eye injection clinics is available in rural or regional areas.

Private hospitals are licensed by the states while the federal government regulates the private health insurance industry. Patients are also able to access care in private hospitals, or registered day case clinics. Some ophthalmologists have been providing injections in private hospitals / day case clinics, enabling some privately insured people to claim costs against their private insurance, depending on the insurer and policy.

An important quality assurance mechanism applied to Australia's public and private hospitals is the National Safety and Quality Health Service Standards[19]. The most recent standards were approved by the federal government in 2011 and released in September 2012.

7.3 Private health insurance

Almost half of the Australian population has some level of private health insurance (PHI). There are two basic components to PHI – hospital cover and general treatment which is also called ancillary or extras cover. Hospital cover helps cover the cost of in-hospital treatment by the doctor(s) of your choice in a private hospital or in some cases, in a public hospital.

Extras cover typically provides partial reimbursement for treatments such as optometry, dental and physiotherapy although the scope and level of coverage varies by policy. Importantly, by law, private insurance does not provide any cover for in-rooms consultations or treatment by GPs or medical specialists, including injections for macular degeneration.

7.4 Implications and options for people with AMD

Most people with macular degeneration will receive an initial diagnosis from an optometrist as part of a normal, periodic eye test. If they are diagnosed with early or dry AMD, most people will continue to see the optometrist for monitoring. The consultation costs for this are generally covered entirely or mostly by Medicare. Some optometry practices may charge a small gap for consultations, and/or a fee for diagnostic tests such as retinal photographs and OCT scans. Any additional fees that the optometrist may charge for retinal photos or OCT scans are not covered by Medicare or private insurance.

Some people may also receive an initial AMD diagnosis when seeing an ophthalmologist for another condition such as cataracts. Ongoing monitoring could be provided by an optometrist or ophthalmologist, depending on the diagnosis.

Any person with a possible diagnosis of wet AMD should be referred immediately to an ophthalmologist for additional diagnostic tests, confirmation of diagnosis, and where indicated, treatment with anti-VEGF eye injections. In most cases, patients are seen in the ophthalmologist's private rooms. Costs for consultations, most diagnostics tests and treatment will be partially subsidised by Medicare. The majority of people will experience out-of-pocket costs for care

as only about 18% of services from private ophthalmologists are bulk-billed. Out-of-pocket costs incurred from in-rooms care cannot be claimed back from private insurance.

Some people may receive a diagnosis and potentially treatment from outpatient eye clinics at a limited number of public hospitals. In this case, consultations, diagnostic tests and treatment are provided at no cost, apart from a co-contribution for PBS listed drugs in some states. It should be noted, however, that these clinics are very limited in number, and are rarely available outside of the state capitals.

They often have a lengthy waiting lists and some will try to move patients to the private system after initial diagnosis and treatment to reduce the burden on the public system.

Some ophthalmologists in private practice choose to administer eye injections to selected people with wet AMD in a theatre setting at a private hospital or day case centre.

In a private hospital theatre setting, privately insured patients receiving treatment for wet AMD are able to claim the gap between the schedule fee and the Medicare benefit. For some policies, full coverage may be possible when the ophthalmologist charges above the schedule fee. Any payment gaps for treatment in a private hospital do not contribute towards the Medicare Safety Net.

Federal legislation prevents private insurers from covering in-rooms treatment. This legislation arguably inhibits innovation and increases costs as it discourages the development and use of safer and lower cost techniques and technologies that enable procedures to be performed only in specialists' rooms that have previously only been performed in a hospital or day case setting to be performed in specialists' rooms. A change to the Private Health Insurance Act to allow people with private insurance to claim for certain procedures performed in doctors' rooms would mean that the patient could be treated for minimal or no out-of-pocket costs and the health fund would have a lower cost procedure to reimburse.

7.5 Issues with health care in Australia[20]

- ageing population
- increasing patient contribution to overall health costs
- rising rates or chronic disease, including obesity and diabetes
- complexity of funding and regulatory arrangements, leading to poor system integration
- Indigenous health indicators
- provision of care in rural and remote locations
- split in responsibilities between community health and primary health
- poor uptake of electronic health records
- cost of treatment
- funding arrangements between federal and state/territory governments
- maldistribution of the health care workforce
- lack of data on the quality and outcomes of care

7.6 Health care homes

In an effort to improve the coordination of health care services for people with multiple chronic or complex conditions, the federal government is trialling a system of primary care, called Health Care Homes, which started on 1 October, 2017.

People with chronic or complex conditions can enrol as Health Care Home patients and expect to receive flexible, coordinated care, usually overseen by a GP, with a shared care plan which will set health goals, include strategies to help patients better manage their conditions and identify the most appropriate local providers to treat the patient's specific needs. The Health Care Home will follow up specialist care, hospital treatment and other services required to manage the person's health. Rather than receiving a payment for each service as applies now, Health Care Homes will receive a monthly payment to manage the person's situation.

8. The role of the pharmaceutical industry

The success of the introduction of anti-VEGF treatment for wet AMD has been due in no small part to the investment and commitment of several international pharmaceutical companies.

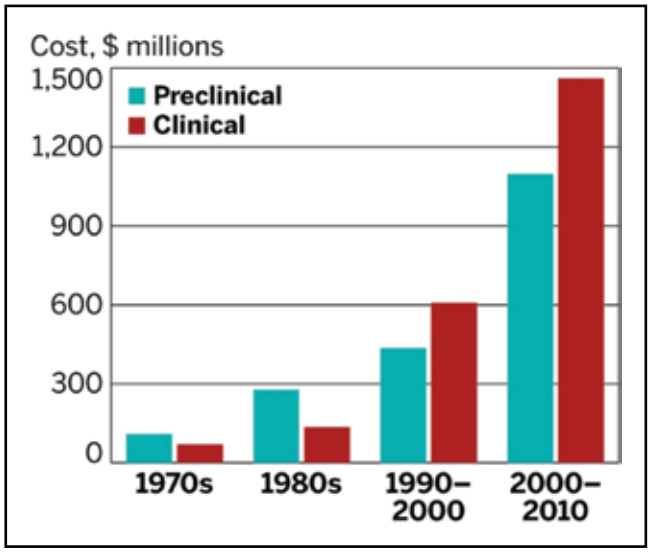
Research and drug development

This is a high risk industry with intense competition, massive development costs and the need to recover those costs quickly due to the short period of remaining patent protection after the long lead times, typically about 12 years, to bring a product to market.

The Tufts Center for the Study of Drug Development estimated that, the cost of developing a drug that gains market approval was almost US$2.6 billion in 2014, comprising US $1.1 billion in pre-clinical and almost US $1.5 billion in clinical costs[21]. This includes the cost of unsuccessful projects. It is estimated that only one in 5,000 drug candidates makes it all the way from drug discovery to registration.

The cost of drug development is also rising more quickly than inflation due to the increased complexity of clinical trials needed to meet higher regulatory standards and public expectations, a greater focus on chronic and degenerative diseases, which usually require longer studies to demonstrate a benefit, and additional studies needed to demonstrate cost-effectiveness for insurers and government payers.

Cost of drug development



The cost of developing a new drug has skyrocketed since the 1970s.
Source: Tufts Center for the Study of Drug Development.

Without the incentive of healthy profits in the longer term, it is doubtful whether investors would allow company boards and management to invest an average of 18% of sales on research and development, arguably the highest of any industry outside the semiconductor industry.[22]

Support of patient health organisations

Pharmaceutical companies have become a partner with the Foundation over many years, along with government and other major supporters, enabling the Foundation to provide a range of services to meet its mission. Independence, transparency and accountability are the three necessary drivers of this successful partnership.

One of the activities supported by industry, and conducted by Macular Disease Foundation Australia over many years, has been a national TV and radio awareness campaign, raising awareness of macular degeneration and urging everyone over 50 to have an eye test and macula check.

The campaign encourages people with early AMD to be diagnosed by their optometrist, which can facilitate early adoption of diet and lifestyle changes. If people are diagnosed with wet AMD and require treatment, high awareness levels increase the likelihood of early initiation of treatment, with better outcomes as explained in Section 14. The referral to the ophthalmologist and the choice of treatment or drug is between the doctor and the patient.

Finally, survey data from optometrists provides strong evidence that by encouraging regular eye testing, the Foundation's awareness campaigns have resulted in the diagnosis of a range of other eye conditions that would otherwise be undiagnosed.

Sponsorship of RANZCO clinical meetings

Industry provides very significant untied funding for major clinical meetings such as the national and state RANZCO scientific congresses and optometry meetings. This funding enables subsidised attendance by Fellows in training as well as reimbursement for travel costs of key local and international guest speakers. Importantly, industry does not have any influence on the speakers chosen or the topics presented. Industry may also sponsor additional satellite sessions with their chosen speakers.

Phase IV adverse drug event monitoring

A vital function of industry is the active collection and reporting to the TGA of adverse events that occur following the introduction of any registered drug. It is only through such reporting that the occurrence of serious complications that were too rare to be detected or quantified in clinical trials can be determined.

Patient support programs

There are several key drivers for improved visual outcomes for people with AMD in general, and wet AMD in particular. These include:

- early detection of disease with prompt referral when required
- timely initiation of anti-VEGF injections for wet AMD
- patient adherence to treatment; this relates to the extent to which patients follow the instructions given by the ophthalmologist, such as frequency of injections
- patient persistence with treatment; the length of time that the patient continues to receive treatment.

In most cases, treatment for wet AMD is required for an extended period – at least for many years and possibly for life. However, several studies[201,202,203] have shown high rates of treatment discontinuation following about 12 months of injections. There are many reasons for this, including the inconvenience, discomfort and cost of ongoing therapy, a perception that a lack of vision improvement means the treatment isn't working or, conversely, that improvement represents a cure. However, even if the disease has remained inactive for a month, more than 90% of people will experience a recurrence of the disease with resultant loss of vision[204].

This highlights the importance of patient and carer education to maximise adherence and persistence with treatment.

The two suppliers of registered anti-VEGF treatments, Novartis and Bayer, have sponsored innovative patient programs that provide educational and emotional support during the critical first 12 to 24 months of treatment when the risk of premature discontinuation is highest. These programs aim to give patients realistic expectations regarding treatment outcomes compared to the natural history of untreated disease. This is not only essential for people who have not experienced any improvement in vision, but also for those whose vision returns to near normal and who mistakenly believe they have been cured. In addition, patients and their carers/family members are given a basic understanding of the disease process, and other measures that can be taken to reduce the risk of disease progression in the other eye.

Having realistic expectations and gaining a greater understanding of the disease process are also likely to improve and reduce their decision making and reduce their anxiety. Analysis of Bayer's SmartSight patient support program demonstrated 93% persistence with treatment at 12 months compared to only 74% in people not receiving the program. (Data on file – Bayer)

These programs also encourage connection to Macular Disease Foundation Australia where patients and their families/carers can receive ongoing non-clinical education and support throughout the course of their condition.

James Boon

James Boon was a senior sergeant on Sydney's northern beaches and spent more than 25 of his 30-year career involved in traffic enforcement and supervision. Now retired, James can still enjoy his 1969 Triumph motorcycle thanks to treatment for wet macular degeneration. Not bad for a man who could well have been blind.

James was having yearly eye tests when in late 2010 his optometrist diagnosed wet macular degeneration in his left eye. A year later the disease was detected in his right eye as well.

Without immediate treatment, James would have lost much of his sight. Fortunately, his vision stabilised due to treatment that involves an injection into the eye. His sight has even shown some improvement.

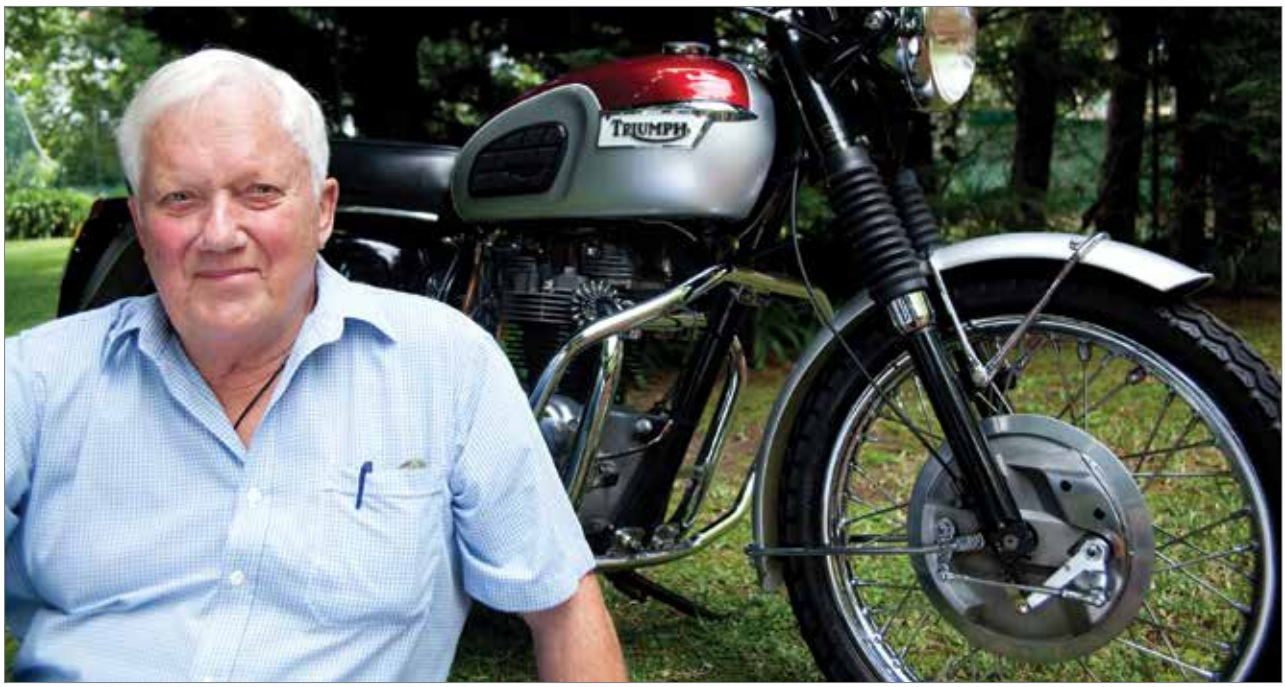
"I am still retaining my sight. I am fine with reading and I still drive and ride my vintage motorcycle when my bad back allows. That's not bad for someone in their 80s!" said James.

"Once you reach 75 in New South Wales you must have regular tests to re-apply for your driver's license. Thanks to the treatment, I keep passing with flying colours."

What is little known by many is that up to 70% of cases of macular degeneration have a genetic link and that people with a direct family history of macular degeneration have a 50 per cent chance of getting the disease.

James' family is well aware that macular degeneration is hereditary. "One of my brothers, who is four years younger than me, has the dry form of macular degeneration. I have two more brothers who are very aware of the genetic link of macular degeneration and the importance of having their eyes checked. We talk about it. I also talk about it with my son who is in his 40s."

"I am still retaining my sight. I am fine with reading and I still drive and ride my vintage motorcycle when my bad back allows. That's not bad for someone in their 80s!"



PART B - THE DISEASE

9. Disease description and classification

Age-related macular degeneration (AMD) is a serious, progressive, chronic disease affecting the central portion (macula) of the retina at the back of the eye. The macula provides the acute, fine, detailed vision that is required to read, drive and see faces clearly. The macula also provides most of our colour vision.

AMD is classified as:

- early stage typically with little or no impact on vision
- late stage, which is vision impairing
- the late stage is further divided into two main forms being 'dry' (atrophic) AMD, or 'wet' (neovascular) AMD[x].

Early stage AMD

It is estimated that just over a million Australians had early stage AMD in 2017[23].

Early stage AMD is characterised by the formation of pale yellow to white coloured lesions beneath the retina known as drusen. Drusen comprise lipid (fat) and protein and are believed to be accumulations of metabolic oxidative waste products from the retinal pigment epithelium (RPE), a layer of cells immediately behind the photoreceptor cells[xi]. RPE cells provide the photoreceptor cells with nutrients and are critical for the removal of metabolic waste products from the eye.

Drusen less than 63µm in diameter, which are known as drupelets[24], are seen in almost all people over the age of 45[25], and should be considered as normal changes of ageing; this is not macular degeneration. The presence of drupelets with no pigmentary changes and no drusen in the retina confers a very low risk of advanced macular degeneration developing (0.4% in five years)[24].

It is only when drusen increase to 63 µm or larger in diameter, with or without pigmentary changes, and are located within two disc diameters of the fovea, should a diagnosis of early AMD be made.

In people with early AMD, it appears that the ability of RPE cells to remove metabolic waste products is impaired, leading to the build-up of drusen. The removal of waste products is also impaired by a lack of certain dietary antioxidants. As the disease develops, drusen become more numerous and grow. They may also coalesce to form much larger drusen. Risk factors for progression to late stage disease include larger size of drusen (especially when larger than 125 µm), increased numbers of drusen and drusen with soft, indistinct edges ('soft' drusen).

As drusen grow, they may start to have an impact on the health of the RPE layer, leading to changes in the distribution and loss of pigment. As the RPE is pivotal to the delivery of nutrients and removal of metabolic waste products from the photoreceptors, the progressive loss of RPE function gradually impacts the health of photoreceptors.

Another type of lesion, known as reticular pseudodrusen (RPD), has also been associated with AMD, and is considered a high risk sign for late stage disease.[26] Reticular pseudodrusen present as small yellow or white lesions in a reticular (net-like) pattern, mostly in the superior (upper) macula. Recent developments in imaging technologies combining near-infrared reflectance using a confocal scanning laser ophthalmoscope and spectral domain optical coherence tomography (OCT) have much greater sensitivity in detecting RPD.[27]

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x It should be noted that dry and wet AMD are not related to dry eye syndrome or to the watery eyes experienced by most people at some stage.

xi Photoreceptor cells are the so-called 'rods' and 'cones' that convert light into electrical signals which are then conveyed to the brain for processing as images.

Late stage AMD

Late stage disease affects about 15% of Australians with AMD[23] (or about 214,000 people in 2017). About one third of those with late stage disease have the dry (atrophic) form, while two thirds have the wet (neovascular) form.

In the dry form, drusen continue to grow, with an increasing impact on the health of the RPE cell layer and ultimately leading to the death or atrophy of this layer. This in turn leads to the gradual death of the photoreceptors, resulting in loss of central vision.

The end stage of dry AMD is known as **geographic atrophy**, as the atrophied area commonly has the appearance of a well delineated island. Geographic atrophy typically takes many years or decades to develop.

It should be noted that many people incorrectly refer to early stage disease as dry AMD. The correct classification of the disease uses 'dry AMD' to refer to the vision impairing late stage without neovascularisation.

In about 10% of people with the early stage and some people with late stage dry AMD, the disease can take a sudden turn with the production of new, unwanted blood vessels from the choroid underneath the retina breaking through Bruch's membrane into the neural retina. This is termed **neovascular, exudative or "wet AMD"**.

The growth of these new blood vessels is in response to the production of a protein known as vascular endothelial growth factor (VEGF).

In the wet form, these unwanted blood vessels tend to have very weak walls and can leak blood or fluid under or into the retina, leading to a marked swelling of the retina, misalignment of the photoreceptors and a sudden drop in vision. The drop in vision can be extremely rapid; some people will have normal vision one day and wake the next day with marked distortion (metamorphopsia), blurring or dark or empty patches (scotoma) in the central visual field. If these leaking blood vessels are not treated quickly, further degeneration and fibrous scarring of the macula will occur and vision loss may be permanent. The scar tissue will frequently have a circular shape and be known as a **disciform scar**.

A meta-analysis of high quality studies on the natural history of wet AMD found that if untreated, 21.3% of people would have severe vision loss, defined as a loss of more than siz lines on the eye chart, within six months of diagnosis, increasing to 41.9% at three years.[28] Vision-related quality of life has also been shown to decline significantly with the progression from early to late AMD.[29]

It should be noted that even though the dry form can "turn to wet", the underlying atrophic process causing the dry form continues. Hence, even if a person with wet AMD is being treated successfully, loss in vision may still result due to atrophy, although this is normally a slow process.

Causes and risk factors for AMD

Understanding the cause of AMD is complicated by multiple pathways involving many age-related alterations to the retinal pigment epithelium (RPE), photoreceptors, Bruch's membrane, the choriocapillaris layer of the choroid, lipid and carbohydrate metabolism, oxidative stress, impairment of lysosomal degradation, accumulation of retinal toxins, local inflammation, complement system dysfunction and hyperexpression of VEGF.[30]

Research into the causes of AMD and the subsequent development of treatments is especially challenging due to:

a) the typically long time course for the development of the disease

b) the lack of a good animal model of the disease. While some models can mimic certain aspects of the pathological features of AMD, none has been able to recreate all of its characteristics. The animals typically used for disease modelling such as rats, mice and rabbits do not possess a macula. While simian primates possess a macula and fovea, large scale research in these animals is prohibitively expensive and ethically problematic.

It is not clear if AMD is a localised disease, occurring only in the eye tissue, a systemic disease, or if aspects of the disease are a combination of both.[31] While the precise cause of AMD if not fully known, it can best be considered a multi-factoral disease, with a number of environmental and genetic risk factors influencing its development and progression.

Smoking and anti-VEGF treatment

Not only do smokers have a higher risk of developing wet AMD, but when requiring treatment, the outcomes are likely to be inferior compared to those of non-smokers. A Korean study of 420 patients requiring intravitreal treatment for wet AMD showed that smokers were seven times more likely to have poor visual acuity improvements after intravitreal injections compared to non-smokers.[40] Poor improvement was defined as less than the median change in visual acuity from the baseline.

In the five year follow up to the CATT study, a large randomised trial comparing Lucentis with Avastin in people with wet AMD, those who continued to smoke after starting treatment were twice as likely to be legally blind after five years compared to non-smokers receiving treatment for the same period. Importantly, people who stopped smoking when starting injections had a much lower risk of becoming legally blind after five years, with a rate approaching that of non-smokers.[41] That is, it is never too late to give up smoking.

Risk factors

Age

This is the strongest risk factor for AMD.[23]

Overall, approximately one in seven people over the age of 50, or 1.25 million people in 2017, has some evidence of age-related macular degeneration.[23]

The risk of disease increases significantly from about age 50, although significant vision loss is unusual in people under 65. The prevalence of early AMD increases from approximately 6% in people aged 50 to 59 to about 23% in people aged 70 or older. Late stage disease (both neovascular and geographic atrophy) increases from less than 1% in people aged 60 to 69 to 8% or more in people aged 70+ and to 16% for those 80 years or older.[23]

Family history

There is very strong evidence that a direct family history significantly increases an individual's risk of developing AMD to 50 %. More than 50 gene variations have been shown to influence risk of AMD but it is not caused by a specific genetic abnormality. More details on the genetics of AMD are in Section 10.

Smoking

At this time, smoking is the only proven modifiable risk factor for the development of AMD. Smoking has consistently been shown to be the most significant preventable risk factor for the development of AMD and its progression.[32] A dose response has also been demonstrated with higher risk in people with increased pack years of smoking.[33,34,35]

Smokers are three to four times more likely to develop macular degeneration in the first place[36] and will, on average, develop it five to 10 years earlier than non-smokers.[33,34,37] Smokers are also more likely to develop late stage disease[33,36] including wet AMD.

People who have lived with a smoker for five years ("passive smokers") have double the risk of developing AMD[35]. Several studies have shown that past smokers have a significantly higher risk of developing AMD than non-smokers,[38,39] however, the level of risk may decline with increasing duration of smoking cessation. In one large study, people who had given up for 20 years had a comparable risk to non-smokers[35].

Other considerations

Race

Significant variation in the incidence and prevalence of AMD has been shown between ethnic groups, with much higher rates reported in Caucasians compared to people of African heritage.[42] Although several studies have suggested a lower prevalence of disease in Asians, a meta-analysis demonstrated rates of disease that are largely similar to those of Caucasians.[43] Age-related macular degeneration is an uncommon cause of vision loss in Australian Aborigines and Torres Strait Islanders.[44]

Diet and lifestyle

There is increasing evidence that lifestyle choices including suboptimal diet, alcohol consumption and being overweight may play a role in disease development.

Research investigating the link between diet and the risk of macular degeneration can pose many challenges, such as difficulties in conducting *post hoc* dietary surveys, the long time typically required for studies due to slow disease progression, maintaining compliance in prospective dietary intervention studies, and controlling for a multitude of confounders. For example, people who consume a healthy diet are more likely to be a healthy weight, be non-smokers, drink in moderation, and exercise regularly. Each of these factors may have an influence on disease risk, making it difficult to measure the influence of a single factor. It is therefore not surprising that some of the research in this field has been either contradictory or inconclusive.

Nonetheless, a large number of high quality, population based, longitudinal and cross-sectional studies show that diet can play a significant role in the development of disease and that certain dietary interventions may help to slow disease progression.

Fish and omega-3 fatty acids.
In the five-year follow-up of the Australian Blue Mountains Eye Study, people who reported eating fish at least once per week had a 40% lower risk of developing early AMD compared to people who consumed less than one serving per month. Those who reported eating fish at least three times a week had a 75% reduced risk of developing late AMD[37].

Many other studies have reported reduced risk, especially when fish has had a high omega-3 content such as salmon, mackerel and sardines.[38,39] Fish are rich in docosahexanoic acid (DHA) and eicosapentanoic acid (EPA), which are long-chain omega-3 fatty acids found in significant quantities in the healthy retina. They are believed to be involved in photoreceptor membrane physiology and reducing inflammation.

Several studies have shown that the benefits of fish intake are reduced in people who also have a high intake of the omega-6 fatty acid, linoleic acid,[50,51] which is found in safflower, sunflower, corn and soybean oils, as well as many dressings and mayonnaises. Omega-6 fatty acids are thought to be pro-inflammatory.

In AREDS2,[68] the consumption of DHA (350 mg) and EPA (650 mg) in a supplement did not demonstrate any benefit in reducing risk. The AREDS2 population was, however, stated to be well nourished, and may have already had adequate omega-3 in their normal diet, negating any beneficial effect of a supplement.

It is recommended that people should eat two to three servings a week of oily fish, such as salmon, mackerel, sardines or trout.

Nuts and other fats
Numerous studies have attempted to assess the effect of other classes of fat on the risk of developing AMD, but the results are often conflicting. This may be related to the difficulty in defining fat types in food questionnaires and the variability of the source of fats.

However, certain recommendations can be made in relation to eye health. In general, and consistent with recommendations for other diseases, the overall intake of fats should be limited.[52] Olive oil has been found to be protective[53,56] and may also improve the absorption of lutein. A handful or two of nuts per week has also been found to be protective in multiple studies[54,57]

Dark green, leafy vegetables
Leafy greens such as spinach, silver beet (Swiss chard) and kale contain especially high levels of the carotenoids lutein and zeaxanthin, which are dark green and yellow pigments, respectively.

There is good evidence that lutein and zeaxanthin, which are found in significant quantities in the healthy retina, but are reduced in people with AMD, play an important role as "internal sunglasses," protecting the retina from the harmful effects of free radicals released by visible light, especially within the high energy blue range. Lutein and zeaxanthin have significant antioxidant and anti-inflammatory properties. Smaller quantities of lutein are also found in dark green vegetables such as broccoli, peas, beans, brussels sprouts as well as eggs, while zeaxanthin is also found in yellow and orange coloured fruits and vegetables including corn, yellow capsicum and oranges.

In the original AREDS[67], a high dietary intake of lutein and zeaxanthin was associated with significantly reduced risk of large or extensive drusen (27% reduced risk), geographic atrophy (35%) or neovascularisation (55%).

In the Blue Mountains Eye Study, people in the top third of dietary intake of lutein and zeaxanthin had a 65% reduced risk of developing neovascularisation and 34% lower risk of soft or reticular (high risk) drusen.[56] Many other studies have shown similar beneficial findings, albeit with differing rates of risk reduction.

In the primary analysis of all people in AREDS2[68], there was no apparent reduction in the overall risk of progression to late stage AMD in people taking a supplement containing lutein 10 mg and zeaxanthin 2 mg. However, in a subset of people with the lowest 20% of dietary lutein intake, a 26% risk reduction was noted. In addition, a post hoc subgroup analysis of people taking the original AREDS formulation *without* beta-carotene (widely used in Australia for many years) plus lutein/zeaxanthin, demonstrated an 18% risk reduction compared to people taking the original AREDS formulation *with* beta-carotene, but no lutein/zeaxanthin. The serum levels of lutein were significantly lower in people who also received beta-carotene, confirming the previously reported competitive absorption between the carotenoids.[57] Hence, the addition of lutein/zeaxanthin may play a role in reducing the risk of progression when beta-carotene is removed from the formulation, as is now generally recommended.

Low glycemic index carbohydrates

Glycemic index (GI) relates to the relative degree of blood glucose elevation two hours after eating a particular carbohydrate compared to the consumption of glucose, and is therefore a measure of the rate of digestion and absorption of that food. High GI carbohydrates produce higher and more rapid peaks in blood glucose compared to low GI carbohydrates. Diets with a high average GI have previously been associated with an increased risk of coronary heart disease, stroke and diabetes.

Several studies now indicate that people with a higher than average dietary glycemic index also have a higher risk of developing early and late AMD.[58,59]

For example, in the 10 year follow-up of Australia's Blue Mountains Eye Study[58], people in the highest 25% of dietary GI were 1.77 times more likely to develop early AMD compared to the people in the lowest 25%. In addition, there was no association between total carbohydrate consumption and the risk of AMD, indicating that it is the quality of the carbohydrates, rather than the quantity, that confers increased risk.

Low glycemic index carbohydrates include wholegrain bread and cereals, most fruit and non-starchy vegetables and most dairy products. In general, the more processed a food, the higher the glycemic index.

Dietary patterns

Most dietary studies have focussed on specific dietary components or nutrients, but as we typically eat many different foods together, it can be very difficult to determine the effect of one food in isolation. Therefore, as certain food types are commonly eaten together, depending on the cultural, geographic or economic circumstances of the individual, several recent studies have looked at various dietary patterns or food groups. Several studies[52,60,61] have shown that a Mediterranean style diet, which is high in fish, fruit and vegetables, nuts, grains and olive oil, is associated with a reduced risk of developing AMD or of it progressing to late-stage disease.

Furthermore, diets high in red meat, especially processed meats, have been associated with a higher risk of developing AMD, although chicken may be protective.[54,62]

Alcohol
Alcohol is known to cause oxidative stress and damage to many organs in the body. Evidence regarding its role as a risk factor for macular degeneration, however, is inconsistent. A detailed review and meta-analysis indicated that long-term consumption of more than 30 g of alcohol per day (three standard drinks) increased the risk of early AMD by 47 – 67% in Western populations, although the risk for late AMD was inconclusive, due to the small number of cases with late stage disease.[63]

Australian research from the Melbourne Collaborative Cohort Study, which examined associations between moderate alcohol intake and AMD prevalence in 20,963 participants, found that drinking more than 20 g of alcohol per day (two standard drinks) increased the risk of early AMD by 21% (p=0.004) compared to those who drank no alcohol, after adjusting for age, sex, smoking and other established risk factors.[64] The risk for late AMD was increased by 44% although this did not reach statistical significance. Consumption of less than 20 g of alcohol per day was not associated with increased risk, nor was there any suggestion of protection (reduced risk) with low alcohol intake, as has been reported for cardiovascular disease.

Diet/gene interaction
There is also good evidence that people with genetic risk factors can, to a significant degree, eat away their increased risk by consuming the right foods. For example, in the Rotterdam Eye Study[65], for people carrying the high risk CFH and/or ARMS2 genetic variants and consumed high amounts of zinc, omega-3 fatty acids or lutein, the rates of AMD were close to those of people with no identified genetic risk factors.

AREDS supplements

Since many dietary factors have been shown to influence risk, several attempts have been made to develop vitamin/mineral supplements to provide additional protection.

To date, the only supplements for which there is good, level one evidence of benefit in slowing the progression of existing macular degeneration from large, long-term randomised controlled trials are those formulated to the AREDS[xii] or AREDS2 formulations.[68]

It should be noted that there is no evidence from randomised controlled trials that people who do not have macular degeneration, or even those with very early signs, should be taking supplements to prevent macular degeneration developing later in life.

AREDS[67] and AREDS2[68] were large, complex, randomised controlled trials conducted in the USA, with funding from the National Institutes of Health, to assess whether high dose supplementary vitamins and anti-oxidants could prevent or reduce the progression of AMD.

The initial AREDS trial involved more than 3,600 people from trial sites around the USA, who were photographically assessed for AMD and then randomised to receive various combinations of daily high doses of anti-oxidant (zinc 80 mg plus copper 2 mg, vitamin C 500 mg, vitamin E 400 IU, beta-carotene[xiii] 15 mg) or a placebo, over an average of five years.

AREDS showed that in people with intermediate stage AMD in one or both eyes or late stage disease in one eye only, a combination including all of the ingredients resulted in a 25% reduction in the risk of progression to advanced disease compared to placebo. The groups receiving zinc alone and antioxidants alone (vitamin C, vitamin E, beta-carotene) also reduced risk of developing advanced disease by 21% and 17% respectively. The risk of developing moderate visual acuity loss was also reduced by approximately 27% in the group receiving zinc plus antioxidants.

During the AREDS trial, two other studies were published showing that high doses of supplementary beta-carotene increased the risk of lung cancer in smokers.[69,70] Two studies have also shown that beta-carotene on its own has little if any beneficial impact on the development of AMD.[70,71] This is not surprising as beta-carotene is not found in the eye. Beta-carotene also inhibits the absorption of the more valuable lutein and zeaxanthin.

xii AREDS – Age-Related Eye Disease Study

xiii Beta-carotene is one of a number of carotenoids, but is not found in the eye. Two other carotenoids, lutein and zeaxanthin, are found in healthy eyes, but tend to be in lower quantities in eyes with macular degeneration. At the time of the initial AREDS, lutein and zeaxanthin were not available as dietary supplements, and beta-carotene was used instead

As a result, most of the AREDS-type supplements sold in Australia since the release of the initial AREDS trial have had beta-carotene removed. This decision was vindicated by the results of AREDS2.

AREDS2 was a follow-up study in more than 4,200 people that was designed to evaluate the effect of adding lutein 10 mg/zeaxanthin 2 mg and/or omega-3 long chain fatty acids (DHA 350 mg + EPA 650 mg) to the original AREDS supplement. The study also evaluated the effect of removing beta-carotene and of reducing the zinc dose from 80 mg to 25 mg per day. The median follow-up was five years. The original AREDS formulation was used as the control; no placebo was used as it would have been unethical to do so. It should be noted that AREDS2 was conducted in a population that was "well nourished", making it more difficult to demonstrate a beneficial effect of supplementation.

In the primary analysis of AREDS2, there was no apparent beneficial effect from the addition of lutein/zeaxanthin and/or omega-3s to the original formulation. However, subgroup analyses revealed some important findings that have translated into clinical practice. When lutein/zeaxanthin was added to the original formulation (including beta-carotene), people in the lowest quintile of dietary lutein intake (ie through normal food) had a 26% reduction (p=0.01) in risk of disease progression compared to people receiving the original formulation only.

More importantly, however, in people who had beta-carotene removed from the original formulation, which has been the generally accepted practice in Australia, there was an overall 10% benefit from the use of lutein/zeaxanthin supplementation, regardless of dietary intake. It was also confirmed that supplementary beta-carotene inhibited the absorption of lutein/zeaxanthin, possibly explaining the lack of effect for lutein/zeaxanthin in the overall primary analysis for all participants, and the beneficial effect in the subgroup analysis when beta-carotene was removed.

The sub-group analyses did not find any beneficial effect of supplementary omega-3s. This result was somewhat surprising as many other smaller studies had suggested a beneficial effect of long-chain omega-3s, and there is also highly consistent evidence that regular consumption of fish is protective. Several possible explanations have been proposed for the lack of effect of supplementary omega-3s in AREDS2. These include:

- participants were well nourished and likely already had sufficient dietary intake of omega-3s
- the dose of omega-3s in AREDS (1000 mg) might have been inadequate to show a benefit
- the ratio of DHA to EPA might have been inappropriate.

The AREDS2 protocol did not allow the use of beta-carotene in current smokers, but it showed that beta-carotene supplementation also increased the risk of lung cancer in former smokers.

Analysis of the reduction of the zinc dose showed a point estimate of a 6% greater effect with the original higher dose, but this did not reach statistical significance. Unfortunately, the study was inadequately powered[xiv] to determine a true difference between the zinc doses. There was no difference in the reported safety of the two zinc doses.

Although the results were inconclusive for zinc dose, when Dr Emily Chew[xv] first presented the AREDS2 data at the ARVO congress in 2013[72], she stated the NEI recommendation was to continue using the higher (80 mg) zinc dose. This was because the high zinc dose was proved and the 10 year follow-up study of the original formulation not only showed good safety, but an impressive and statistically significant 17% reduction in all-cause mortality in people receiving high dose zinc compared to no zinc.[73]

Other supplements

While there have been many claims made for other supplements including saffron, bilberry and astaxanthin, based on animal studies or small uncontrolled trials, there is still no good evidence of a reduction in disease progression from any of

xiv Inadequately powered means it did not included sufficient patients to demonstrate a true difference.

xv The primary investigator for the AREDS and AREDS2 trials.

Jill Falls

Prior to a diagnosis of macular degeneration in 2009 Jill Falls, now 86, knew all too well the impact of macular degeneration and how important early detection could be in saving sight. Four of her siblings were already living with the disease.

Now retired, Jill says, “I was at work when I had the first indication my sight was playing up. I was 78 at the time and I noticed the lines I was reading were ‘wonky’. As my siblings already had macular degeneration, I knew the symptoms and that I had to have my eyes checked immediately.”

Jill made an appointment with her eye specialist and was diagnosed with the wet form of macular degeneration. “When I was first diagnosed the experience was quite shattering. It was an awful feeling. With a sister blind from dry macular degeneration, and another three with the disease, it was horrible to hear I had it too,” said Jill.

Fortunately, thanks to Jill’s quick action, she started treatment immediately, which saved her sight. “I sought help as soon as I noticed changes and this has allowed me to remain independent and continue doing all the things I love. This includes my hobby of painting, which brings me so much joy. I’ve been painting for over 25 years.”

“It’s incredible that I still have my sight. I’ve now had almost 100 injections. I will never ever miss an injection, or delay it. It’s just far too important.”

Although Jill’s sight has been saved thanks to injections, she is acutely aware that for her siblings with dry macular degeneration the outcome isn’t as good. “I’m just so thankful for the treatment that has saved my sight, but it really saddens me that there isn’t a treatment for my siblings,” said Jill.

“When I was first diagnosed the experience was quite shattering. It was an awful feeling. With a sister blind from dry macular degeneration, and another three with the disease, it was horrible to hear I had it too. I will never ever miss an injection, or delay it. It’s just far too important.”

10. Genetics of AMD

There is very strong evidence that a direct family history significantly increases an individual's risk of developing AMD.

Unlike some related eye conditions such as Stargardt's disease and Best's macular dystrophy, which are directly linked to one or two specific gene defects, the risk of age-related macular degeneration is influenced by a large number of genetic variants, each with a relatively modest effect on the risk of disease.

A direct family history (parent, sibling) confers an estimated 50% risk of developing the disease[74] compared to an overall 12% risk in the general population. Genetic factors explain between 46% and 71% of the variation in the severity of disease, but estimating one's individual risk remains challenging. There are at least 52 gene variants on 34 gene 'locus regions' or locations that can influence disease risk or severity.[75]

Genetic studies have revealed very strong associations between AMD and several gene variants associated with the complement pathway - part of the innate immune system. Complement-pathway associated variants include CFH, CFHR1, CFHR3, CFB, C2 and C3, and may be involved in up to 50% of cases of AMD.[76]

Several genes not directly associated with the complement pathway have also been consistently shown to increase risk. In particular, a variations of the ARMS2 gene have been demonstrated to have an increased risk of similar magnitude to the CFH gene. The precise role of this gene is still not clear, but it appears to play a role in the formation of a protein located in the choroid beneath the retina. It has recently been suggested that ARMS2 protein deficiency may play a role in the formation of drusen.[77]

To date, the majority of evidence indicates that genetic risk is shared by geographic atrophy and neovascularisation, although recent research suggests that at least one variant (MMP9) appears to be specific to neovascularisation[75].

If substantiated, the fact that nearly all disease-associated gene variants appear to influence risk for both neovascularisation and geographic atrophy has major therapeutic implications. As people at high risk of neovascularisation also appear to be at high risk of geographic atrophy, any treatments that address only neovascularisation (as is now the case for all available treatments) may only provide only temporary relief to patients. Such people will likely ultimately progress to geographic atrophy even if neovascularisation is effectively controlled.

At this time, there is no convincing evidence that the delivery of existing treatments should be modified based on one's genetics, although this remains an active area of research. Some studies have suggested that the efficacy of the AREDS[xvi] vitamin/mineral supplements (see Section 9) may vary depending on one's genetics[78,79]. However, other research could not confirm these findings.[80,81] The American Academy of Ophthalmology does not recommend the use of routine genetic testing to drive decisions on the use of supplements.

Early (phase II) results with at least one investigational treatment (lampalizumab for geographic atrophy) suggested that it may have meaningful efficacy in certain genetic sub-groups,[82] although subsequent phase III findings are disappointing[83] (See Section 18). If this, or other similar treatments ultimately progress to registration, then future treatment decisions and potentially reimbursement may be influenced by genomics. This is an important conversation that has already been initiated in the health arena.

Evidence from twins studies also indicates that behavioural and nutritional factors associated with epigenetic[xvii] mechanisms may be involved in the causation of age- related macular degeneration, in addition to genetic susceptibility.[84]

A key message from the genetics of AMD is that people with AMD should give information to their first degree relatives about their increased risk. They should also be advised on the importance of regular eye tests, good eye health nutrition and avoidance of smoking.[85]

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xvi AREDS – Age Related Eye Disease Study

xvii Epigenetics involves potentially heritable changes in gene activity and expression that do not involve a change in the underlying DNA sequence. Epigenetic changes can be influenced by environmental influences, such as diet, lifestyle, age, and disease state.

11. The continuum of care

Age-related macular degeneration is a chronic disease and it is useful to consider that as the disease progresses, patients should move through a continuum of care. This means that regardless of where the person is in the disease process, there is always something that can be done to help the person's situation, and ideally prevent or slow the progression to the next level. A person should never be told "there's nothing that can be done". This continuum moves through management of risk factors and disease prevention, early detection, treatment and rehabilitation.

11.1 Risk reduction

As detailed in Section 9, the most significant modifiable risk factor for the development of AMD is smoking, with smokers being at three to four times greater risk of developing the disease, and of developing it an average of five to 10 years earlier than non-smokers. Smokers are also more likely to develop the more aggressive wet form, and treatment does not work as well in smokers. Quitting smoking is of major benefit.

A number of other simple interventions have been shown to reduce risk including:

- dietary modifications (detailed in Section 9)
- the use of an AREDS type supplement in certain people (Section 9)
- maintaining a healthy weight and regular exercise has been shown to reduce risk in several studies

11.2 Early detection

Eye tests
Regular eye tests including a macula check by an optometrist or ophthalmologist can help to detect the disease before it becomes symptomatic. People with early stage disease may require more regular eye testing, and should certainly take greater steps to improve their diet, reduce weight and stop smoking. When the disease has progressed to the intermediate stage, the use of an AREDS formulation supplement may be considered.

Amsler grid
RANZCO recommends that people with early AMD should be reviewed by an optometrist at least every 12 months[86], but it is essential for people to understand that the disease can rapidly progress to the wet form, and they therefore need to be aware of the relevant symptoms. Regular self-monitoring at home using an Amsler grid, one eye at a time, while wearing normal reading

Age-related macular degeneration is a chronic disease.

AMD requires the status of a national health priority given its significance and need for health promotion and prevention actions as outlined in the federal government's *National Framework for Chronic Conditions,* released in June 2017. This states that health promotion and prevention activities can:

- lessen predisposing factors for chronic conditions through improved environmental and social conditions, and reduce the development of behavioural and biomedical risk factors (primordial prevention)
- prevent the occurrence, or delay the onset, of chronic conditions (primary prevention)
- minimise or prevent disease progression in people with chronic conditions (secondary prevention)
- reduce the risk of developing additional chronic conditions, complications and/or associated disabilities (tertiary prevention)
- support improved quality of life
- reduce demand on the health care system

glasses, can help to detect sudden changes in central vision that may indicate progression from early or dry disease to the wet form, which would indicate the need for immediate treatment.

The Amsler grid can also be useful for people receiving treatment for wet AMD when the gap between treatments is being increased, as it can help to detect a drop in vision that may occur if the gap between treatments is too long.

Although the Amsler grid has reasonable sensitivity to detect new distortion, compliance with its correct use and the reliability to detect increasing distortion have been questioned.[87] The grid can nonetheless be a useful tool if used regularly, with appropriate training including clear instructions of what to do in the event of any abnormalities being seen.

Without regular eye tests and/or self-testing, many people remain undiagnosed until their second eye is affected. This is because the brain is able to compensate for poor vision in one eye - essentially only accepting information from the better eye. Only when the second eye is affected does the person notice a drop in their vision. This may mean that in some people, damage in the first eye is already beyond repair, making preservation of the second eye even more critical.

11.3 Treatment for wet AMD

People with wet macular degeneration will typically require ongoing injections of an anti-VEGF drug to control leakage or bleeding and preserve vision. The best outcomes occur when people start injections as soon as there is evidence of leakage when vision is still good. In contrast to cataracts, where a delay in treatment will typically have minimal to no impact on the ultimate outcome, a delay of even four weeks in the initiation of injections for wet AMD can result in significant, permanent vision loss.[88]

Most people will require injections on an ongoing basis, at a frequency determined by the treating clinician using both visual outcomes and measurement of retinal structure using optical coherence tomography (OCT) scans. More detailed information on treatment with injections is in Sections 12 and 14.

11.4 Rehabilitation

Some people with AMD may still progress to serious vision loss including those people:

- with the end stage of the currently untreatable dry form known as geographic atrophy
- with the wet form of disease who might have missed treatment, started treatment too late, or stopped prematurely, leading to the formation of permanent fibrotic scarring (disciform scar)
- who are responding well to treatment for wet AMD but still experiencing gradual loss of vision due to the atrophic (dry) form of the disease
- who may not respond adequately to injections (between 5$ and10%) and will experience a significant loss in vision

People with significant vision loss can be helped to maximise their use of remaining vision to maintain mobility, personal safety and involvement in social activities, employment, volunteering, sports and hobbies. This may involve a variety of rehabilitative interventions, training and the use of a wide range of aids and technologies designed to help people maintain independence and quality of life.

It has been estimated that low vision affects a conservative estimate of at least 100,000 Australians.[89] This includes those defined as having vision worse than 6/12 in both eyes, which cannot be improved with spectacles or cataract surgery. An individual with vision loss not only experiences a loss of sight, but is susceptible to negative functional, social, economic and psychological consequences.

There is clear evidence that low vision interventions, including suitably timed low vision assessments and the provision of low vision aids, equipment and assistive technologies appropriate to an individual's specific needs, can enhance visual performance and assist in maintaining independence and quality of life.

One of the key factors for successful outcomes in low vision rehabilitation is early intervention, ideally as soon as possible after a person's vision falls below 6/12 in both eyes, as this is the level at which quality of life starts to be affected and morbidity and mortality increases.[90,91] Moreover, it is generally easier to learn new technologies

and skills while there is still some functional vision remaining. Unfortunately, the provision of low vision services in Australia is variable and fragmented, often with poorly defined referral pathways, meaning that many people are not referred to low vision services until their vision is very poor, if they are referred at all.

An Australian aged under 65 with legal blindness can now access supports and services through the new National Disabilities Insurance Scheme (NDIS), as an entitlement, for life. However, people who become blind after the age of 65 are excluded from the NDIS and are expected to obtain their supports and services through the aged care system, which is neither funded nor structured to provide comparable low vision services.

As most people who lose vision from age-related macular degeneration will do so after the age of 65, it is imperative that appropriate steps are taken to address this inequity to ensure that older people have affordable access to the supports they need. This includes the establishment of a nationally funded program to provide subsidised low vision aids and technologies for people over the age of 65 who do not qualify for the NDIS, as well as people aged under 65 who may not have sufficiently poor vision to qualify for NDIS entitlements.

A comprehensive report on the status of low vision services in Australia, including recommendations for improvements, is available from the Macular Disease Foundation Australia website at: www.mdfoundation.com.au/sites/default/files/MDFA_LowVision_Aids_WEB_25%201%202017.pdf

Low vision services

The majority of low vision services in Australia are provided by the not-for-profit sector, although some optometrists in private practice also provide some support. Unfortunately, it is reported that in Australia only about 20% of people with significant vision loss, who could benefit from the use of rehabilitative services, actually use them.[90]

There are many barriers for the uptake of these services, including:

- assuming or being told that nothing can be done to improve sight or one's management of reduced vision
- accepting poor vision as an inevitable consequence of ageing
- a lack of awareness of services offered among those with visual impairment and referring professional
- difficulty in accepting vision loss and specialised services;
- poor understanding of the potential benefits of rehabilitation or the extent to which it may help
- misconceptions that rehabilitation services are only for those with severe vision loss
- confusion with the referral process
- problems using transport to access rehabilitation services
- cognitive impairment
- cost of new technologies
- lack of a consistent or equitable national system to provide affordable access to aids and technologies
- cultural, language and ethnicity barriers;
- complications of co-morbidities.

12. Treatment of AMD

12.1 Early and dry AMD

At this time, there are no drugs or surgical interventions available to either stop the development or slow the progression of early or dry AMD, although several potential treatments are in the late stages of clinical testing.

As discussed in Section 9, there is good evidence that certain lifestyle and dietary changes can reduce the risk of developing AMD and/or slow its progression. These include:

- smoking cessation
- exercise and weight control
- regular consumption of oily fish, leafy green vegetables, other fruits and vegetables, nuts, low glycemic index carbohydrates in preference to high GI.

For people with intermediate stage AMD in at least one eye or late stage AMD in one eye only, there is also good evidence that the use of certain vitamin and mineral supplements (namely the AREDS or AREDS2 formulations) can help to reduce the risk of progression to late stage disease by approximately 25% (see Section 9).

Several investigational treatments for early and/or dry AMD are in late stage (phase III) clinical testing and could potentially become available within the next few years (see Section 18).

12.2 Wet AMD

In the past 10 years, several highly effective treatments have been introduced that have revolutionised the management of people with the most serious form of AMD - 'wet' or neovascular AMD. For the first time, it is now possible to save sight in a significant proportion of people with wet AMD using intravitreal[xviii] injections of drugs that inhibit the effect of a protein known as vascular endothelial growth factor (VEGF). These so-called anti-VEGF treatments, which are considered one of the most significant medical developments in the history of ophthalmology, are discussed in detail in Section 14.

12.3 Treatments with no evidence or poor evidence

A large number of alternative therapies have been touted to treat macular degeneration, often with the use of compelling personal testimonials to justify high costs, but little, if any, proper evidence. Some of the treatments that are claimed to be of benefit, but should be avoided until there is evidence from properly conducted randomised controlled trials, include the following:

- hyperbaric oxygen therapy
- microcurrent stimulation
- ayurvedic therapy
- acupuncture
- eye exercises
- undifferentiated stem cells
- homeopathy

12.4 Prognosis of AMD

For the majority of people with early AMD, the disease will have little or no impact on vision for the duration of their life.

On average, about 4% of people with early AMD progress to late stage disease each year. Many studies have identified several factors that increase the risk of developing early stage disease and the likelihood with which it progresses to late stage. These include age, genetic factors and ethnicity and smoking. In addition, there is a growing body of evidence that certain dietary factors can play an important role in decreasing risk. These are discussed in Section 9.

For those people who do progress to late stage disease, the prognosis depends upon:

a) the form of the disease

i. **Dry AMD/geographic atrophy** is now untreatable, although the loss of vision typically takes many years to become

xviii Injections directly into the eye.

significant. Once established, however, vision loss can be significant, including potentially legal blindness[xix], and is permanent. It should be stressed that providing the person does not also have some other eye condition, geographic atrophy will not lead to total blindness as some degree of peripheral vision remains. While peripheral vision typically does not provide the fine, detailed vision needed for reading, driving and recognising faces, it will generally allow adequate vision for moving around the house and community, albeit with some difficulties.

ii. **Wet/neovascular AMD**, while usually much more aggressive than dry AMD, can now be treated very successfully in most people using intravitreal injections of anti-VEGF drugs. Many people have now been treated for up to 10 years, and still maintain good functional vision. Although the neovascular component of the disease can be successfully treated, vision may still gradually deteriorate in some people due to the underlying dry or atrophic disease that is not currently treatable.

b) when treatment is initiated

If intravitreal injections are indicated for wet AMD, the best outcomes are achieved when treatment is initiated as soon as possible after the new blood vessels form and start leaking, while vision is still good.

Early treatment will result in the majority of patients maintaining good, functional vision.

If treatment is delayed until vision has already deteriorated, vision may improve slightly following injections but it will typically remain poor. In some cases, a delay of as little as two to four weeks in initiating treatment can have a significant effect on outcomes[88]. This is quite different to the treatment of cataracts where a delay in surgery will typically have little or no impact on the overall outcome.

Although the frequency of injections can typically be reduced over time, most people need to continue injections indefinitely to maintain vision. As stated above, people with wet AMD also have the underlying dry AMD disease process continue in the background, which can gradually lead to a reduction in vision even though injections are effectively controlling the neovascular process. Regardless, the vast majority of people receiving injections for wet AMD will experience substantially better vision over an extended period compared to people who are not treated.

xix In this context, legal blindness refers to vision of worse than 6/60 in the better eye. A person with legal blindness is no longer able to read the top line of a standard eye chart

Denis Sutton

It is unusual to see a wave the size of a mountain on the horizon, but that's exactly what Denis Sutton, now a retired fisherman on the north coast of New South Wales, saw back in 2014 as he was preparing for another day of mullet fishing. Even more unusual was that the wave shifted on the horizon every time Denis moved.

In fact what Denis was seeing were changes taking place at the back of his right eye, changes that were threatening his sight, and these symptoms had been with him for a few days.

"A couple of nights before, when I was logging into my computer, I'd noticed the lines on the screen curved up at one end. I thought maybe it was a blood vessel that had burst or something and it would go away … it came on so quickly; to be honest I was a bit frightened," said Denis.

"The next day my wife Joy was at me to see someone about it, but me being me, I thought it would right itself."

Fortunately, Denis saw an advertisement in the local paper for Macular Disease Foundation Australia and decided to call.

After Denis described his symptoms, the first thing he was told was "you're not going fishing today; you've got to see an optometrist immediately". Denis wasn't keen to follow this instruction as he didn't want to let the fishing crew down. In the end though, an appointment was made.

"Once I'd been seen by my optometrist in Macksville, the same thing happened. I was told, 'you've got to get to Coffs Harbour (50km away) for treatment today'. I wasn't given a choice," said Denis.

Denis now admits it was just as well he followed orders. "I had my first treatment for wet macular degeneration in Coffs Harbour that afternoon. A few months later, and once I'd had a couple of treatments, my ophthalmologist told me I was very lucky. I'd have been blind in that eye if I hadn't seen him when I did."

Instead, with regular treatment, Denis still has great vision and this has allowed him to enjoy his retirement to the full.

"Once I'd had a couple of treatments, my ophthalmologist told me I was very lucky. I'd have been blind in that eye if I hadn't seen him when I did."

13. Impact of AMD

Age-related macular degeneration can have a significant impact on the person with the disease, as well the person's family, carer, the broader community and nationally. The impact can be emotional, financial, social or vocational and result in a significant reduction in independence and quality of life. The emotional consequences can include pain and suffering from depression, confusion, anxiety and fear, especially fear of the unknown.

Loss of vision affects the ability to read, see faces and colours clearly, drive, cook, engage in hobbies and sport, maintain employment or volunteering, to navigate with safety and confidence in the home and community, and any other activity that may require detailed, acute vision. Many people lose the confidence to leave the house, thereby losing social interaction and friendships. It is not surprising that people with vision loss have three times the risk of depression of their normally sighted peers.

13.1 Emotional impact during early stages

Macular degeneration can also have a significant emotional impact on people in the early stages of disease before any vision loss has occurred, possibly due to fear of the unknown. This can be exacerbated by inadequate information provided to the person following a diagnosis, or possibly because many people do not adequately comprehend further information after hearing the disease.

13.2 Financial impact

The cost of the registered drugs for treatment of wet AMD is subsidised by the Pharmaceutical Benefits Scheme (PBS) and treatments costs are subsidised by Medicare. (more details in Section 6.2).

Despite the PBS and Medicare subsidies, people with AMD can incur significant out-of-pocket costs associated with the diagnosis, management and treatment of their disease, especially if they are receiving injections. This depends on numerous factors. People living in rural or remote communities have the burden of extra transport costs and, in many cases, the cost of overnight accommodation for themselves and their carer. Most people requiring treatment are elderly and are pensioners or self-funded retirees on limited fixed incomes.

In a 2015 survey of 1308 Foundation clients across Australia regarding the costs of treatment, the average charge for an injection (Medicare item 42738) for people receiving private treatment was $453, ranging from $383 in Victoria to $549 in Queensland. The highest fee reported was more than $800. As the Medicare Schedule fee for this item was $300.75 with a rebate of $255.65, patients had an average out-of-pocket cost of $197 per injection until the Extended Medicare Safety Net threshold was reached. In addition, patients may have had additional out-of-pocket costs for consultations, and diagnostic tests. The average fee charged for ongoing OCT scans was approximately

Vision loss is associated with[1]:

- risk of falls is doubled
- risk of hip fracture increased by four to eight times
- risk of depression tripled
- admission to nursing homes three years earlier
- twice as likely to use health services
- reduced employment and volunteering
- higher risk of all-cause mortality

$60 per scan, which is not reimbursed by Medicare[xx]. Even after the Extended Medicare Safety Net threshold is reached, each calendar year, many patients had out-of-pocket costs exceeding $100 per injection, which may double if treatment is needed in both eyes.

As treatment is required on an ongoing basis, it is not surprising that the OOP costs can be a barrier to treatment. Indeed, 13.5% of the patients in the Foundations 2015 survey had considered stopping treatment due to costs. In Queensland, where the average cost of treatment was highest, almost 20% of people stated that they had considered stopping treatment due to cost.

AMD has a massive financial cost to society. A 2011 report[23] by Deloitte Access Economics estimated that the total societal cost of the disease in 2010 exceeded $5 billion per year. This comprised $360 million in health system costs, $390 million in other financial costs such as productivity losses, carer opportunity costs, and other indirect costs, plus $4.4 billion in loss of wellbeing.

The report also calculated that every dollar spent on anti-VEGF treatment saved at least $2 in societal costs. This ratio will be even better in 2017 as the per-patient cost of treatment has fallen significantly since 2010.

13.3 Impact on carers

While several studies have investigated the psychosocial impacts of macular degeneration in those patients, relatively little was known about the impact on carers of people with the disease. As the health and wellbeing of the person with AMD can be significantly affected by the wellbeing of their carer, in early 2013 Macular Disease Foundation Australia undertook a comprehensive survey of 500 people with advanced AMD and 500 carers in early 2013.[93,94]

This cross-sectional, self-completed survey demonstrated a high degree of distress in people caring for someone with advanced AMD. More than one in two caregivers reported a negative state of mind, with only 23% saying their caring role had no impact on them mentally or emotionally. However, 11% of carers self-reported depression, a significantly higher rate than in their peers of equivalent age. Two thirds of carers also had a significant health condition themselves, and 55% stated their role as a carer had negatively impacted other people, mostly other family members. Not surprisingly, the greater the level of vision loss of the patient, the greater the impact on the carer.

13.4 Mortality

The medical significance of vision loss is sometimes downplayed with the statement “but it doesn’t kill you”. In fact, people with major vision loss (from any cause) are at significantly higher risk of all-cause mortality compared to their normally sighted peers[95,96], a finding that has also been shown for people with late stage macular degeneration.[97] The higher mortality risk may have many causes including:

- difficulty seeing medication labels leading to dosing errors
- increased falls and hip fracture - a leading cause of mortality in the elderly
- reduced mobility and exercise impacting cardiovascular health
- increased rates of depression leading to higher suicide rates
- increased rates of trauma.

Just as vision loss has been shown to increase all-cause mortality, restoration of vision has been shown to reduce mortality, at least for cataract surgery.[98] After adjusting for factors that were associated with mortality, older people in the Blue Mountains Eye Study who had vision impairment that was corrected by cataract surgery had a 40% lower mortality risk over 15 years compared to people who remained vision impaired due to cataract. Data on mortality risk after restoration of vision with macular degeneration treatment are not available, although it is reasonable to assume a similar favourable effect.

xx Since December 2016, one OCT per year is reimbursed for the initial diagnosis of wet AMD (and some other neovascular conditions) to demonstrate eligibility for PBS treatment. Reimbursement is not allowed for ongoing OCTs to monitor the response to treatment.

Jackie Baxter

Jackie Baxter is in her mid-50s and has lived with wet macular degeneration in both eyes for four and half years. An artist from Western Australia, she said receiving the diagnosis was a life-changing moment.

“I was diagnosed with dry macular degeneration some years ago and when one eye developed wet macular degeneration, my specialist told me to expect the other eye to turn within six months. He was right. I now have injections in both eyes every eight weeks,” said Jackie.

Although injections are helping Jackie’s wet macular degeneration, she is still experiencing slow reduction in vision. This may be because there is still some underlying dry macular degeneration which can’t be treated.

“My sight is still deteriorating slowly, even with the injections. I’m starting to use my peripheral vision as things aren’t as clear as they used to be.”

Although still able to drive, Jackie has restricted her driving and says, “I don’t drive at night and, if I do drive now, I keep it very close to home on streets I’m familiar with.”

“Not being able to drive any distance has been hard to deal with. I live in the hills outside Perth and used to love to take myself and my paints off to the coast for the day.”

A self-taught artist, Jackie has been passionate about drawing and painting in all mediums since she was a young child. For many years she taught others to paint, exhibited and sold her works.

“My favourite mediums for painting have always been watercolours, oils and pastels but more recently I have started to paint with acrylics. Because of my vision loss I’ve also changed my style. Its freer now, fine detail is now limited.

“I’m also finding that colours are bleaching out. Jacaranda flowers are losing the vibrant purple colour I know they have, and my paints

in their tubes are dark and hard to define. It is only when I spread the paint across the canvas that the true colours appear to me.”

Jackie acknowledges that she has struggled with periods of depression and has sought professional help to come to terms with her changing vision.

“It’s a bit like grief ... grief for my sight. I realised I needed support on this journey and have been working with a counsellor. I also have wonderful family support. It’s not all doom and gloom. I’ve discovered things within myself I didn’t know and I’m now looking at new and inventive ways to do things.”

Jackie Baxter is in her mid-50s and lives with macular degeneration. An artist from Western Australia, she said receiving the diagnosis was a life-changing moment.

14. History of treatment for AMD

Age-related macular degeneration has been described in the medical literature for more than 100 years, often with other terminology such as senile macular degeneration. For almost all of this time, the condition has been untreatable. In the 1990s, some treatments were demonstrated to slow the disease to a small extent, but these were all still inadequate. It was only in the mid 2000s that truly effective treatments became available.

14.1 Laser photocoagulation

The treatment of neovascular ("wet") age-related macular degeneration originally focused on the physical closure or destruction of the leaking blood vessels. Following the publication of the Macular Photocoagulation Study Group randomised clinical trial in 1991[99], laser photocoagulation became the mainstay of treatment through the 1990s. This involved intense thermal damage to the new blood vessels in the choroid resulting in retinal death in the treated area. This immediately produced small blind spots in the visual field, which were hopefully smaller than the typically large area of scarring that eventually resulted from untreated wet AMD – "you give up a little to save a bit more".

Unfortunately, 85-90% of people with wet AMD were not eligible for this treatment, as it could not be used when the new vessels were inside the central macula (fovea) because the laser burn would result in immediate central blindness. By the time most people present with symptomatic wet AMD, the leaking vessels usually involve the central fovea, making this treatment inappropriate.

Even in cases where the fovea was initially not affected, and laser could be used, the laser scar frequently expanded to involve the central area, and recurrence of new vessel formation more centrally was common. At best, laser photocoagulation inevitably caused a degree of vision loss in order to slow down further, more significant loss.

Laser for eyes with drusen

Several studies have investigated whether the use of low intensity laser given in a grid pattern across the macula in people with early stage disease (drusen), would reduce the risk of the disease progressing to the neovascular form. Two of the studies[100,101] showed that grid laser *increased* the likelihood of progression to wet AMD. A third study[102] reported no change in the growth of new vessels but a four letter improvement in visual acuity after three years of follow-up.

The 2RT laser, which uses 12 spots of an ultra-low energy 532 nm nanosecond laser applied evenly across the macula at a safe distance from the fovea in people with early stage disease, is being investigated. Further details on 2RT laser are in Section 18.

14.2 Surgical management

Several surgical approaches have also been investigated.

One method involved a vitrectomy, which is the surgical removal of the vitreous gel from the middle of the eye, with evacuation of the sub-retinal blood vessels. The National Eye Institute in the USA sponsored a large, prospective, randomised controlled trial (the Submacular Surgery Trial or SST), which demonstrated that surgery did not provide any improvement or stabilisation of vision. As the surgery also incurred a significant risk of a retinal detachment, the technique is essentially no longer used.[104,105]

Other methods involved the surgical separation and repositioning of the macula to an adjacent area with healthier retinal pigment epithelium cells. This required either formation of a partial[106] or full[107] retinal detachment. Although some small pilot studies have demonstrated a minor improvement for a small proportion of people, the surgery is technically very challenging with significant risk of complications. The introduction of safer, highly effective intravitreal drug therapies has essentially made surgical intervention obsolete.

14.3 Photodynamic therapy

Photodynamic therapy (PDT) with verteporfin (Visudyne®- Novartis) was registered in Australia in August 2000 and made available via Medicare in August 2002. It was transferred to the PBS in August 2007 when ranibizumab (Lucentis®- Novartis) was also introduced onto the PBS.

Photodynamic therapy involves the intravenous administration of Visudyne, a light activated

compound. The drug passes through the blood system, including the retinal vasculature.

Fifteen minutes after injection, when some of the drug will be within the retinal blood vessels, a low-energy, non-thermal laser is applied. The laser activates the drug, which generates singlet oxygen that damages the interior walls (endothelium) of the new vessels, resulting in thrombosis, and stopping the damaging leakage.

The pivotal study assessing the efficacy of Visudyne (the TAP study) showed that an average of 3.5 treatments given at three-monthly intervals slowed the progression of disease in a proportion of patients. While more effective than any previous treatment, most people still lost vision.

At one year, only 16% of treated patients with predominantly classic[xxi] lesions gained one or more lines of vision and 15% lost more than six lines. Further analysis of TAP and other studies showed that PDT was even less effective on other lesion types such as occult lesions.

Although PDT enjoyed moderate success in the early 2000s, its role was effectively usurped by anti-VEGF treatment from the mid 2000s. PDT with Visudyne is still occasionally used in selected patients, especially those with a form of macular degeneration known as polypoidal choroidal vasculopathy (PCV). This form is often difficult to treat with anti-VEGF injections alone. PCV is most commonly seen in people of east Asian descent.

14.4 Transpupillary thermotherapy (TTT)

A further variation of laser treatment was tried in the early 2000s in which low energy 810 nm diode laser was applied slowly to the area of CNV for one minute. Some initial pilot trials suggested some potential, however, a larger prospective randomised trial could not show any benefit of treatment compared to PDT.[108]

14.5 Radiation therapy

Low dose radiation therapy was also investigated in a number of small trials in the mid 2000s, producing conflicting results. Definitive randomised trials for standalone radiation treatment have never been completed. Given the potential for delayed and potentially blinding radiation retinopathy, and the introduction of anti-VEGF treatment, the use of radiation as standalone treatment did not gain widespread favour.

In recent years, there have been a number of attempts to use highly targeted radiation therapy as adjunctive treatment to help reduce the number of anti-VEGF injections.

Epimacular brachytherapy (NeoVista) involved the use of a vitrectomy[xxii] and the delivery of highly targeted low-dose radiation over the macula through an endoscopic probe placed inside the eye. In a large phase 3 randomised trial in the UK (CABERNET)[109] in people with wet AMD already receiving intravitreal anti-VEGF injections, the treatment was found to produce worse vision than injections alone, increase the number of injections needed and carry a small but important risk of delayed radiation retinopathy.

Another treatment using stereotactic radiotherapy with a device known as IRay (Oraya Therapeutics) utilised three low-energy x-ray beams which overlapped on the macula, delivered from outside the eye, avoiding the need for a vitrectomy. The technology incorporates three dimensional eye tracking so that excessive eye movement shuts off the beams, ensuring the xrays are applied only to the central macula area.

In a randomised controlled trial in 230 people with wet AMD already receiving intravitreal anti-VEGF treatment, there was a comparison of the safety and efficacy of two different doses of IRay plus anti-VEGF injections as needed versus sham IRay plus anti-VEGF injections as needed.

There was no clinically significant difference in visual outcomes between the groups. The researchers highlighted that the groups receiving IRay required approximately one third fewer anti-VEGF injections than the control (sham IRay) group, however this translated to only about one injection per year over two years.[110]

xxi These are lesions where the choroidal neovascularisation occupies at least 50% of the lesion

xxii Surgical removal of vitreous gel from the middle of the eye

This treatment is now approved in the European Union and is occasionally used in some countries such as the UK, Germany, Switzerland and Greece. However, the manufacturer (Oraya) is no longer in operation. Zeiss is now supporting the existing treatment centres[111], although it is understood there are no plans to expand its use.

14.6 Intravitreal triamcinolone

Several corticosteroids had been shown to inhibit neovascularisation in animal models. Steroids also have anti-inflammatory and anti-oedematous properties. In 1995, Gillies and colleagues reported a small uncontrolled trial of off-label intravitreal triamcinolone for treating wet AMD.[112] After a single injection, the treatment was reasonably well tolerated in the short term and appeared to result in slower disease progression compared to natural history. In the 18 month follow-up[113], 30% of eyes experienced a visual acuity loss of six or more lines. Only four eyes received two or more injections, but three of these experienced progression of cataract or intraocular pressure rises, requiring either cataract surgery or glaucoma filtering surgery.

In 2000, Danis et al[114] published the six-month results of a small randomised controlled trial involving 27 patients with wet AMD, 16 of whom received a single 4 mg in 0.1 mL intravitreal triamcinolone acetonide injection. While the treated group experienced short-term stability in visual acuity, the proportion demonstrating worsening angiographic signs with continued growth of neovascular membranes increased between three and six months, suggesting a short-term effect only. Quite predictably, intraocular pressure increases were seen in 25%, and progression of cataract was more frequent.

Over the next few years other researchers investigated whether the addition of intravitreal triamcinolone to photodynamic therapy would further improve outcomes.[115] While some improvements were seen, most people continued to lose vision and the side effects of cataract progression and IOP rises remained. Once anti-VEGF treatments became available, essentially all interest was lost in the use of intravitreal steroids for AMD.

14.7 Retaane®

Anecortave acetate suspension (Retaane® Alcon) was a synthetic analogue of cortisol without some of the negative side effects of steroids such as increasing intraocular pressure and increasing cataract development. It appeared to inhibit angiogenesis (the formation of new blood vessels) in the eye, through several mechanisms that might have included suppression of certain extracellular proteinases, inhibition of VEGF and blocking proliferation of retinal endothelial cells. It was administered as a depot injection behind the eye, beside the sclera using a novel curved cannula, a so-called posterior juxtascleral injection. A 15 mg in 0.5 mL injection was given every six months.

Clinical trials showed Retaane was superior to placebo in inhibiting vision loss, and vision was maintained (defined as a loss of no more than three lines) in approximately 73% of patients at 24 months compared to 47% for sham treatment (placebo).

In a pivotal phase III clinical trial[116], Retaane showed no statistically significant difference to PDT with Visudyne over 24 months. In this trial about 55% of cases experienced mild or greater reflux[xxiii] of the drug at baseline (51% at the month six injection), which was likely to have substantially reduced the efficacy and duration of effect, since an inadequate dose was delivered. Following this trial, the manufacturer provided a simple anti-reflex tool to be placed over the injection site; this was shown to consistently control reflux. However, no further randomised trials were conducted to confirm whether avoiding reflux improved efficacy. There were also no head-to-head trials conducted against the newer anti-VEGF treatments.

Retaane received an approvable letter from the FDA in May 2005, although the final registration was not received. In Australia, Retaane was supplied in 2004 and 2005 for compassionate use through the Special Access Scheme. The drug was registered in Australia in December 2005 for classic containing lesions and added to the PBS in April 2007. By the time of Retaane's registration, the use of off-label intravitreal

xxiii Leakage of the drug back through the injection site, meaning the full dose was not delivered

Avastin (see below) was already rising and Retaane failed to make an impression due to its lower efficacy and more time-consuming, albeit safer[xxiv], injection procedure.

Retaane was not registered in any other significant market and it was withdrawn in Australia after a few years.

14.8 Identifying the role of VEGF

The genesis of our understanding of wet AMD and other neovascular conditions in the eye, along with the recent development of a treatment, started almost 70 years ago.

In the late 1940s, Michelson proposed[117] that the normal development and growth of the retinal blood vessels depended on the presence of a biochemical "factor X". He also proposed that the same factor was possibly required for the development of pathologic blood vessels. In 1956 George Wise postulated that this "factor X" developed in retinal tissue that was deprived of oxygen and stimulated the formation of new blood vessels.[118] Identification of "factor X" remained a mystery for decades.

Research in the 1970s by Folkman[120] that investigated how cancerous tumours formed a supporting network of blood vessels, lead to the identification of acidic and basic fibroblast growth factors (FGF-1 and FGF-2).

In 1989, Leung and co-workers[111] reported that they had isolated an endothelial mitogen[xxv] from follicular cells in the pituitary gland in the brain, which they named vascular endothelial growth factor (VEGF). At the same time, Keck et al[121] described and purified a tumour-derived factor that was able to increase the permeability of blood vessels; they called this the vascular permeability factor (VPF). Cloning and sequencing of the genes encoding for VEGF and VPF demonstrated that these two factors were identical.

In 1994, Jean Miller reported that sections of monkey retinae could be made ischaemic[xxvi] by burning blood vessels with laser photocoagulation. This resulted in the formation of new blood vessels forming on the iris at the front of the eye. Increased levels of VEGF in the eye were shown to be linked to the formation of the new blood vessels.[122]

At the same time, Aiello et al reported high levels of VEGF in the ocular fluid of humans with neovascular disease, but not in people without disease.[123]

Definitive evidence for the role of VEGF[124] came with the development of anti-VEGF sera[xxvii], which was able to reverse the neovascularisation, as well as the development of a soluble VEGF receptor and anti-VEGF aptamers[xxviii].

14.9 Anti-VEGF therapy

In 1997, Genentech started phase 1 human trials of the intravenous use of an anti-VEGF antibody bevacizumab (Avastin®) for the treatment of certain cancers. The rationale was that if the tumour could be prevented from growing a blood supply, the tumour would die.

Subsequent trials showed that when used in combination with other chemotherapeutic agents, Avastin improved survival with minimal toxicity. It was approved by the FDA in the US in February 2004 for combination treatment of colon cancer.

At the same time as anti-VEGF antibodies were being developed for the treatment of cancer, other work was underway investigating their use for treating neovascular eye conditions. Pre-clinical studies began in the early to mid 1990s with phase 1 human trials started in the late 1990s for Macugen and in February 2000 for Lucentis.

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xxiv The injection was given behind and outside the eye, avoiding the potential risk of a blinding infection inside the eye (endophthalmitis), which occurs at a rate of about one in 3000 with intravitreal injections

xxv A chemical substance that triggers a cell to divide, in this case endothelial cells that line the inside wall of blood vessels

xxvi Restriction of blood supply to a tissue

xxvii Blood plasma from which clotting factors have been removed

xxviii Peptides (small proteins) that bind to a specific molecule such as a receptor

14.9.1 Macugen

The first intra-ocular anti-VEGF agent approved by the US FDA (in December 2004) was Macugen® (pegaptanib, Eyetech Pharmaceuticals). This was shown to bind and neutralise a particular variant (isoform) of the VEGF known as VEGF[165] and resulted in a significant reduction in the loss of vision resulting from wet AMD.

At one year, about 10% of people treated with Macugen experienced severe vision loss with a loss of six lines or more, compared to 22% in a sham treated group.[125] In addition, 70% of treated people had preserved vision, defined as a loss of no more than three lines at 12 months, compared to 55% in the sham-treated group.

While the outcomes were clearly superior to the then standard of care, (photodynamic therapy with Visudyne), most patients continued to lose vision as the neovascular lesions continued to grow with Macugen, albeit at a slower rate than people treated with Visudyne. Macugen has achieved only modest usage in the US and was not released in Australia.

14.9.2 Avastin

Genentech also considered the intravitreal use of Avastin for treating eye conditions, however, as it was such a large molecule, it was deemed unlikely that it would be able to diffuse through the full thickness of the retina into the choroid following intravitreal injection.[126] This belief was based on earlier pre-clinical work in monkeys using a different, but similarly sized antibody (HER2) that did not penetrate the retina.[127] The retinal penetration of Avastin was never tested in monkeys, and Genentech did not pursue eye studies with the drug. However, Avastin was still to play an important role in the management of macular degeneration, which will be described later in Section 14.9.11.

14.9.3 Lucentis

To avoid the theoretical problem of its large molecule size, Genentech developed a modified version of Avastin, known as Lucentis. This contained the antigen binding fragment (Fab)[xxix] of the same monoclonal antibody[xxx] as Avastin. The fragment blocks the binding of VEGF to its receptor on endothelial cells, thereby stopping or reducing its activity.

Following successful phase I and II studies, Genentech began the pivotal and landmark phase III MARINA and ANCHOR trials in March 2003 and June 2003 respectively.

xxix The antigen binding fragment (Fab) is the section of an antibody that attaches to the antigen, effectively neutralising the immune response of that antigen. Antibodies are commonly depicted as Y-shaped molecules; the Fab is one of the arms of the Y

xxx Monoclonal antibodies (mAb) are laboratory produced antibodies that are derived from cell division of a single ancestral cell

xxxi ETDRS letters. This is the number of letters that can be read on a standardised eye chart developed for the **E**arly **T**reatment of **D**iabetic **R**etinopathy **S**tudy. Each line contains five letters. This chart is now accepted as the standard chart for use in clinical trials

ANCHOR was an international, multicentre, randomised, active treatment-controlled[xxxi] study, initially involving 423 patients. Patients were at least 50 years old, with a best-corrected visual acuity between 20/40 and 20/320 (6/12 and 6/96). Patients were randomised to receive one of two doses of intravitreal Lucentis (either 0.3mg or 0.5mg) plus sham treatment with PDT or else sham intravitreal injections plus active PDT treatment. Injections (or sham injections) were given monthly for two years. PDT (or sham PDT) was given at the start of the study and as needed at three, six, nine and 12 months. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

The initial 12 month outcomes from MARINA were first presented by Joan Miller at the 23rd annual meeting of the American Society of Retina Specialists on 18 July 2005 in Montreal, Canada.[128] These results showed that not only did monthly treatment with Lucentis maintain vision (defined as a loss of no more than 15 letters or three lines), there was an average 17 letter difference in visual acuity in the treated group (which gained an average of seven letters) compared to the control group (which lost an average of 10.5 letters) at 12 months.

These results showed, for the first time, that a treatment could improve vision in a significant percentage of people with wet AMD, rather than just slowing the progression of vision loss.

The initial 12 month results of ANCHOR were announced on 14 January 2006 at the Macula 2006 symposium in New York. The results demonstrated that monthly treatment with Lucentis 0.5 mg resulted in a 21 letter improvement in visual acuity at 12 months compared to the use of PDT with Visudyne. In the first 12 months of the study, patients treated with Lucentis 0.5 mg gained an average of 11 letters from baseline, whereas people treated with PDT lost an average of 9.5 letters.

In addition, 96% of people receiving the 0.5 mg dose lost fewer than 15 letters of vision, which was the study's primary endpoint, compared to 64% of people treated with PDT.

A total of 40% of people receiving Lucentis 0.5 mg improved vision by 15 letters or more, compared to only 6% of people receiving PDT. In addition, 39% of people receiving Lucentis 0.5 mg achieved visual acuity of 20/40 (6/12) or better at 12 months, compared to only 3% of people receiving PDT.

The safety profile of Lucentis in ANCHOR and MARINA was shown to be similar to that observed in earlier trials and adverse events were generally mild to moderate. Serious adverse events were uncommon.

These stunning results enabled Genentech to submit Lucentis for registration, which was granted a six-month priority review by the US FDA leading to registration and marketing approval on 30 June 2006.

Although the Lucentis pivotal trials employed fixed monthly dosing, Genentech also conducted some additional trials to determine if less frequent dosing was viable.

PIER[129] was a phase IIIb prospective, multicentre, double masked trial involving 184 patients who were randomised to receive Lucentis 0.3 mg, 0.5 mg or sham treatment, with a fixed regimen of one injection per month for three months, then every three months.

While the initial response to the three monthly injections was positive with a mean gain of about five letters, by 12 months, mean visual acuity had fallen back below baseline. In all 90% of the Lucentis groups lost fewer than 15 letters (three lines), compared to 50% of the sham group. However, the outcomes were clearly less impressive than had been seen with monthly dosing in ANCHOR and MARINA. One important finding, however, was that at least for some people, relatively infrequent treatment was highly effective.

PRONTO[130] was an open-label, prospective, single centre uncontrolled trial in 40 patients in which patients initially received monthly injections for three months. Patients were then still seen every month, but until the end of the first year, an injection was given only if there was a significant rise in disease activity/leakage as measured by an increase in central retinal thickness of more

xxxii Rather than using a placebo, the control group was given another active treatment, in this case photodynamic therapy with Visudyne

than 100 um (measured by OCT), or a loss of visual acuity of five letters or more. In the second year, re-treatment was also given if there was any increase in fluid detected on OCT imaging.

After the third injection in year one, a mean improvement of 10.8 letters was achieved. At month 12, vision had largely been maintained with a mean improvement from baseline of 9.3 letters. By month 24, using a slightly more aggressive rationale for re-treatment in the second year, a mean of 11.1 letter improvement compared to baseline was achieved.

This was the first time that a treatment regimen based on individual outcomes had been reported, and indicated that outcomes approaching those of monthly therapy could be obtained with less frequent dosing, providing there was careful follow-up and OCT imaging of treatment response. PrONTO was, however, a small, uncontrolled trial and the data were inadequate for registration purposes.

14.9.4 Clinical practice in 2005 to 2006 – off-label Avastin

From early 2005 and during 2006 while the FDA and other regulatory agencies were reviewing the Lucentis registration dossier, some ophthalmologists in the US started experimenting with the off-label[xxxii] use of the recently registered Avastin, used for treating colon cancer. This was partly because many patients given the already registered Macugen were responding poorly.

Treatment with Avastin for wet AMD was initially given as an intravenous injection. An initial open-label[xxxiii], single centre, uncontrolled[xxxiv] trial of intravenous Avastin for wet AMD by Michels, Rosenfeld and colleagues showed a dramatic response. After 12 weeks of therapy, vision could be improved by a mean of 12 letters – more than two lines on the eye chart.[131] Cross-sectional imaging of the retina using optical coherence tomography (OCT) also showed that the swelling was dramatically reduced and angiography showed that the bleeding and leakage was well controlled.

To reduce the systemic exposure of intravenous Avastin, and to determine whether a more cost-effective dose could result, Rosenfeld started investigating the use of intravitreal Avastin. In July 2005, Rosenfeld published the first case report of the use of a single intravitreal injection of approximately 1 mg Avastin (0.04 mL of commercially available Avastin at a concentration of 25 mg/mL) for wet AMD, again as off-label treatment.[132] The female patient had previously responded poorly to three injections of Macugen and had demonstrated a poor response to PDT and intravitreal triamcinolone in her other eye. Within one week of the Avastin injection, an OCT scan revealed resolution of subretinal fluid, which was maintained for at least four weeks, with no signs of inflammation or other obvious safety issues.

Over the next several months, Rosenfeld and colleagues treated numerous patients with intravitreal Avastin and reported their results at the retina sub-specialty day at the American Academy of Ophthalmology in Chicago in October 2005.[133]

Although Avastin had not undergone any randomised clinical trials for retinal disease at this stage, there was extraordinary interest in the discussion as the results appeared to be similar to those reported in the Lucentis pivotal trials, despite earlier concerns about the theoretically poor penetration of Avastin into the retina. Following this academy meeting, there was a rapid increase in the use of off-label intravitreal Avastin globally, including in Australia, as Lucentis was still undergoing regulatory review and was therefore not freely available.

In Australia, this increase in use was evidenced by the rapid growth in the claims for Medicare item number 42740[xxxv] which rose more than five-fold between November 2005 and August 2007 when Lucentis was PBS listed.

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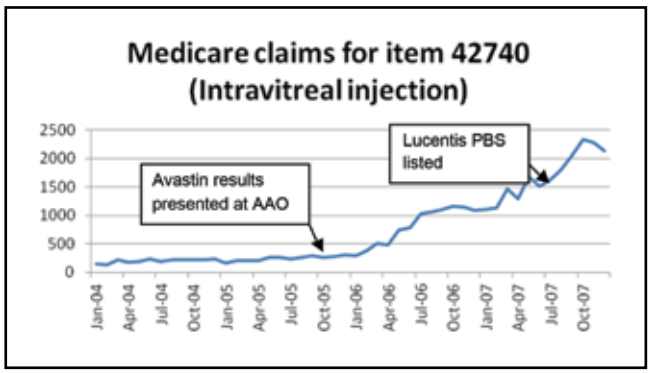
xxxiii Once a drug is registered (approved) for a particular indication, doctors are legally allowed to use it for other indications, providing they give the patient full informed consent regarding the evidence supporting the other indication. The clinician accepts medico-legal responsibility for this “off-label” use. In most countries (and certainly in Australia), off-label treatments do not attract reimbursement or subsidies

xxxiv The patient and doctor knew which treatment was used. That is, the study was not blinded or masked

xxxv No placebo or control treatment was used

xxxvi From 2005 to 2010, item 42740 was the only Medicare item number available for paracentesis of the eye, which included intravitreal injection of therapeutic substances

Medicare claims for intravitreal injection 2004 to 2007, demonstrating increase in use of Item 42740 due to rapid uptake of Avastin following the 2005 AAO presentation by Rosenfeld in 2005.



Although Avastin was commercially available, it was only registered for intravenous use for treating colon cancer, and it was not presented in a dose form suitable for intra-ocular use. Nor did it conform to the US or EU Pharmacopoeial requirements for intraocular use. It was nonetheless relatively inexpensive, as a 4 mL single dose vial containing 100 mg of Avastin could be split into multiple 1.0 mg in 0.04 mL or 1.25 mg in 0.05 mL single dose syringes by a compounding pharmacy. Although this procedure was performed by licensed pharmacists, it was not without risk, and potential medico-legal consequences. (see Section 14.9.15).

By the time of the World Congress of Ophthalmology in Brazil in February 2006, just four months after Rosenfeld's presentation in Chicago, there had been extensive off-label use of Avastin for wet macular degeneration and other neovascular conditions of the retina and many clinicians reported their initial, albeit uncontrolled, experiences.[134]

Although this was an off-label treatment, with no long-term evidence of efficacy or safety, there was a rapidly growing consensus that it should be offered as first line treatment, as the visual and anatomic outcomes appeared to be comparable to those reported in randomised trials with Lucentis, which was still not registered or generally available.

Through 2006, several peer-reviewed studies were published documenting the short-term safety and efficacy of Avastin[135,136], and confirming that it did indeed penetrate the full thickness of the retina following intravitreal injection.[137]

14.9.10 Lucentis in Australia

In Australia, following the registration of Lucentis for wet AMD on 19 February 2007, and prior to its listing on the PBS on 1 August 2007, Novartis conducted a Patient Familiarisation Program (PFP) in which ophthalmologists were provided with free product to put patients on treatment before the product was added to the PBS. This also gave opinion leaders the opportunity to gain real-world experience in its use to enable informed discussion and debate at clinical and educational meetings.

While the pivotal clinical trials used fixed monthly dosing, it quickly became apparent, both in Australia and overseas, that in real-world use, ongoing, fixed monthly dosing with either Avastin or Lucentis was neither necessary in a significant number of people, nor willingly accepted due to the substantial personal, emotional and financial burden of treatment imposed on elderly, often frail, patients. As a result, clinicians quickly started to investigate the use of individualised dosing, based on treatment response. The two treatment regimens used were "as needed" (*pro re nata* or PRN) dosing, as reported in the PrONTO trial in 2007, and another variation which became known as "treat and extend" (T&E).

14.9.11 Different approaches to reducing treatment burden

PRN

The PRN (*pro re nata* "as needed") approach, starts with a "loading dose" of one injection per month for three months. Patients are then seen monthly and assessed for visual function and retinal structure, normally with the use of OCT imaging. If the patient shows evidence of continued or renewed lesion activity, an injection is given and the patient is instructed to return in a month. If there is no evidence of lesion activity and vision is stable, an injection is not given, but the patient is still instructed to return in a month.

The PRN approach gained rapid acceptance by significant numbers of ophthalmologists in the USA and Europe, as it reduced the number of injections, although the number of consultations on a monthly basis remained unchanged.

A major criticism of the PRN approach is that if leakage resumes a few days after the monthly consultation, it could remain untreated for almost a month, especially if it remains asymptomatic.[xxxvi]

There is good evidence that the longer any leakage remains untreated, the greater the likelihood that permanent fibrotic scarring will occur, resulting in irreversible vision loss.[138] In addition, when using the PRN approach, many patients feel significant anxiety if they have a negative examination result requiring reinjection[139]. They feel as though they have "failed" if they needed an injection. It has also been reported that when using a PRN approach, a busy ophthalmologist's practice may not always be able to provide an injection on the same day[140], resulting in a need to reschedule the patient, causing a considerable additional time burden and expense for the patient. A significant proportion of patients will therefore be undertreated when the PRN approach is used, with sub-optimal vision outcomes. Over time, evidence has accumulated confirming this conclusion.

Treat and Extend

While PRN is a reactive approach, Treat and Extend (T&E) adopts a somewhat different, proactive approach. Treatment again involves an initial "loading dose" of one injection per month (or four-weekly), normally for three months. After three injections, OCT is used to reassess the patient for visual function and retinal structure. If there is evidence of continued leakage or if vision hasn't stabilised, the patient will receive an injection and be asked to return again in four weeks. If vision is stable and there is no evidence of active leakage, the patient will still receive an injection but the gap to the next injection may be increased by one or two weeks.

At the next or second subsequent visit, the patient is again reassessed, treated and extended by another one or two weeks if stable, and so on. Should a patient experience mild recurrence of leakage, the gap between injections will typically be shortened by one or two weeks less than the gap that resulted in recurrence. If major leakage occurs, the patient may be brought back to four-weekly treatment until stable, when extension will again be attempted.

This approach means that the patient can be treated as often as needed, but as little as possible.

Where possible, this process continues until the gap between injections is increased to 12 weeks but only rarely beyond this.

Patients receiving consecutive maintenance injections using a Treat and Extend approach (where they expect to be treated each visit) are less susceptible to recurrence of disease activity, when compared to PRN regimens where the gap between consecutive injections tends to be prolonged.

Long-term studies and clinical experience have shown that very few people can stop injections altogether. If treatment is stopped, recurrence of leakage nearly always results.[141] Every time there is recurrence, there is a risk that vision will not fully recover. Ophthalmologists were concerned that some people would not initially notice recurrence, and not return for immediate treatment. When people have untreated active leakage, they are more likely to develop a permanent fibrotic scar on the macula with resultant serious and permanent vision loss.

As evidenced by several surveys of clinicians at the annual scientific meeting of the Australian and New Zealand Society of Retinal Specialists (ANZSRS), T&E quickly became the dominant treatment approach. Despite an initial lack of hard evidence, most clinicians felt it was resulting in good outcomes that approximated those seen in the pivotal studies using monthly injections. Of particular relevance was that this approach reduced the number of injections and office visits, lowering the cost and treatment burden for patients and significantly decreasing the workload on already overstretched ophthalmology practices, as the awareness

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xxxvii Patients are typically instructed to advise the practice if vision deteriorates in between visits, but even if the person is self-monitoring using an Amsler grid, reactivation isn't always symptomatic

levels rose and the number of people diagnosed dramatically increased. It also reduces the small but important risk of sight-threatening endophthalmitis[xxxvii] that is associated with every injection.

With Treat and Extend, patients expect to receive an injection each visit and find this to be less mentally traumatic than not knowing whether they will be getting an injection using the PRN approach.[133]

The widespread use of T&E has, to a significant extent, preceded the availability of hard evidence supporting its use, although several studies have been published in recent years which have confirmed that T&E typically provides similar outcomes to monthly treatment and superior results to PRN, while reducing the number of visits required.

Only one of these studies, however, has been a randomised controlled trial directly comparing T&E to monthly treatment.[143] In this small, two year study involving 20 patients receiving monthly injections and 40 patients receiving T&E, patients treated monthly gained a mean of 10.5 letters while patients treated with T&E gained a mean of 8.7 letters, a clinically insignificant difference. Interestingly, more people in the T&E group gained at least 15 letters (30% versus 20%) although 13% of T&E patients lost at least 15 letters compared to 0% in the monthly group. Both groups had similar structural results as measured by central macular thickness. Overall, at two years, 37% of T&E patients could be extended to injections every 11 or 12 weeks, while one-third still needed monthly injections to maintain adequate control.

Changing from PRN to T&E

Further evidence for the benefit of T&E versus PRN came from a retrospective analysis of 146 eyes in 134 consecutive, treatment-naive patients who were initially given Lucentis on a PRN schedule and then changed to T&E.[144] Mean visual acuity improved slightly from 20/41 (approximately 6/12) during the PRN maintenance phase to 20/36 (approximately 6/10) 12 months after the switch to T&E. Mean individual variation in visual acuity was reduced with T&E and the central retinal thickness was also improved. These improvements were achieved with an increase in the mean number of injections given (from seven to 8.8 per year) with a reduction in the mean number of visits (from 12.7 to 8.8. In this study, 18.5% of eyes still required monthly treatment on the T&E regimen, whereas 22.6% could be extended to the maximum of 12 weeks.

These results highlight that PRN treatment can result in undertreatment in some patients, resulting in inferior outcomes compared to T&E.

14.9.12 CATT

Even after the registration of Lucentis in the USA in 2006, the use of off-label Avastin remained widespread there, especially when patients did not carry adequate health insurance. This extensive use was despite the lack of any large randomised trials confirming its safety and efficacy, nor any trials comparing it to the registered, proven treatment Lucentis.

In addition, most ophthalmologists in the USA had rapidly adopted a treat as needed (PRN) approach, rather than the fixed monthly dosing as per the approved product label.

To establish whether the continuing use of off-label treatment was reasonable and also to assess the merits of PRN dosing, the US National Eye Institute sponsored the Comparison of Age-related Macular Degeneration Treatment Trials (CATT), a large randomised trial comparing Lucentis to Avastin.[156]

In this study, 1208 people aged 50+ with neovascular AMD were recruited at 44 US clinics between February 2008 and December 2009. Patients had baseline visual acuity of between 20/25 and 20/320 (6/7.5 and 6/96) and had received no previous treatment. Patients were randomly assigned to one of four treatment groups:

a. Lucentis 0.5 mg every four weeks (“Lucentis monthly”) – Baseline n=301

b. Avastin 1.25 mg every four weeks (“Avastin monthly”) – Baseline n=286

c. Lucentis only when active neovascularisation was present, with four-weekly evaluation (“As needed Lucentis”) – Baseline n=298

xxxviii Endophthalmitis is a serious, sight-threatening infection inside the eye which can occur whenever the interior of the eye is exposed following an injection, surgery or trauma. Unless treated promptly, it can result in total blindness and in some cases, may result in the need to remove the eye

d. Avastin only when active neovascularisation was present, with four-weekly evaluation (As needed Avastin") – Baseline n=300

Some important differences to ANCHOR and MARINA included:

a. People with any sign of activity, including fluid or haemorrhage under the fovea resulting from juxtafoveal neovascularisation, were allowed entry into CATT.

b. People with up to two lines better starting vision (20/25) were allowed entry in CATT compared to ANCHOR and MARINA (20/40). Subsequent research has clearly demonstrated that the better the starting vision, the better the outcomes.

c. CATT did not include any entry restriction on lesion size.

d. The mean age of participants in CATT was three to four years older than ANCHOR or MARINA

e. CATT did not include full blinding (masking) of study participants.

The primary outcome end point was the mean change in visual acuity between baseline and one year with a non-inferiority limit[xxxviii] of five letters. Secondary outcomes included the proportion of patients with a change in VA of 15 letters or more, the number of injections given, change in fluid and foveal thickness (using OCT imaging), change in lesion size (using fluorescein angiography), incidence of adverse events, and cost. Examiners of visual acuity and graders of OCT and angiograms were unaware of the treatment given.

There were no substantial differences between the four treatment groups at baseline. At 12 months, the overall visual acuity outcomes with Avastin were found to be equivalent to Lucentis, both for monthly treatment and for treatment as needed. As needed Lucentis was found to be equivalent to monthly Lucentis. The comparison of as needed Avastin to monthly Avastin was inconclusive.

In the primary analysis, the mean number of letters gained (+/- standard error) was:

- Lucentis monthly = 7.2 (+/- 0.7)
- Avastin monthly = 7.3 ()+/- 0.8)
- Lucentis as needed = 6.4 (+/- 0.6)
- Avastin as needed = 6.1 (+/-0.7)

While the visual acuity results for PRN treatment were statistically non-inferior to monthly treatment, there were some minor differences suggesting that Avastin may not have been drying the macula as completely as Lucentis. For example, at 12 months, 43.7% of monthly Lucentis patients had a dry macula compared to 26% of monthly Avastin patients. For patients treated with a PRN regimen, 23.9% of Lucentis patients had a dry macula compared to 19.2% of Avastin patients.

Consistent with the presence of sub- or infra-retinal fluid, patients treated with Lucentis tended to have better reduction of sub-foveal thickness, indicating better restoration of normal retinal architecture. These differences may have been responsible for the higher number of doses required for the Avastin PRN group (7.7) compared to the Lucentis PRN group (6.9). That is, people treated with PRN Avastin needed more injections to achieve the same outcome as PRN Lucentis.

Perhaps the most controversial aspect of the CATT study was the analysis of adverse events. While there were no statistically significant differences between the drugs in relation to deaths or arteriothrombotic events, including non-fatal stroke and non-fatal myocardial infarction, there was a significant difference in all serious adverse events, primarily all-cause hospitalisation, with 19.0% of all Lucentis patients experiencing at least one serious adverse event, compared to 24.1% of Avastin patients, a statistically significant difference (p=0.04).

After adjusting for demographic differences and co-existing illnesses at baseline, there was

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xxxix Non-inferiority trials aim to determine whether the study treatment is 'no worse than' a reference treatment for which efficacy versus placebo has already been established. A critical aspect of non-inferiority trials is to establish the acceptable margin of variation that would determine that the study treatment is non-inferior

a 29% increased risk of at least one serious adverse event with Avastin (p=0.04). As there did not appear to be any particular organ class responsible for this difference and because the PRN groups had higher serious adverse event rates, despite having less total drug, significant debate has subsequently ensued as to whether this is a real difference, a difference due to undetermined variations between the study groups or a chance event. Importantly, the difference continued and actually increased after the two year analysis (see below).

In the second year of CATT, patients who had originally been on a monthly regimen were re-randomised to either stay on monthly treatment or move to an as needed (PRN) regimen, while staying on the same drug.

The two-year results[157] largely reinforced the outcomes reported at the end of year one. The overall visual acuity with Avastin remained statistically non-inferior to Lucentis, and again, more Lucentis-treated eyes had complete resolution of fluid. This resulted in an average of 1.5 more Avastin injections being needed over two years compared to Lucentis to achieve comparable results. In general, PRN treatment resulted in slightly less improvement in vision compared to monthly treatment, with the differences between monthly and as needed continuing to become greater.

Interestingly, the frequently debated difference in serious adverse events reported at year one was slightly greater at year two, with Avastin patients having a cumulative 30% higher risk of a serious adverse event. As before, the rates of death, stroke and myocardial infarction did not differ between the groups at two years.

14.9.13 Other comparative studies (IVAN, LUCAS, GEFAL, MANTA, BRAMD)

A number of other smaller trials comparing Lucentis to Avastin have been conducted including IVAN[145] (UK), GEFAL[146] (France), BRAMD[162] (Netherlands), LUCAS[159] (Norway) and MANTA[161] (Austria). These have consistently shown that the visual acuity outcomes are similar between the two drugs over 12 months, but that Lucentis produces superior anatomical outcomes as measured by retinal thickness and removal of fluid.

A meta-analysis by Kodjikian[160] of CATT, IVAN, MANTA, GEFAL and another study by Subramanian[147] confirmed the non-inferiority of Avastin compared to Lucentis for change in visual acuity at one year and the better anatomical results with Lucentis. However, the pooled evidence still indicated a higher risk of serious systemic adverse events with Avastin, although the evidence did not show which types of adverse events occurred more frequently.

14.9.14 Eylea® (aflibercept)

In the early 2000s, a small US biotech company, Regeneron, started testing a new type of anti-VEGF treatment, then known as VEGF-trap, for treating cancer. Following the initial successes reported for ranibizumab by Genentech, Regeneron started human trials for VEGF-Trap in 2004 for treating neovascular eye diseases. VEGF-Trap for use in the eye became known under its generic name of aflibercept and then its brand name of Eylea.[xxxix] Encouraging initial results led to the establishment of an agreement between Regeneron and Bayer in 2006 to continue the development of Eylea for markets outside the US, with Bayer to assume marketing responsibility for these markets should it be registered. Eylea would be marketed by Regeneron in the US. With additional funding, and positive preclinical results, the clinical (human) development of the agent progressed quickly, leading to its registration in 2011 in the US and early 2012 in Australia.

Unlike Lucentis and Avastin, which are monoclonal antibodies (mAb) to VEGF, Eylea is a decoy receptor fusion protein. It is made by joining DNA sequences encoding the second immunoglobulin (Ig) domain of human VEGF receptor 1 to the third Ig domain of human VEGF receptor 2, which is then fused to the constant region of human IgG1. While the monoclonal antibodies attach to VEGF-A, like a key in a lock, Eylea can attach to all isoforms of VEGF-A as well as the related placental growth factor (PIGF). It does this by “grabbing the VEGF with two hands”, and trapping it to block receptor binding.

xl A modified version of aflibercept, known as ziv-aflibercept under the brand name Zaltrap, is now also available for treating certain cancers

Not only does aflibercept bind to all isoforms of VEGF-A and PlGF, the binding to VEGF-A is substantially stronger than that of bevacizumab and ranibizumab, suggesting it should have a longer duration of effect.

In a range of animal models, aflibercept was highly effective at stopping the formation of new blood vessels and vessel leakage. In particular, intravitreal aflibercept was able to rapidly stop the leakage from new blood vessels that formed in rodents and primates following laser-induced neovascularisation, an animal model that most closely mimicked the start of "wet" macular degeneration.

Safety studies in animals also demonstrated a good safety profile.

Phase I and II human studies established the effective dose range (between 0.5 mg and 2 mg) and suggested that an eight-weekly dosing regimen may provide sufficient activity to control disease.

Phase 3 registration studies

VIEW1 and VIEW2
Following the successful phase I and II program, Eylea was evaluated for safety and efficacy in two large prospective, randomised, multicentre, double-masked, active-controlled phase III trials for the treatment of wet AMD.

The two studies, VIEW1 and VIEW2, had similar protocols, with VIEW1 being conducted at 154 sites in the USA and Canada, while VIEW2 was conducted at 172 sites in Europe, the Middle East, Asia Pacific (including Australia) and Latin America. In total, 2419 patients aged 50 years or older with active, subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea were entered into the studies. Eligible patients had baseline best corrected visual acuity between 20/40 (6/12) and 20/320 (6/96), and had received no previous treatment.

The study design was established following consultation with the US FDA to ensure consistency with the previous studies for the comparator drug, Lucentis.[148]

In both studies, patients were randomised 1:1:1:1 to one of the following dosing regimens:

- 0.5 mg Eylea every four weeks
- 2.0 mg Eylea every four weeks
- 2.0 mg Eylea every eight weeks, following three initial doses at week zero, four and eight. To maintain four masking, sham injections were also given at the interim four-weekly visits after week eight
- 0.5 mg Lucentis every four weeks (per the product label)

The primary end point of both studies was non-inferiority of the Eylea regimens to Lucentis regarding the proportions of people maintaining vision, defined as losing no more than 15 ETDRS letters. The pre-specified non-inferiority margin was determined to be 10%, and the FDA suggested that a 5% margin would determine clinical equivalence.

Numerous secondary end points were measured including mean changes in best corrected visual acuity between zero and 52 weeks, proportions of people gaining more than 15 letters, change in NEI VFQ-25 scores[xl], and changes in the area of the neovascularisation based on fluorescein angiography. Changes in retinal thickness and persistence of fluid were determined with OCT.

In both studies, the proportion of people maintaining vision was similar in all treatment groups and ranged between 94.4% and 96.1%. All Eylea groups met the pre-specified criteria for statistical non-inferiority to Lucentis, with confidence intervals of the differences within the 10% margin. Moreover, the point estimates of the differences in the mean results favoured Eylea in all groups. All groups also met the pre-specified 5% margin for clinical equivalence.

Mean changes in BCVA were mostly similar between groups, although the Eylea 2 mg four-weekly group was statistically superior to Lucentis four-weekly by 2.8 letters. Small numeric differences between the treatment groups in one study at a given time point were not reproduced in the other study, suggesting they were random variations.

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xli NEI VFQ-25 is a reliable and validated visual functioning questionnaire containing 25 questions developed by the US National Eye Institute. This is a useful tool to determine the vision-related quality of life including general vision, social functioning, visual dependency, near and colour vision

In both VIEW studies, the proportion of people gaining 15 or more ETDRS letters between baseline and week 52 was similar in all treatment groups, as were other measures of visual outcome and improvements in the vision-related quality of life measures (NEI VFQ-25). Close review determined that for analytical purposes, results from the two studies could be combined to improve statistical power.

Previous studies with Lucentis using dosing that was less frequent than monthly showed that average retinal thickness was greater as fewer patients were able to achieve a dry macula. Importantly, Eylea was able to demonstrate similar reduction of retinal thickness and drying of the retina with an eight-weekly dosing regimen.

In the follow-up period from week 52 to 96 in the VIEW studies, patients continued to receive the same dose of study drug as the first 52 weeks, buta PRN regimen was used, with monthly follow-up. Reinjection criteria were:

- new or persistent fluid on OCT or fluorescein angiography, or
- an increase in central retinal thickness of 100µm or more compared to the previous lowest thickness, or
- a loss of five or more EDTRS letters from the previous best score in conjunction with recurrent fluid on OCT, or
- a new onset neovascularisation, or
- new macular haemorrhage.

Importantly, even if patients did not meet any criteria for re-injection, they received an injection if there was a time lapse of 12 weeks since the last one. That is, all patients were mandated to receive at least four injections in the second year, even if there was no evidence that they needed treatment. This regimen was called “capped PRN”.

In all, 91.4% of patients completed the first 52 weeks of the study, and 84% completed 96 weeks. The mean visual acuity gain over 96 weeks was largely similar, varying by only 1.3 letters between groups. However, they represented a one to two letter decrease compared to the gains reported at week 52. A small loss in the anatomic improvements apparent at week 52 was also seen. The proportion of people who gained 15 letters from baseline was similar between groups and ranged from 28.1% to 33.4% of patients. A higher proportion of patients receiving Eylea 2 mg, regardless of the timing of dosing in the first year, had no retinal fluid on OCT.

During the PRN phase in the second year of treatment, a post-hoc analysis showed that slightly fewer injections were needed for Eylea 2 mg compared to Lucentis. This was mostly because 26.5% of Lucentis patients continued to need six or more injections per year (eight weekly or more frequently), compared to 14 to 15.9% for Eylea patients.

Over the two years of treatment, a generally favourable safety profile was demonstrated for both drugs, with no meaningful differences noted.

Switching studies

Approximately one quarter of people receiving treatment with Lucentis continue to need monthly injections to maintain control of leakage and to stabilise vision, and a small number – in the order of 5% to 10% – fail to respond adequately to treatment. There is also evidence that in some people, the effect of treatment may start to wane over time, and/or a higher dose or more frequent dosing may be required to maintain efficacy, a phenomenon known as tachyphylaxis. To determine if switching patients to Eylea could have a beneficial effect in these cases, a large number of switching studies have been conducted.

A 2017 review and meta-analysis[149] of 28 switch studies demonstrated that switching from Lucentis to Eylea in “non-responders” had little or no impact on overall visual function, although anatomic outcomes of retinal fluid and central macular thickness were significantly improved after switching, consistent with the improved “drying” effect from Eylea noted in the VIEW studies.

In the VIEW studies, people on eight-weekly Eylea, on average, had similar outcomes to people receiving four-weekly Lucentis. In the switch studies, however, where most people are primarily treatment resistant (poor- or non-responders), as many as 79% of people receiving Eylea may need treatment more frequently than eight-weekly.[150] This highlights the resistant nature of this population group and the need for individualised therapy to maximise outcomes while minimising visits.

It was also noted that studies that included a "loading dose" after switching (that is, three x monthly doses, before any attempt to extend) achieved better results than those that did not include a loading dose. It therefore appears important to stabilise poor Lucentis responders with aggressive Eylea treatment before any attempt is made to increase the gap between dosing.

Although other approaches have been suggested to improve outcomes in treatment-resistant people, including increasing the frequency of treatment intervals[151] (to two or three weeks), increasing the dose of the same agent used[151,152] or adding another modality such as PDT with Visudyne[153], switching to a different anti-VEGF agent may be the most appropriate and effective approach.[149]

Similarly, some studies have shown that for people who do not respond adequately to Avastin, a switch to Lucentis or Eylea may again provide anatomical improvements, without necessarily improving vision.[154]

Eylea registration and reimbursement issues
Eylea gained marketing approval for wet AMD in the USA on 18 November 2011.

Eylea was registered in Australia for the treatment of sub-foveal neovascular (wet) age-related macular degeneration on 7 March 2012, and recommended for PBS listing at the March 2012 PBAC meeting.

At that meeting, the PBAC noted that there was no clinical evidence provided in Bayer's Eylea submission for people who had failed or were unable to continue treatment with Lucentis, and consequently recommended that reimbursement for Eylea should be provided only for treatment naive-patients.

Prior to listing, Bayer made a submission to a special PBAC meeting in August 2012 presenting some data that was supportive of switching patients who had demonstrated a response to Lucentis. Data on non-responders were not yet available. While the PBAC considered that it would be appropriate to restrict switching to responders, they acknowledged that this would be complex and difficult to administer. They also noted that the restriction for Lucentis did not require a demonstration of response to continue treatment, and that the invasive nature of treatment would likely limit use in those not achieving a clinical benefit.

Concurrently, Macular Disease Foundation Australia implemented an advocacy campaign, previously explained in Section 4, providing the PBAC with thousands of letters from clients requesting that ophthalmologists be given the option of switching patients (from either drug), when considered appropriate.

The restriction to treatment-naive patients was overturned in time for PBS listing on 1 December 2012. This allowed switching to occur between either registered drug, and also for people who were switched from the off-label, unreimbursed Avastin to either of the registered drugs.

When Eylea was PBS listed, certain additional limitations on its use were announced without any warning. These included the requirements that:

a) when people were switched from Lucentis to Eylea, they should be immediately placed on an eight-weekly regimen

b) when patients were initiated on Eylea, they should be moved to the eight-weekly regimen immediately after the initial three monthly "loading" doses

The PBAC's requirement that people who were to be switched from Lucentis should be moved immediately to eight-weekly injections was not well accepted by ophthalmologists. Doctors stated that for patients who had been switched to Eylea due to a suboptimal response to Lucentis, good clinical practice would require aggressive treatment using four-weekly injections of Eylea until disease had stabilised, and then to gradually try to extend people to six- or eight-weekly injections, depending on the individual response.

In addition, ophthalmologists stated that while the pivotal studies showed that *on average*, eight-weekly Eylea was equivalent to monthly Lucentis, not all patients were average. Since standard of care with Lucentis now involved individualisation of treatment using a treat and extend approach, ophthalmologists uniformly believed the same approach with Eylea was appropriate. As it is not always possible to predict *a priori* which patients will respond well, this meant that they needed to have the flexibility to:

a) keep poorly responding patients on monthly treatment as long as they remained uncontrolled

b) extend the gaps between injections *gradually* in certain situations, such as when the person had only one good eye remaining

c) extend the gaps between injections to longer than eight-weekly when a patient was responding well.

As neither of the PBAC's limitations on Eylea dosing were considered to be in the best interests of patients, Macular Disease Foundation Australia again advocated to the PBAC to allow ophthalmologists the flexibility to utilise treat and extend regimens. Following an extraordinary meeting of the PBAC, these restrictions were lifted shortly after listing. These advocacy efforts are also detailed in Section 4.

Uptake of Eylea since registration

The market acceptance of Eylea in Australia was extremely rapid, exceeding 40% share of PBS scripts within four months of PBS listing and 50% share within nine months. This is clearly a much faster uptake rate than would be achieved with use in new patients alone, and reflects a large number of patients who have been switched, either due to an inadequate response to Lucentis, or a perceived possibility of reducing the number of injections needed.

14.9.15 DUSC reviews

As part of the regular analysis of the use of high cost drugs, the Drug Utilisation Sub Committee (DUSC) has conducted three formal reviews on anti-VEGF treatment – in June 2009 and December 2011 to assess the use of Lucentis since registration, and again in June 2015 to also assess the impact of the introduction of Eylea.

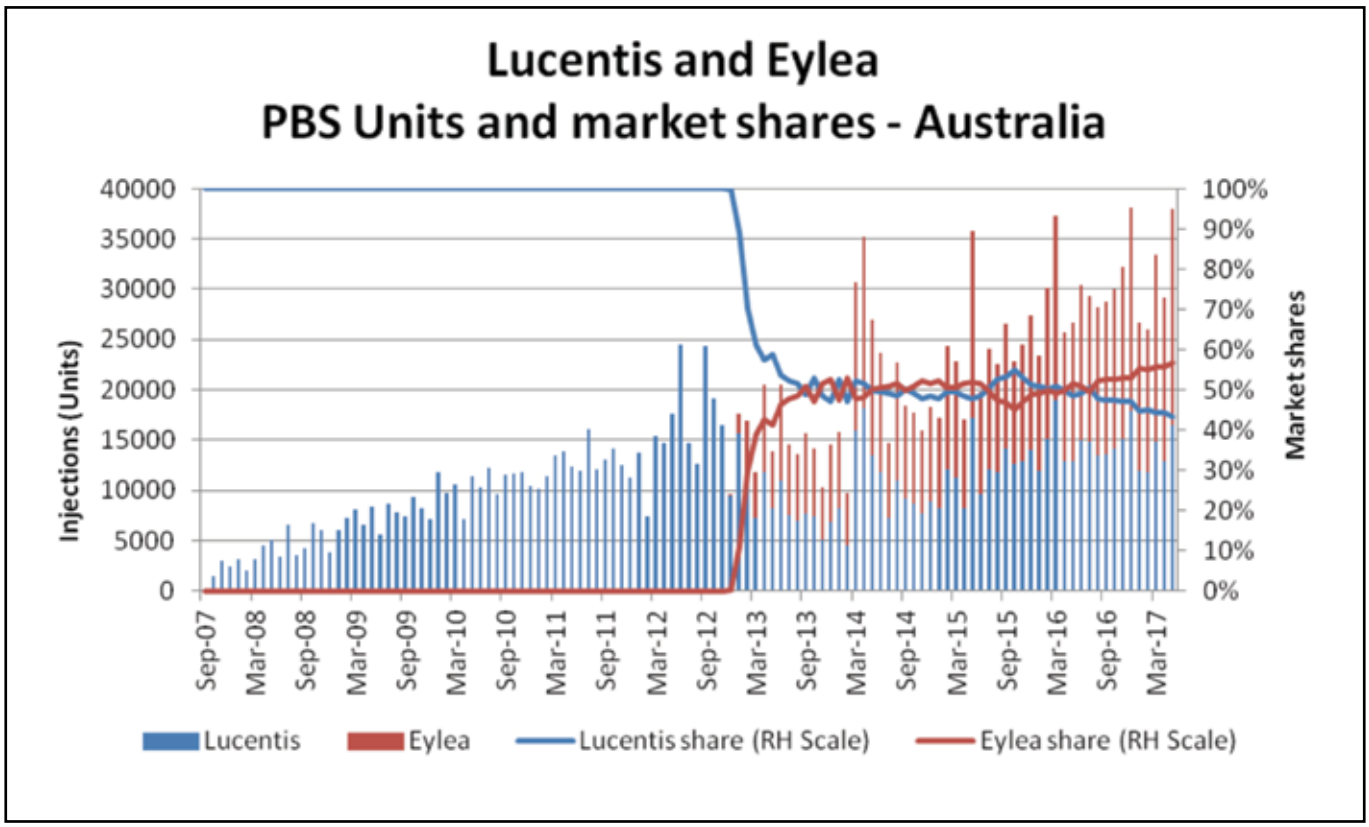
The results of the 2009 and 2011 reviews were not released publicly and remain commercial-in-confidence. Certain aspects of the 2011 review were, however, included in the publicly available 2015 review.[155]

The 2011 DUSC review found:

a) the number of patients initiating treatment each year was remarkably stable at about 8,000

b) the number of people receiving Lucentis was greater than originally estimated, but the

Growth and shares of registered anti-VEGF treatments since launch



number of prescriptions/injections supplied and benefits paid were less than expected.

c) in the cohort starting treatment in August 2007, patients received an average of 5.84 injections in the first 12 months. In the ensuing years, there was a gradual increase in the number of doses given in the first year of an individual's treatment, rising to 7.42 in the first 12 months for people beginning in August 2010.

d) patients were not receiving injections each month. DUSC questioned the reasons for this, given that the PBAC had determined monthly treatment was the cost-effective manner in which the drug should be given, based on the pivotal ANCHOR and MARINA studies. PBAC had also rejected quarterly treatment based on PIER.

e) patients were staying on treatment longer than was expected in the original Lucentis submission considered by the PBAC

f) in August 2010, about 20% of use was for bilateral treatment. When treated bilaterally, half were receiving both injections on the same day, and half on separate days.

DUSC questioned whether the treatment patterns were based on age, and if more aggressive treatment protocols were used in younger patients.

Responses to DUSC highlighted that the primary reason for the differences in treatment patterns compared to the pivotal trials (and PBS listing) was that clinicians were using an individualised 'treat and extend' regimen.

DUSC was especially concerned with the lower number of injections being given, in the belief that it wasn't as effective as monthly treatment, and therefore not as cost effective. Its concerns were largely allayed when RANZCO and Macular Disease Foundation Australia explained the use of individualised treatment using space T&E or PRN regimens.

The gradual increase in the number of doses given in the first and subsequent years was due to a progressive realisation that in an effort to reduce treatment burden, some patients may have been under-treated.

There was also an initial view that it might be possible to stop treatment in people once vision had been stabilised, and there was no evidence of ongoing leakage. Longer term experience clearly showed that very few people could have their treatment stopped without risking recurrence.

Again, with longer term experience, ophthalmologists became increasingly concerned that if patients stopped treatment prematurely, they may not initially notice recurrence of disease with resulting leakage, scarring and permanent vision loss. Over a few years, clinical experience showed that most people needed to stay on treatment indefinitely, although many could be managed with injections given as infrequently as 12 weekly.

June 2015 review

This second review, which included patients treated with Eylea, confirmed many of the findings of the first review. A redacted public copy of the review noted that:

a) The number of new patients starting treatment was still stable at between 7,000 and 8,000 per year

b) As at June 2015, more than 60,000 people had received anti-VEGF treatment

c) The number of injections *per treated patient* increased between 2007 and 2011 but had since stabilised. Importantly, the number of injections in the first 12 months of treatment increased from 5.7 for people starting injections in 2007 to more than eight injections in the first year for people starting treatment from 2010

d) The majority of patients remain on treatment for many years with half treated for at least four years. Almost 3,000 people were in their seventh year of treatment

e) The percentage of people continuing treatment in the second and subsequent years is steadily increasing. In 2012, 75% of patients continued to receive treatment into the second year. This compared to only 65% in people who started treatment in 2007

f) The rate of bilateral treatment appeared to be increasing, although this was inferred, as specific left/right eye data were not available.

Average number of injections supplied in each 12 months of therapy for patients by initiating year

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Initiated 2007[a]	5.70	5.95	7.19	7.67	7.96	7.88	7.66
Initiated 2008	6.11	6.12	6.98	7.37	7.62	7.38	-
Initiated 2009	7.23	6.78	7.30	7.51	7.27	-	-
Initiated 2010	8.08	7.20	7.43	7.47	-	-	-
Initiated 2011	8.31	7.20	7.10	-	-	-	-
Initiated 2012	8.48	7.04	-	-	-	-	-
Initiated 2013	8.29	-	-	-	-	-	-

[a] This cohort may also contain some patients who were grandfathered on to ranibizumab and therefore are initiators to the therapy.

Percentage of continuing patients from the number of initiators in year 1

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Initiated 2007	100%	65%	57%	52%	48%	44%	39%
Initiated 2008	100%	62%	52%	48%	43%	39%	
Initiated 2009	100%	66%	57%	51%	46%		
Initiated 2010	100%	70%	60%	54%			
Initiated 2011	100%	73%	64%				
Initiated 2012	100%	75%					
Initiated 2013	100%						

g) The number of injections *per patient* appears to be similar between Lucentis and Eylea. Patients started between December 2012 and November 2013 and only treated with one agent received 9.3 Lucentis injections or 8.28 Eylea injections

h) Continuing patients who swapped to Eylea from Lucentis had a higher number of injections (8.71) compared to those who stayed on Lucentis (6.9)

i) The addition of Eylea to the PBS did not appear to increase the number of people being treated

j) Eylea reached 50% PBS share within six months. It was being used for both new and switch patients.

Some key issues and commentaries with this review include:

- Treatment rates were per patient, not per eye. Even though ophthalmologists must declare left or right eye when writing a script, the PBS does not record this in a way that can be extracted. In a response to the DUSC review, Macular Disease Foundation Australia recommended that this represents a major deficiency in PBS data collection and should be corrected

- Point (h) above likely reflects the fact that people who were swapped from Lucentis to Eylea were more likely to be poor responders and hence require more injections, possibly including three monthly “loading doses”. In contrast, continuing patients who remained on Lucentis were more likely to be responding well, and to have been extended to less frequent dosing

- The increased rate of bilateral treatment probably reflects the fact that as patients remain on first eye treatment longer, the likelihood of second eye involvement naturally increases

- It is noteworthy that as the average number of injections per patient increases, the proportion of people staying on treatment also rises. This result is seemingly anomalous result, given that a high frequency of injections represents a major treatment burden to people, may be related to the improved outcomes that are being achieved with more frequent treatment. Better outcomes mean that happier patients are more likely to see the benefits of remaining on treatment.

14.9.15 Avastin® (bevacizumab)

The role of intravitreal Avastin in the management of AMD and other eye diseases remains somewhat controversial. The use of Avastin for treating eye conditions remains an off-label indication. While a small number of countries have allowed reimbursement for Avastin, there does not appear to be any jurisdiction that has registered the drug for this purpose. Indeed, the manufacturer Genentech/ Roche has publicly stated that it will not be submitting the agent for registration nor making the formulation changes that would be required to enable registration.

While governments could decide to register Avastin without the manufacturer's sponsorship, this would most likely require that the registering government accepted all medico-legal risk for its use. In Australia, this would also require significant changes to the system of registration and reimbursement.

In the interim, there remain significant medico-legal concerns about its use, as the administering clinician is typically required to accept all risk for the off-label use of drugs. In mitigating these concerns, clinicians are required to obtain full informed consent to patients, ensuring they are fully cognisant of any risks.

Efficacy
As detailed in Section 14.9.7, the 12[156] and 24[157] month results of a large NIH-sponsored randomised controlled trial (CATT) comparing Lucentis and Avastin in wet AMD demonstrated that the use of Avastin results in non-inferior visual outcomes to Lucentis for the treatment of wet AMD, although some anatomical measures such as retinal thickness slightly favoured Lucentis.

Several other smaller studies (IVAN[145], LUCAS[159], GEFAL[146], MANTA[161], BRAMD[162]) have confirmed the similarity in visual acuity outcomes of the two agents over 12 to 24 months in wet AMD, although again, small differences in anatomical outcomes (e.g. retinal thickness and residual fluid) have favoured Lucentis in a number of these studies.

In the two year analysis of the CATT study, Ying and colleagues[163] found that patients treated with Avastin were more likely to experience sustained visual acuity loss after two years (defined as a loss of 15 or more letters from baseline) compared to people treated with Lucentis (7.4% versus 4.6%, Adjusted Odds Ratio = 1.83, 95% CI, 10.7-3.14, p=0.03). Large randomised controlled comparisons between Avastin and Eylea for AMD have not been conducted.

Safety
When Avastin is used by intravenous administration for the treatment of specific cancers, it has been associated with an increased risk of thromboembolic events, haemorrhage and mortality. The dose used for intravitreal administration (1 to 2.5 mg), however, is at least 150 times less than the dose used for treating cancer.

In CATT, there was a similar overall safety profile for Lucentis and Avastin, and there were no differences in the rates of death, stroke or myocardial infarction.

It should be noted, however, that reliable detection (≥80% power) of even a doubling of risk between drugs for relatively rare events (~2%) required a sample size that was at least twice the 1200 patients enrolled in CATT.[164]

One area of potential concern and continued controversy from the CATT study is that patients treated with Avastin experienced higher rates of serious systemic adverse events, primarily hospitalisation, compared to Lucentis at 12 months (24.1% versus 19.0%, Risk ratio = 1.29, 95% CI = 1.01 - 1.66). This trend continued to diverge at the two year analysis (39.9% versus 31.7%, Risk Ratio = 1.30, 95% CI, 1.07-1.57, p=0.009). As most of the excess events had

not previously been associated with anti-VEGF therapy, controversy continues as to whether this result was due to chance, imbalances at baseline not captured with multivariate analysis, or a truly higher risk.

One retrospective analysis[165] of 77,886 US Medicare claims between 2005 and 2009 (46% Lucentis, 56% Avastin) found an 11% higher overall risk of all-cause mortality in the Avastin group, after adjusting for baseline co-morbidities, demographics and socio-economic status. No differences were seen in the risk of myocardial infarction or ischaemic cardiovascular events. This analysis has been criticised as it may not have adequately accounted for differences in socio-economic factors including smoking status.

In another retrospective analysis in the US[166] involving Medicare claims for 38,718 Avastin and 19,026 Lucentis injections between January 2005 and December 2006, after adjustment for patient characteristics, a significantly lower hazard of all-cause mortality, incident myocardial infarction, and incident stroke was observed with Lucentis therapy compared with Avastin therapy.

Avastin and intraocular pressure
At the annual scientific congress of the Association for Research in Vision and Ophthalmology in Baltimore in May 2017, Atchison et al reported[167] an analysis of more than 23,000 patients on the of the Association for Research in Vision and Ophthalmology comparing intraocular pressure (IOP) changes in people receiving intravitreal Avastin, Lucentis or Eylea injections for wet AMD, diabetic macular oedema or central retinal vein occlusions.

While there were only small and clinically insignificant differences in IOP in the short term, this was not the case for those on long-term treatment receiving more than 25 injections. In this group, 9.5% of people receiving more than 25 injections of Avastin experienced an IOP increase of at least 6 mmHg (and IOP $\geq$ 21 mmHg[xli]) compared to 2% for people receiving Eylea or Lucentis. Professor Mathew MacCumber suggested[168] that this may be due to clogging of the trabecular meshwork from long term exposure to the subvisible particles in Avastin, as previously reported[169,170] and discussed below.

Repackaging issues
Avastin was originally developed for intravenous use for treating certain cancers. It is not formulated for use as an intravitreal injection, nor is it provided in a dose or pack form suitable for use in the eye.

For it to be used as an intravitreal injection, Avastin must be prepared by a compounding pharmacy where a 4 mL vial is broken into multiple smaller doses and repackaged into single dose syringes. This is a manual process, normally performed under laminar flow to reduce the likelihood of contamination.

The compounding of Avastin for intravitreal use results in the production of doses of highly variable and questionable quality. An English study[169] compared the quality and stability of repackaged Avastin from five licensed compounding pharmacies and found:

a) A significant difference in sub-visible particle density between batches from the five suppliers on day one

b) An increase in the particle density between days one and 14 for repackaged product from all suppliers. This increase was not observed with a reference vial.

c) The particle density of all repackaged product and the original control vial exceeded the range specified by the US Pharmacopeia for injectable ophthalmic solutions at day one and day 14. Even in its original packaging, Avastin did not conform to the accepted limits for particle size of ophthalmic injection solutions. The authors suggested that particulate matter may be a contributing factor in some of the reports of clusters of ocular inflammation after intravitreal Avastin.

A US study[170] compared repackaged Avastin from three compounding pharmacies in the USA with Avastin obtained directly from the manufacturer. Analysis revealed that two of the

xlii Elevated intraocular pressure is a key risk factor for the development of glaucoma. Although there is no universally accepted definition of "normal" IOP, a pressure in excess of 21 mmHg would typically be considered as elevated and may justify treatment

three compounded batches had significantly less functional IgG in solution. The same batches also had 10 times the number of micron-sized particulate matter; this was hypothesised to lead to obstruction of aqueous outflow and pressure elevations after intravitreal injection. (This phenomenon has subsequently been observed clinically – see above). This study also demonstrated:

a) significant variation in the concentration and ELISA titre of the drugs

b) significantly lower drug concentration compared to product obtained directly from the manufacturer

c) more protein aggregation in the compounded samples

Perhaps the greatest concern, however, from the compounding of single use Avastin vials, intended for intravenous treatment of cancer, into multiple smaller doses for intravitreal use in multiple patients is the demonstrated risk of contamination. This has resulted in dozens of cases of endophthalmitis[xlii] and blindness globally.

In one notorious episode in the US, 12 patients received contaminated injections from a single compounded batch, which resulted in 11 eyes being blinded. Seven of these patients ultimately required evisceration[xliii] or enucleation[xliv] of the eye.[171] Despite widespread publicity of these cases and the release of new compounding guidelines in 2012[172], further cases of contamination continue to occur around the world[173], although to date, none has been reported in Australia.

xliii Serious inflammation of the interior of the eye, usually due to infection. Serious cases can lead to total blindness.

xliv Removal of eye contents

xlv Complete removal of the eye

Elisabeth Macdonald

Now in her 80s, amateur cellist Elisabeth Macdonald describes herself as “one of the lucky ones”. Injections for wet macular degeneration have worked miracles in saving her sight. It has meant Elisabeth can still drive, travel and, best of all, read her music scores.

Elisabeth was initially diagnosed with dry age-related macular degeneration (AMD) in her right eye in 2005, which turned to wet in 2010. The left eye developed wet AMD two years later.

Although she started treatment in 2010 for wet AMD, Elisabeth was one of the 5% to 10% of patients who did not respond adequately to treatment. Her vision deteriorated and this was compounded by unrelated corneal complications and cataracts.

After changes to the Pharmaceutical Benefits Scheme in late 2012, which allowed ophthalmologists to switch patients between registered drugs for wet AMD, in 2013 Elisabeth changed to a new treatment with remarkable results.

“There was a time my eyesight got very poor. That’s why I’m so thankful for the injections I am now on. I got to experience what it is like to live with vision loss,” says Elisabeth.

“Once on the new treatment my sight improved dramatically. I can read without a magnifier, drive confidently and, most importantly, read my music again.

“I know I have been lucky and that not everyone has had the spectacular results I have. I asked my specialist if all his patients showed the same improvement, to which he replied that 30% have a marked improvement, 40% are stable and the rest are smokers!”

Elisabeth now receives injections in both eyes every eight weeks and is keen to point out that the injections are definitely not as scary as they sound.

“I know people can be terrified with the idea of having an injection into the eye. It can be a confronting thought. I tell everyone not to be afraid as it really isn’t that bad,” says Elisabeth. “Living with macular degeneration is an inconvenience, but it’s not a major life sentence.”

Elisabeth puts her positive attitude down to her mother. “My mother had macular degeneration and completely lost the sight in one eye and had limited sight in the other. She faced vision loss, as she did with everything in life, with an amazingly positive attitude. I’m so thankful that aside from inheriting macular degeneration, which she has passed on to three of her four children, I have inherited her ‘can do’ attitude. Being able to see the good in a situation has served me well my whole life,” says Elisabeth.

“I know people can be terrified with the idea of having an injection into the eye. It can be a confronting thought. I tell everyone not to be afraid as it really isn’t that bad. Living with macular degeneration is an inconvenience, but it’s not a major life sentence.”

15. Diagnostic developments

The early stages of AMD typically do not exhibit any obvious symptoms to the patient, although the initial signs at the back of the eye can be easily seen by an optometrist or ophthalmologist during a normal, comprehensive eye exam using standard equipment.

Vision loss from late AMD can be insidious, and patients may initially be unaware of the symptoms if late stage disease is present in only one eye. This highlights the importance of patients with early disease being instructed on the correct use of an Amsler grid, one eye at a time, to help detect changes in vision. (See also Section 5.2d)

The improved accuracy of diagnosis has been a major advance in the management of macular degeneration.

Ophthalmoscopy and retinal fundus photography

Historically, ophthalmoscopy and retinal fundus photography have been the mainstay of initial diagnosis of early AMD. Serial retinal photographs are especially useful to track the progression of early stage disease. Retinal cameras are now relatively inexpensive and are widely available in optometry practices. Surprisingly high-quality images can now be obtained with inexpensive detachable lenses for smartphones. These provide acceptable images taken by non-optometric staff in remote locations where traditional retinal cameras are unavailable and/or too difficult to transport. Retinal photos can then be emailed to an optometrist or ophthalmologist for review and referral if required.

Fundus autofluorescence

In recent years, the use of colour filters has greatly enhanced the interpretation of the retina's natural autofluorescent properties to map the presence of certain materials (fluorophores) in the retina. In particular, fundus autofluorescence has improved identification of lipofuscin, a key retinal waste product that is a characteristic feature of ageing. It is especially valuable to determine the health of the (RPE) with the characterisation of geographic atrophy, the end stage of dry AMD demonstrates areas of decreased autofluorescence due to loss of RPE cells.

Fundus fluorescein angiography (FFA)

FFA is only performed in ophthalmology clinics and involves the intravenous injection of a fluorescent dye into the arm. The dye then passes through the venous system, including the retina, where it can be photographed over a 10 minute period under different wavelengths of light to provide sequential images of choroidal and retinal blood flow and leakage. Despite a small but significant risk of serious complications, fluorescein angiography remains the gold standard for the initial diagnosis of neovascularisation. It can also be especially useful to exclude non-AMD causes of neovascularisation.[174]

Indocyanine green angiography (ICG)

This is similar to FFA but uses a dye with different absorbance properties. It is especially useful to distinguish deep choroidal leakage, particularly when associated with polypoidal choroidal vasculopathy (PCV), a form of macular degeneration that can be difficult to treat, and is more prevalent in certain Asian populations. The procedure is not routinely available but may be used by some retina specialists.

Optical coherence tomography (OCT)

In the past 20 years, the remarkable development of OCT has provided a rapid, non-invasive means of producing exquisite, high resolution[xlv] cross-sectional images and volumetric three-dimensional analysis of the retina. It is useful at the initial diagnosis of wet AMD to give an accurate baseline measurement

xlvi The latest OCT machines provide a resolution of a few microns

of retinal architecture, including the presence of blood or fluid within or under the retina. While OCT is now funded by Medicare for the initial diagnosis[xlvi] of wet AMD and other neovascular conditions to demonstrate eligibility for PBS funded treatments, it should ideally be used in combination with fluorescein angiography for this purpose. This is because angiography is still the preferred diagnostic technology to help exclude non-AMD causes of neovascularisation such as myopic macular degeneration, birdshot choroidopathy, pseudo-xanthoma elasticum, which could respond differently to treatment.[166]

Perhaps the most important function for OCT is the monitoring of response to anti-VEGF treatment for wet AMD to inform decisions concerning the need for, or timing of, subsequent injections. OCT is now globally considered to be standard of care for this indication; the use of individualised treatment with Treat and Extend or PRN dosing regimens would simply not be possible without the technology. OCT is reimbursed for this use in almost all countries that provide subsidised health care. **It is therefore of great concern that in Australia, Medicare funding is still not available for OCT scans to direct ongoing anti-VEGF treatment.**

A recent development with OCT is the addition of software that allows comparison of sequential scans taken a fraction of a second apart to map blood flow at different levels in the retina, a technology known as OCT-Angiography or OCT-A. At this time, OCT-A does not appear to provide any additional diagnostic sensitivity for wet AMD, although it may play an important role in future research.

As a result of user-friendly interfaces and falling prices, retinal photography and OCT imaging are increasingly used by optometrists to enable earlier detection as part of a normal eye test. This means that most people can have early stage disease monitored locally in the primary care setting without the additional cost, travel and waiting times often associated with specialist care.

New diagnostic directions

Several diagnostic technologies are also being validated to determine whether they can reliably determine biomarkers of early disease and particularly to help predict people at greatest risk of disease progression. Earlier detection will firstly enable greater clinical attention on people who are more likely to lose vision. Equally important, however, is that earlier identification of changes that reliably predict disease progression will enable better selection of patients for clinical trials and the use of different earlier, clinical end points. This will potentially accelerate clinical trials and enable the use of smaller numbers of people to produce more meaningful results.

OCT

The increasing resolution of OCT technology is allowing more detailed analysis of early changes in the structure of the retina. For example, Guymer and colleagues[176] have reported that the use of high resolution OCT enables the identification of subtle changes in the retina, not visible with retinal photography, that occur before the development of drusen-associated atrophy. It appears that these changes, termed nascent geographic atrophy, can not only predict people who are more likely to develop sight-threatening geographic atrophy, but could also be used as an earlier surrogate end point for clinical trials that are targeting earlier disease.

Microperimetry

While standard visual acuity measurement is the cornerstone of functional testing of people with AMD, the tests only measure the function of cone cells in the central foveal area, typically in bright light. In early AMD, rod photoreceptors degenerate earlier and more rapidly than cones. The greatest loss of rod function occurs just outside the central foveal area, but this is not picked up by standard acuity testing. Microperimetry, is a non-invasive method to measure rod function in the area immediately outside the central fovea, in a variety of light conditions. At this time, microperimetry is primarily a research tool, but it is increasingly being used to help identify people with early disease at high risk of progression. It can also be used to help identify an area known as the preferred retinal locus (PRL), which people with

xlvii A maximum of one Medicare claim per year can be made for the initial diagnosis of wet AMD or certain other neovascular conditions to determine if the requirements relating to the PBS listing are fulfilled. In most situations, this means that a maximum of two OCT scans will be funded in the person's lifetime

central vision loss may be able to use to improve reading speed by fixating (focussing) on an area with better function, just to the side of the fovea.[177]

Dark adaptation

It has been known for many years that people with AMD and many other macular conditions tend to take longer to adapt to darker conditions. It also appears that these changes occur before any loss in normal visual acuity occurs. Significant research effort is being directed to improve ways to measure the response to changes in light as a means to identify people at high risk of progression. Initial tests tended to take up to an hour to perform, which is unacceptable in clinical practice. Recent modifications have significantly reduced the time required, and the combination of dark adaptation with microperimetry using light with different colours is being investigated to improve the reliability of the test.[178]

The impact of early detection

Office monitoring

Evidence from the pivotal ANCHOR and MARINA studies clearly demonstrated that people with wet AMD achieve significantly better outcomes if treatment is begun when the neovascular lesion is small or immature, and when the baseline vision is still good.

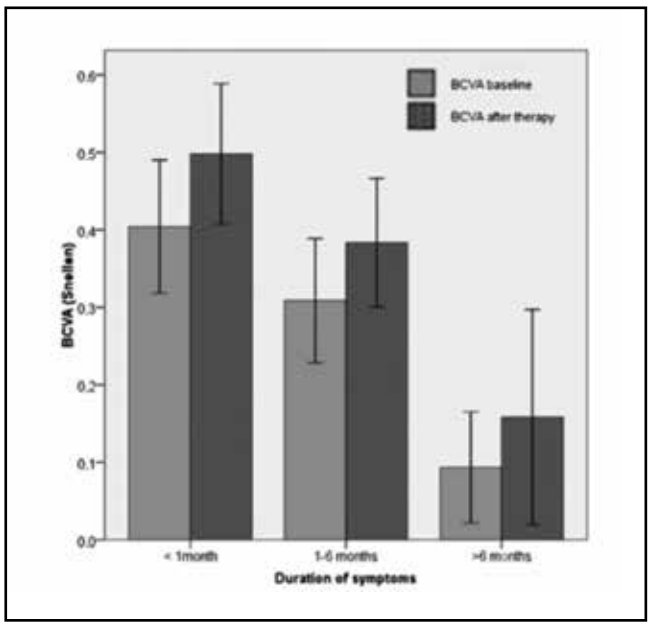
In CATT, a larger area of neovascularisation was associated with worse visual acuity at one year, less gain in acuity at one year and a lower proportion of people gaining three or more lines of vision.

A small retrospective study in 45 patients with wet AMD showed that duration of symptoms of less than one month was associated with a significantly better visual acuity following treatment compared to people with symptoms of longer standing, although the number of letters gained was similar between groups.[88]

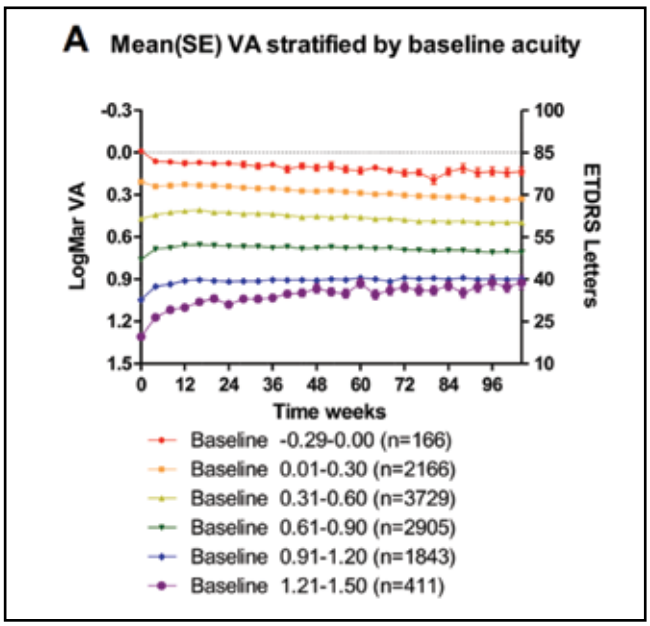
Perhaps the most impressive demonstration of the importance of early detection and treatment was in a detailed analysis[3] of real world treatment of 11,135 patients receiving 92,976 injections in the UK. While people starting treatment with poor vision may have gained the highest number of letters, their final vision typically remained poor (Fig 9. purple line). In contrast, people starting treatment while their vision was still good to excellent may not necessarily have gained vision (due to a ceiling effect), but most importantly, they maintained good to excellent vision (Fig 9. red line) over two years.

This analysis also highlights that it is the final vision achieved, rather than the amount gained, that should be the primary objective of treatment. Although people with poor starting

Impact of delay in treatment. Longstanding symptoms with poor baseline visual acuity do not recover good vision.



Visual acuity outcomes in the UK stratified by visual acuity when starting treatment.[3]



A LogMar of 0 or 85 ETDRS letters is equivalent to 6/6 vision while LogMar of 1.0 is 6/60 or 35 ETDRS letters (legal blindness)

vision will commonly be quite satisfied with the improvement achieved following treatment, earlier intervention could have resulted in much better outcomes.

Important diagnostic research, much of which is being conducted in Australia, is focussing on the use of so-called multi-modal imaging, where a battery of tests can be performed to not only diagnose disease early, but to determine whether there are certain physical appearances (phenotypes) or functional tests that can help predict which patients are at greatest risk of progression to late stage disease. This is important for a number of reasons:

a. Since only a proportion of people with early stage disease progress to late stage, there are potentially substantial efficiencies to be gained if the remainder can be determined to be low/no risk.

b. Currently, a diagnosis of early AMD frequently results in substantial emotional stress and even depression for the patient and family, due to the uncertain potential for vision loss. Knowledge that the person falls into the low/no risk category will remove this stressor.

c. Determination of people at high risk of progression will enable these people to receive more intensive testing and support

d. Clinical trials of new treatments can be accelerated significantly using fewer patients if recruitment is limited to people at highest risk of disease progression. This has been a significant issue for the development of new treatments for dry AMD as it can take many years to determine whether a new therapy is of any benefit.

Home monitoring

While RANZCO recommends that people with early stage AMD should be reviewed by an optometrist at least every 12 months[86], it is critical that patients understand that they need to self- monitor at home to help detect sudden changes in vision in between optometric reviews. The standard self-assessment tool, the Amsler grid, has been in use for almost 70 years, but until recently, it had a low clinical relevance for AMD as there were no treatments available. Studies assessing its sensitivity and specificity for detecting progression to wet AMD have had highly variable results. However this may partly be due to inconsistent or incorrect use. Nonetheless, its successful use depends on a patient subjectively identifying that the appearance of the grid has changed and then scheduling an appointment with the ophthalmologist.

A number of new technologies can remotely monitor vision in the home and send an automatic alert to the ophthalmologist if the patient experiences a change in vision using a more objective measure.

The ForeseeHome® monitoring program (Notal Vision) was used in the AREDS2 trial and led to earlier detection of conversion from dry to wet AMD. A follow-up study showed that the device resulted in changed management of patients and better outcomes.[179] The device, which is FDA approved, uses objective measurements of hyperacuity to detect changes in vision, and any significant changes from baseline are automatically notified to the treating ophthalmologist. In the US, the device requires a doctor's prescription and the cost is covered by some insurance companies and by Medicare for eligible patients. It is not available in Australia.

A second device which has also received FDA clearance is the myVisionTrack® app. This smartphone or tablet accessible app uses shape discrimination testing that has been validated in several studies.[180,181] It also sends an alert to the prescribing ophthalmologist when results suggest a drop or change in vision. Use of the device costs US$19.95 per month although it is not available in Australia at this time.

Gordon Stace

It was on a drive home to Sydney after holidaying in South Australia that Gordon Stace knew something wasn't quite right with his vision. Straight lines started to appear wonky – the guard rails, telegraph poles, road markings and bridges.

Gordon says, "I immediately went to see an ophthalmologist and he arranged for me to see a retinal specialist straight away. I was there the next morning at nine o'clock and the diagnosis was wet macular degeneration in my left eye."

Gordon's diagnosis was in 2003, before anti-VEGF injections were available to treat wet-macular degeneration.

"After discussion with my specialist about treatment options, it was decided to monitor the eye every two months. Then after three years my specialist recommended that we start injections in the left eye to maintain my sight," he said.

Gordon continued with this treatment on his left eye and at every appointment his ophthalmologist would check his "good" right eye. It was at one of these appointments in 2007 that the specialist noticed a bleed in that eye too. It was just at the time that treatment for wet macular degeneration was listed on the Pharmaceuticals Benefits Scheme.

"While having the bleed in the right eye wasn't great news, I was lucky because we picked it up so early. I began injections in that eye immediately and they have held the sight in my right eye ever since."

Describing his experience with macular degeneration as a 14 year journey, Gordon, now in his early 80s, says that his macular degeneration hasn't slowed him down. He's still able to do most things.

"I have always worked as a structural engineer, a profession I have enjoyed being part of for a lifetime, and still practise. When drafting, I do need to use a binocular magnifier, but my sight is still good enough to be out on work sites, navigating planks and checking on details."

Gordon is very positive about the ever increasing research into macular degeneration and the advancing knowledge regarding the efficacy of new treatments.

"Injections have revolutionised the treatment for macular degeneration and I have been lucky to benefit from this. A needle in the eye might sound terrifying, but in reality the use of anaesthetic drops, and the methodology of the actual injection, make it a quite painless experience. Sometimes the anaesthetic drops do tend to dry the eyes and make them itchy, but that can be countered with moisturising ointment. Any discomfort involved is a small price to pay for maintaining one's sight!" said Gordon.

"Injections have revolutionised the treatment for macular degeneration and I have been lucky to benefit from this."

16. Treatment burden, injection fatigue, patient expectations and compliance

While anti-VEGF treatment has proved to be highly effective in preserving and, in many cases, improving vision, there is nonetheless a substantial personal burden in receiving treatment. This burden can be emotional, financial and physical.

Emotional burden: although eye injections usually impose minimal, if any pain, for some, the thought of an injection in the eye can be stressful, especially the first few times.

Financial burden: while the registered anti-VEGF drugs are subsidised through the PBS, the majority of people are treated privately and usually incur regular out-of-pocket costs for the consultations, diagnostic tests and the injection procedure itself. For some people, out-of-pocket costs can be high, especially until the Extended Medicare Safety Net applies. Transportation costs and, for people living in regional or remote areas, overnight accommodation may be needed for the patient and a carer.

Physical burden: The higher the number of injections, the higher the overall risk of experiencing sustained IOP elevation[182], retinal detachment and sight threatening endophthalmitis.

Time burden: While the injection itself may only take a few minutes, patients will commonly set aside a full day for the procedure or more if they need to travel long distances.

The burden of treatment may affect the ability of some patients to continue treatment which is critical to saving sight.

The fact that those with good starting vision typically do not experience any meaningful improvement in vision following treatment (and some may even have a small drop in vision) means that some of these people choose to stop treatment as they do not perceive any benefit. If they stop treatment, however, reactivation of neovascularisation and vision loss invariably occurs. Similarly, people with poor starting vision will frequently notice several lines of improvement in vision, but then think that they are ‘cured’.

They may also decide to stop injections prematurely, with further reactivation of leakage and vision loss.

This highlights the importance of educating patients that the primary purpose of injections is to preserve existing vision. Any improvement should be regarded as a bonus.

PART C – THE OUTCOMES

17. Long-term outcomes in Australia and globally

While there is no universal register of treatment outcomes in Australia, a large, cloud-based register known as Fight Retinal Blindness! (FRB!) which logs real-world outcomes from a number of ophthalmologists has been in place since 2007.

The long term results from FRB! of anti-VEGF treatment in 1212 eyes in 1047 patients starting treatment at least five years earlier were reported in 2015.[183] These injections were provided by 23 ophthalmologists in Australia, New Zealand and Switzerland, although 83% of the injections were given in Australia.

The mean baseline (presenting) visual acuity (i.e. when treatment began) was 55.1 logMAR letters (approximately 6/24). Key findings included the following:

- the average Australian patient held vision that was as good or better than their starting vision for six years. This compared to four years for the US[183] and only two years for the UK[3], as reported in other studies
- 40% of Australian patients maintained driving vision (6/12 or better) after seven years of treatment compared to 23% in the US
- 60% of eyes that started treatment with an acuity of 6/12 or better maintained this level of vision over seven years. This again highlights that when people start treatment early, and remain on treatment with adequate frequency, outstanding outcomes are possible
- 45% of Australian patients remained on treatment for at least five years
- a median of six injections and nine visits were recorded in the first year, with five injections per year and seven to nine visits per year recorded subsequently
- Less than 10% of eyes dropped out of the study in the first two years of treatment
- patients who started treatment early, tended to remain on treatment for longer, indicating that they were continuing to receive benefit from treatment.

Notably better long-term outcomes were reported in this study compared to other similar studies from other countries. Comparisons between these studies are not necessarily precise due to different methodology and reporting methods but some analyses are informative.

For example, in the seven year follow up of the ANCHOR, MARINA and HORIZON studies (known as the SEVEN-UP study)[184] which included 65 eyes followed for seven years, only 23% achieved a VA equal to or better than 6/12, compared to 40% of 131 eyes in the FRB! study. There was also a mean loss of 8.6 letters in SEVEN-UP over seven years compared to only 2.6 letters in FRB! This is despite the fact that in MARINA and ANCHOR, patients were treated with monthly injections for the first two years of the study. A major difference between the studies was that patients in FRB! received twice as many injections in the latter three years compared to SEVEN-UP, highlighting that treatment needs to be maintained at sufficient frequency in the longer term to preserve vision.

In a large observational study in the UK[3], the reported mean visual acuity had declined by two letters from a baseline of 58 letters after only three years of treatment. By contrast, in FRB!, eyes with a baseline VA of 60 letters that were followed up for five years still had no mean loss of acuity. In the UK study, where clinicians almost universally use the PRN regimen, the mean number of injections was lower, while the number of visits was greater compared to the FRB! study, where most clinicians use a “treat & extend” approach.

In the five-year follow-up of the US CATT trial[185], patients were released from the CATT clinical

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xlviii In the original CATT study, patients were initially randomly assigned to one of four treatment groups to receive either ranibizumab or bevacizumab either monthly or as needed (PRN). At one year, patients initially randomised to monthly treatment were further randomised to stay on monthly treatment or move to PRN, on the same drug as year one

trial protocol[xlvii] at the end of two years and then treated using standard care, with most (91.3%) continuing to receive care in a CATT centre. They were then recalled at five years to assess results. Despite the good outcomes achieved following the initial two years of intensive monitoring and aggressive treatment via strict clinical trial protocols, outcomes fell away when patients received standard care. Although 50% of eyes maintained visual acuity of 6/12 or better at five years, the mean change in VA from baseline was three letters lost, with 11 letters lost from the two year period until the mean 5.5 year follow-up. During the follow-up period, patients were still seen regularly (mean of 8.0 visits in year three, 7.2 in year four and 6.5 in year five) although fewer injections were given (mean of 4.8 in year three, 4.5 in year four and 4.0 in year five), with a mean total of 13.3 injections given in year three to five. This compares to 15.2 injections given in the FRB! trial.

PART D – THE FUTURE

18. Future research

Although the introduction of anti-VEGF treatment has revolutionised the management of wet AMD, this treatment is only appropriate for about 10% of people with AMD. Key areas of unmet medical need exist for several areas:

a. improved diagnostics to better predict those who are at greatest risk of disease progression

b. treatments for people with early AMD to prevent or slow progression to vision-impairing disease

c. treatment for dry AMD (geographic atrophy)

d. improved treatments for wet AMD, with reduced treatment burden (fewer injections, other modes of administration, lower cost of treatment) and higher efficacy

e. improved treatments to restore vision in people who have already lost vision.

Early AMD

Since the early signs of AMD (drusen and pigment changes) will often appear many years before the onset of obvious symptoms or sight-threatening complications, there would be ample opportunity to intervene with a treatment aimed at early stage disease, if one existed. Other than diet and lifestyle modifications discussed in Section 9, there is currently no treatment that has been shown to slow or reverse the early changes seen with AMD.

To address this, numerous attempts to use laser to remove drusen have been tried over many years, but none has proved to be successful. Indeed, in a randomised, multicentre prospective trial of 240 people with wet AMD or geographic atrophy in one eye, but only drusen in the other eye, not only was grid laser treatment of the eye with drusen ineffective, it dramatically increased the risk of neovascularisation in the treated eye at one year (15.8% versus 1.4% p=0.05). In addition, treated eyes showed a much higher rate of vision loss.[186]

"Retinal rejuvenation therapy" – 2RT laser
A different approach is with a novel, ultra-low energy "nanosecond" laser, now undergoing a pivotal phase III study, following promising early phase pilot trials. The laser, which was developed in Adelaide, uses very short (3 ns) pulses of 532 nm spots of 400 µm diameter. Twelve spots are placed in a clock face pattern about 2,000 µm from the central fovea. The spots do not specifically target drusen, as the effect appears to be widespread. The energy used is about 1,000 times less than conventional laser for treating diabetic macular oedema and the pulses are 33 million times shorter in duration.

A non-randomised pilot study[187] showed that at 12 months follow-up, the nanosecond laser is able to reduce or remove drusen in 44% of treated eyes and that visual acuity and macular sensitivity, measured with flicker perimetry, may be improved. Short-term safety also appears good with no clinically visible lesions to the lasered areas. Interestingly, unilateral treatment also appears to have reduced drusen size in 22% of fellow (untreated) eyes.

A large, three year, double-masked randomised controlled trial[188] (LEAD) is evaluating the safety and efficacy of the treatment with specific emphasis on whether the treatment has any impact on progression to neovascular disease or geographic atrophy. Other research by the same group has shown that when drusen naturally regress, the RPE immediately above the area of regression is frequently the site of future (nascent) geographic atrophy.[176] It will be critical to determine whether the removal of drusen with nanosecond laser unintentionally accelerates the formation of geographic atrophy.

The study is due for completion at the end of 2018. If this treatment proves successful, it will be the first intervention available for early AMD.

Drug treatment for early and dry AMD

Numerous drugs have been tested for the treatment of early and dry AMD. Many have demonstrated encouraging short-term efficacy

when trialled in animal models, but have failed when tested in humans. This highlights the major differences that exist between humans and the normal animal models used for drug testing, including mice, rats and rabbits, none of which has a macula.

Most of the treatments under development fall into one of five categories:

- anti-inflammatories e.g. lampalizumab, Zimura® (anti-C5 antibody), Oracea® (minocycline),
- neuroprotective agents
- visual cycle modulators
- choroidal blood flow restoration agents
- stem cell based treatments.

Lampalizumab (Roche)
Until recently, the most promising new treatment for dry AMD had been lampalizumab (Genentech/Roche), a humanised monoclonal antibody targeting complement factor D.

This drug is given as an eye injection every four or possibly six weeks, and blocks a key enzyme in the "complement" immune system which is believed to trigger the development of geographic atrophy. An earlier phase II trial called MAHALO showed that this treatment produced 20% less growth of the damaged area of the macula after 18 months. In a subset of people with a reasonably common gene, 44% less growth of the damaged area was seen.

Two large phase three trials (CHROMA and SPECTRI) to confirm safety and efficacy are underway and include sites in Australia. The initial analysis of the SPECTRI trial was announced in September 2017. Unfortunately, the drug failed to meet the trial's primary end point as it did not demonstrate any difference in lesion size in patients treated with lampalizumab compared to sham treatment. Results from the CHROMA trial were announced in November 2017 and were also disappointing. The future of this agent is now in question.

Zimura (Ophthotech)
A phase II/III randomised controlled trial in 300 people with geographic atrophy is now assessing the safety and efficacy of an injection that inhibits complement factor C5. The study is planned for completion at the end of 2018.

Oracea (Galderma)
The US National Institutes of Health is sponsoring a study investigating the use of minocycline, an old antibiotic, which has anti-inflammatory properties and appears to reduce the loss of photoreceptors. Initial results are expected at the end of 2018.

Treatments for wet AMD

Although there are now two registered and highly effective treatments for wet (neovascular) AMD, significant research effort continues to develop treatments that can reduce treatment burden through longer duration of effect or less invasive means of administration, or provide a higher efficacy for more people.

Brolucizumab (RTH258 - Novartis)
Brolucizumab has just successfully completed two 96 week phase III registration trials (HAWK and HARRIER) for treating wet AMD. More than 1800 patients were treated with either brolucizumab eye injections or Eylea as follows:

a) brolucizumab injections given every 12 weeks after three initial loading doses given four weeks apart. Where patient response was inadequate, adjusting the dosing to every eight weeks was allowed

b) Eylea given according to label – one injection per four weeks for three injections, then every eight weeks

In all, 57% and 52% of the brolucizumab patients were maintained exclusively on the 12-weekly regimen through to week 48 with non-inferior changes in visual acuity and comparable safety profile, when compared to Eylea.

It should be noted that in real-world practice, many patients treated with Eylea and Lucentis can also be treated effectively on a 12-weekly regimen after extension using a Treat and Extend approach rather than the fixed eight-weekly regimen used in the HAWK and HARRIER trials. It will be interesting to see whether brolucizumab can be extended longer than 12-weekly when used with individualised T&E dosing.

Abicipar (DARPin – Allergan)
Two large phase III trials assessing this agent with injections given every eight or 12 weeks began in 2015. The agent has a small

size, high potency and a long half-life inside the vitreous, with an expected longer duration of effect. Initial top-line results are expected in 2018 with completion slated for mid-2019.

Gene therapy
Several companies and university research units are currently testing different gene therapies for wet macular degeneration. Unlike gene therapies for monogenic[xlviii] diseases where the intention is to replace the disease-causing defective gene with a correct version of the gene, the objective of gene therapy in the polygenic[xlix] wet AMD is to insert a gene behind the retina which instructs the retina to produce a protein with anti-VEGF properties over an extended period, a so-called "bio-factory". This treatment essentially has the same function as anti-VEGF injections, but can hopefully be performed as a one-off procedure, or at least one that lasts for many years.

In a phase IIb trial in 32 patients[189], the largest gene therapy trial to date in wet AMD, patients received either:

a) an adeno-associated virus vector implanted under the retina to carry genes encoding for sFlt1 protein, combined with Lucentis injections as needed

b) Lucentis monotherapy as needed

The gene therapy and the surgery to implant the gene were found to be safe and visual acuity was maintained over 52 weeks. The distribution of the sFLT1 protein outside the target tissue in the retina was limited and transient. Most patients in the study had received prior treatment with anti-VEGF injections, possibly reducing the potential for large vision gains with the gene therapy. The study was primarily designed as a safety study and no major impact on visual acuity or retinal thickness was expected *a priori*. After excluding three control arm patients who lost more than 20 letters, there was no statistically significant difference in visual acuity between the two groups. While the gene therapy group had a trend towards fewer Lucentis treatments, results were inconsistent. The company has restructured and is now testing modified versions of the therapy.

Other treatments for wet AMD
In contrast to the existing anti-VEGF agents which only block VEGF-A, Ophthea, a Melbourne-based company, is developing OPT-302, a compound that blocks VEGF-C and VEGF-D. Initial phase I/IIA trials using OPT-302 alone or in combination with Lucentis in treatment naive patients are ongoing.

Despite highly promising results in smaller phase II trials, an phase III trials of agent (Fovista – Ophthotech) blocking platelet derived growth factor (PDGF) did not show any additional benefit when added to Lucentis, when compared to Lucentis given alone. The agent is no longer being pursued for this indication.

An eye drop (squalamine – Ohr Pharmaceuticals) with anti-VEGF and anti-PDGF properties has been shown to further improve vision in many people who are also receiving anti-VEGF injections. It does not appear to be sufficiently effective as monotherapy nor does it appear to reduce the number of injections required. A phase III trial (MAKO) in 200 patients commenced in 2016 has recently found that adding squalamine provides no additional benefit over injection monotherapy.

Several companies are also developing novel delivery devices including refillable pumps, slow-release microspheres and gels that may enable the delivery of existing drugs over an extended period to reduce the number of injections needed.

Cell replacement therapy (stem cells)

Once RPE cells and photoreceptors have died following wet AMD or geographic atrophy, they are not replaced with new cells. Vision loss is therefore permanent.

In an attempt to replace lost RPE and photoreceptors, several centres are investigating the use of transplanted RPE cells derived from stem cells. Since the loss of RPE cells also leads to the permanent loss of photoreceptors, there is also a significant effort to grow new photoreceptors from stem cells, although this work is not as advanced.

The first human trial on the use of embryonic stem cell-derived RPE cells was reported in 2012[190] in two patients with major vision loss – one with AMD and one with Stargardt's disease.

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xlix Diseases that are due to a specific gene defect, such as Stargardt's disease, Leber's congenital amaurosis

l Influenced by a number of different genes, each of which may influence risk without necessarily causing the disease

This group has subsequently expanded its trials to 18 patients using increasing doses of cells, with a median follow-up of 22 months.[191] There was no evidence of adverse proliferation, rejection, tumour formation or serious ocular or systemic events. While the study was not designed or powered to measure efficacy, there was evidence of an improvement in vision in some patients. A larger phase Ib/II safety and efficacy study in 150 patients is planned to start in late 2017 with primary completion in 2020 and long-term follow-up to 2026.

To avoid some of the ethical issues relating to the use of embryonic stem cells and the need for lifelong immunosuppression, many centres are now developing and testing RPE cells derived from induced pluripotent[i] stem cells (iPSCs) using techniques first developed by Yamanaka[192], for which he received a Nobel prize in 2012. This technique is able to reprogram already differentiated somatic (body) cells back into stem cells which then have the ability to be "coaxed" into becoming any type of cell. This approach not only avoids any potential ethical issues relating to the use of embryonic stem cells, but can enable the use of autologous cells (taken from the same person that is to be treated) to reduce the likelihood of cell rejection and the need for lifelong immunosuppressants.

The world's first clinical study to evaluate human iPSC derived cells occurred in 2014 at the Riken Institute and Kyoto University in Japan in a patient with macular degeneration. Some skin cells from a patient with severe vision loss from macular degeneration were extracted and converted to stem cells using the Yamanaka technique and then coaxed to become RPE cells. These cells were then transplanted into an eye of the same person to replace the RPE cells destroyed by AMD. The treatment reportedly improved vision.[193] Treatment of a second patient was halted when two small genetic changes were identified in the patient's iPS cells and the RPE derived from them. While there was no evidence that either mutation was associated with tumour formation, the trial was suspended. The technique was also very slow as the cells took many months to grow and validate, and considered too expensive to be viable on a wide scale for common diseases such as macular degeneration[194].

In an attempt to improve the practicality and reduce the costs of iPSC treatment, the same researchers subsequently created banks of stem cells derived from skin cells from many donor adults to produce allogenic graft tissue for implantation into another person. By matching a protein known as major histocompatibility complex (MHC) on the surface of the harvested skin cells with the MHC of the recipient, they aim to attenuate the immune response which would otherwise occur with the implantation of cells derived from another person, thereby reducing the likelihood of rejection. The technology has been successfully trialled in monkeys and an *in vitro* human model. Approval to start human trials with this technology was granted in February 2017.

While the use of cell replacement therapy will not cure AMD, it offers hope to those people who have already lost significant sight from the disease.

Warning about unproven stem cell treatments

While the use of treatments derived from stem cells offers great promise, a cautionary note is justified. Taking advantage of regulatory loopholes in many countries regarding the use of autologous cells (cells harvested from a patient to be used for treating the same patient), some companies have been offering so-called stem cell treatment for people with macular degeneration using undifferentiated stem cells taken from adipose (fat) tissue, which are then injected into the eye. As these cells have not been differentiated into retinal cells, they have the potential to become any type of cell, including non-retinal cells or even tumour cells.

In a recent case in Florida, three women with reduced but still functional vision from late stage macular degeneration were injected in both eyes with undifferentiated stem cells taken from their own fat.[195] All three women paid US$5,000 to the clinic for an unregistered procedure that had never been studied in a clinical trial, lacked sufficient clinical data and, remarkably, was performed in both eyes on the same day. All three women were rendered blind by the procedure, experiencing retinal detachments and with severe vitreoretinopathy in all treated eyes. After one year, the patients' visual acuity ranged from 6/60 (legal blindness) to perception of light only. At least one of the patients mistakenly thought that the treatment was part of a clinical trial.

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[i] Able to become any cell type in the body

19. The data revolution

The development of new and improved treatments as well as the monitoring of disease symptoms and treatment outcomes with existing therapies is poised to undergo major change as a result of a revolution in the capture and use of data. While the use of massive datasets carries significant potential privacy concerns, if properly managed, the opportunities to better understand the response to new treatments are substantial.

A few examples of how improved data collection may change medical practice and research in the near future include the following:

- The availability of affordable smart devices such as phones and watches can enable the capture and distribution of real time, accurate patient data. Apps on phones will enable patient reminders for appointments or taking drugs, and also allow easy collection of patient feedback, such as changes in symptoms and treatment side effects. Wearable devices will allow the collection of real time, continuous individual physiological data with little or no input from the patient, and irrespective of the patient's location, which can then be automatically sent to the treating clinician or study coordinator.
- The capture of quality of life data such as mobility, using motion sensors and GPS tracking, will increasingly be used to determine the impact of a treatment, enabling a more holistic evaluation of a treatment's benefit, rather than crude, and often misleading data such as simple visual acuity.
- Other devices such as the ForeSightHome monitoring system are already being used to provide ophthalmologists with real time objective data on visual function and disease progression, without the patient leaving the home, to enable earlier intervention.
- Linking treatment response and other data with patients' genetic sequencing may also enable the use of gene-directed treatments with higher efficacy and greater cost-effectiveness.
- Google has developed a contact lens that can continuously measure blood sugar, which could help to better characterise the risk of diabetes and diabetic retinopathy and response to treatments.
- Other devices such as drug pumps will be able to monitor drug levels or physiological response to treatment and adjust dosing accordingly, again with real time dissemination of data to clinicians or researchers if appropriate.

In 2014, the federal government's Financial System Inquiry (the Murray inquiry) recommended that the Productivity Commission should inquire into the benefits and costs of options for increasing availability of and improving the use of public and private sector data by individuals and organisations. In addition, the 2015 Harper Review (the Harper report) of Competition Policy recommended that the government consider ways to improve individuals' ability to access their own data to inform consumer choices.

In response, the Productivity Commission conducted an inquiry, with public hearings and submissions, to report on data availability and use. It was released in May 2017.

Key findings include:

- Australian data frameworks and legal protections are grossly outdated and need major reform.
- The use and value of Australia's data are diminished greatly by a lack of trust by both custodians and users regarding data access processes and protections.
- Reforms require moving from a system based on risk aversion and avoidance to one based on transparency and confidence in data processes, treating data as an asset, not a threat.

There is a need for the creation of a data sharing and release structure that indicates to all data custodians a strong and clear cultural shift towards better data use that can be utilised for the sharing or release of higher-risk datasets.

20. Future challenges

While Australia is producing arguably the best treatment outcomes in the world, there remain a significant number of challenges and areas for improvement.

a) Macular degeneration as a major chronic disease.

In June 2017, the COAG[li] Health Council issued the *National Strategic Framework for Chronic Conditions,* prepared under the auspices of the Australian Health Ministers' Advisory Council. This document presents high level guidance to all governments to deliver a more effective and better coordinated response to the growing burden of chronic conditions.

This framework is in response to the major shift in the past 40 years away from the episodic treatment of infectious diseases and injury towards chronic conditions requiring greater attention to prevention activities and coordinated management. As a result of changing lifestyles, chronic conditions are occurring earlier in life, but people are also living longer, meaning that many people will require more health services for longer, placing great strain on the sustainability of the entire health system.

A major focus of the Framework is the role that prevention can play to significantly reduce the volume and severity of chronic conditions, delivering long-term cost-savings and better outcomes. In addition, when treatment is needed, outcomes are typically better with early intervention. Finally, if a chronic condition results in morbidity or disability, every effort must be made to intervene early to reduce the impact of the condition including mental health problems, and reduce the ripple effects to the person's family and wider community.

By every measure, macular degeneration should be considered a major chronic disease, yet it is rarely, if ever mentioned in discussion or policy on the topic. Although the federal government has provided significant funding for treatments for age-related macular degeneration since 2007, the disease is still not recognised as a priority chronic disease. Such an acknowledgment would facilitate an appropriate shift in policy focus, leading to a greatly needed allocation of resources to support disease awareness, promotion of risk reduction measures, earlier intervention, improved referral pathways and better support for people who have unfortunately still lost vision.

b) Falling support for research

Despite having some of the world's leading researchers in retinal disease, the levels of government funding for research in the area are falling. In 2016, NHMRC only funded two AMD projects totalling $885,000 compared to 150 cancer research projects totalling over $145 million.

c) No national register of AMD

Currently, only those people with neovascular AMD – approximately 10% of the total AMD population – are able to receive proven treatment with anti-VEGF injections. A national register of people diagnosed with AMD, regardless of the type or stage of disease, could provide a number of major benefits and improve outcomes.

- A national register would serve as a source of patients for large scale clinical trials, and could encourage investment from international companies in medical research.
- A register could facilitate faster rollout of new treatments when available.
- As many future treatments are likely to be appropriate for certain genetic variants only, availability and reimbursement will probably be restricted based on genomic testing. The progressive development of a national register including genetic data would enable targeted treatment delivery once an appropriate treatment became available. Without a register, there would likely be a chaotic rush for gene testing to determine eligibility for a specific gene-based treatment.
- A register would allow comprehensive follow-up of treatment outcomes based on a range of demographic, socio-economic, geographic or genetic factors, and enable improvements in the delivery of care.

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lii COAG – Council of Australian Governments. An intergovernmental organisation with representatives from the federal government, plus each of the state and territory governments

d) Inadequate data on blindness and vision loss

Although the 2016 National Eye Health Survey estimated the number of Australians with vision loss and blindness, the survey methodology had a major emphasis on determining vision loss due to uncorrected refractive error and untreated cataract, neither of which result in permanent or irreversible vision loss or blindness.

The survey methodology did not include routine pupil dilation or any OCT imaging, which was likely to have resulted in an underestimation of the extent of retinal disease. For example, in people with poor vision and a dense treatable cataract, the cause of vision loss would have been determined to be cataract, when it might have been primarily due to undetected retinal disease.

This survey also did not include many people over the age of 80, where the majority of severe vision loss and blindness from macular degeneration occurs, or people in residential aged care facilities, where significantly higher rates of major vision loss and blindness have been reported in several Australian studies.[196-199]

While Australia does maintain a blind registry based on usage of the blind pension, the registry is likely to be incomplete as many blind people do not register for the blind pension. This is because there are no additional payments if you are already receiving a regular pension.

e) High out-of-pocket costs for many in private care.

As wet age-related macular degeneration is primarily a disease affecting people in their 70s and beyond, a substantial proportion of patients are pensioners or live on a limited fixed income, making long-term out-of-pocket costs for diagnostics and injections difficult to manage.

f) Lack of availability of public treatment

As discussed in Section 7, there is a significant lack of free public outpatient treatment services available around Australia for people who are unable to afford the out-of-pocket costs commonly associated with ongoing private care. Services that are available are typically under-resourced with long waiting lists. Public treatment is almost non-existent in rural and regional areas. In addition, there is no readily available list of public treatment facilities.

g) Poor accessibility and affordability of treatment in many rural and regional areas

Most rural and regional centres have no visiting ophthalmologist. Others may be visited a few times per year, but this is inadequate to enable the regular injections that are required for optimal individualised care of wet AMD. As a result, most people in rural and regional areas need to travel long distances for care, further increasing costs and the likelihood of poor compliance. When an ophthalmologist does visit a regional centre, there may be little or no competition, so that higher fees can be an issue.

h) Lack of Medicare reimbursement for OCTs for ongoing care

Medicare now provides an item number for an initial OCT scan to enable confirmation of suitability to start PBS treatment, with a maximum of one claim per year. As initiation of treatment will normally only occur once per eye, this generally means that only two OCTs will be reimbursed by Medicare. This also means that if the person's second eye progresses later in the same year as the first eye, an initial OCT will not be funded.

On the other hand, the use of ongoing OCT scans by ophthalmologists to monitor the response to treatment is not funded by Medicare. OCTs for this purpose are globally considered to be standard of care, and essential if individualised treatment using Treat & Extend or PRN regimens are to be used, thereby reducing the number of injections for the patient and for the PBS/Medicare to fund. It is therefore grossly discriminatory that these tests are not reimbursed, and that elderly patients have to shoulder the entire financial burden for their use, which is commonly $40 to $60 per scan. Macular Disease Foundation Australia continues to advocate for the reimbursement of up to six OCT scans per year for monitoring of response to anti-VEGF treatment, when performed by an ophthalmologist.

i) Eye health for people in residential aged care facilities (RACFs)

People with significant vision loss from any cause enter residential aged care facilities at an average of three years earlier than their normally sighted peers. There is also significant evidence that people living in RACFs:

- have higher rates of undiagnosed eye disease
- have lower rates of ongoing monitoring of eye disease and treatment
- may receive inappropriate care or a lack of rehabilitative support for their low vision

when compared to their equivalent aged peers living at home.

Macular Disease Foundation Australia is completing a research project funded by the federal government which has confirmed the high rates of eye disease and vision loss in RACF residents. The project has also identified the policies and procedures used by RACFs to care for people with eye disease. Further work is underway to develop recommendations and education to further improve early diagnosis, access to treatment and the provision of rehabilitative support and general care.

j) Exclusion from the National Disability Insurance Scheme of people developing major vision loss over the age of 65

The vast majority of people who develop major vision loss (i.e. legal blindness) from macular degeneration will do so after the age of 65. While legally blind people under the age of 65 can access the reasonable supports and services they need through the NDIS, as an entitlement for life, people who become legally blind after their 65th birthday are excluded from the NDIS. They are expected to access the supports and services they need through the aged care system, on a means tested basis. Even though the aged care system is also undergoing substantial reform, it is neither funded nor staffed to provide appropriate disability services, such as low vision support. As a result, older people with low vision are falling between the cracks of the disability and aged care systems, and continue to receive sub-optimal care and support.

k) Lack of funding of low vision aids and technologies for those who have lost vision

As detailed in Section 5.4, there are substantial variations between jurisdictions in the level of funding available for low vision aids and technologies, and even when available, they are generally inadequate. Since these can significantly improve independence and quality of life for people with significant vision loss, there is a strong case for a nationally funded, means tested subsidy program, consistent across the states and territories, to support people with vision loss. It is illogical and unfair that substantial federal subsidies are available for hearing aids, but not low vision aids.

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OUR VISION

To reduce the incidence and impact of macular disease in Australia

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Our focus is your vision

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