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Eyes on the future

A clear outlook on
Age-related Macular
Degeneration

Macular Degeneration
Foundation

2011

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Report prepared by:

Deloitte Access Economics and Professor Paul Mitchell

Professor Paul Mitchell

MBBS, MD, PhD, FRANZCO, FRACS, FRCOphth, FAFPHM

Professor Paul Mitchell is a world renowned medical retina specialist and Professor of Ophthalmology at the University of Sydney, and Director of Ophthalmology for the Sydney West Area Health Service.

Professor Mitchell served as Director on the Board of the Macular Degeneration Foundation since its inception in 2001 until 2004. He was appointed National Research Advisor to the Foundation in 2006 and has served for ten years as a member of the Foundation's Medical Committee.

Professor Mitchell has made outstanding contributions in the fields of public health and ophthalmic epidemiology especially through his work on the landmark Blue Mountains Eye Study. This was the first large Australian population-based study of age-related eye disease and is recognised throughout the world.

With contributions by:

Julie Heraghty – Macular Degeneration Foundation

Robert Cummins – Macular Degeneration Foundation

With special thanks to:

Dr Paul Beaumont

Professor Jill Keeffe OAM

Clinical Professor Helen Beange AM

Elena Rochtchina

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Glossary

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
AMD	age-related macular degeneration
ARM	age-related maculopathy
AREDS	Age- Related Eye Disease Study
BDES	Beaver Dam Eye Study
BMES	Blue Mountains Eye Study
BMI	body mass index
CKD	chronic kidney disease
CFH	complement factor H
CNV	choroidal neovascularisation
CVD	cardiovascular disease
DALY	disability adjusted life year
DHA	docosahexaenoic acid
DWL	deadweight loss
EPA	eicosapentaenoic acid
FA	fluorescein angiography
FTE	full time equivalent
GDP	gross domestic product
GP	general practitioner
HDL	high-density lipoprotein
IPC	idiopathic polypoidal choroidopathy
MBS	Medicare Benefits Schedule
MVIP	Melbourne Visual Impairment Project
NHS	National Health Survey
NICE	National Institute of Health and Clinical Excellence
OBPR	Office of Best Practice Regulation
OCT	optical coherence tomography
PBS	Pharmaceutical Benefits Scheme
PDT	photodynamic therapy
QALY	quality adjusted life year
RAP	retinal angiomatous proliferation
RPBS	Repatriation Pharmaceutical Benefits Scheme
RPE	retinal pigment epithelium

TAP	Treatment of Age-Related Macular Degeneration with Photodynamic Therapy
UK	United Kingdom
US	United States
VEGF	Vascular Endothelial Growth Factor
VSL(Y)	value of a statistical life (year)
WARMGS	Wisconsin Age-Related Maculopathy Grading Scheme
WHO	World Health Organization
WTP	willingness to pay
YLD	year of healthy life lost due to disability
YLL	year of life lost due to premature death

Acronyms for trials are in the next table e.g., ANCHOR, MARINA. Genetic acronyms are described in that section and acronyms contained in tables are identified under the table.

Definitions

ANCHOR	ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD) is a randomised, multi-centre, double-masked, active-treatment-controlled Phase III study comparing two different doses of Lucentis to PDT in 423 patients.
Classic CNV	Angiographic findings in which the CNV appears as an area of bright, well demarcated hyperfluorescence (see also Predominantly classic CNV, Minimally classic CNV, and Occult CNV).
Choroid	The layer in the eyeball between the retina and the sclera. It contains blood vessels and a pigment that absorbs excess light to prevent blurring of the vision.
Choroidal neovascularisation (CNV)	A process in which blood vessels grow through the choroidal membrane and enter the sub-retinal pigment epithelial and/or sub-retinal spaces.
Cost-effectiveness analysis	A form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action. Cost-effectiveness analysis is distinct from cost-benefit analysis, which assigns a monetary value to the measure of effect.
Disciform scar	A subretinal scar, typically round or oval in shape, consisting of fibrovascular tissue, most often located in the macular area. It results from the haemorrhages that sometimes follow choroidal neovascularisation in the exudative type of macular degeneration. It causes irreparable damage to vision.
Drusen (singular - druse)	Small yellow deposits of lipid and protein that accumulate on Bruch's Membrane, under the retina. The presence of large and/or numerous drusen is an indication of AMD progression.
Dry (atrophic) AMD	A late stage of AMD in which there are sharply delineated areas of retinal and RPE scarring and loss, leading to significant loss of vision. Dry AMD normally progresses slowly.
Early AMD	Drusen or pigment changes at the macula which may be associated with either no vision loss, or early changes in reading/ central vision.
Extrafoveal CNV	CNV that comes no closer than 200 microns to the centre of the fovea.
Fibrosis	Thickening and scarring of tissue.
Fibrovascular retinal pigment epithelial detachment	A form of occult CNV with areas of irregular elevation of retinal pigment epithelium associated with stippled hyperfluorescence.

Fluorescein angiography	A method to examine the blood flow in the retina using fluorescein, a yellow-green dye which fluoresces under blue light.
Fovea	A pinpoint, depressed area of the central retina. It is the retinal area with the greatest visual acuity. It normally lacks retinal blood vessels.
Geographic atrophy	A round, well-defined, nearly transparent spot in the centre of the macula of a person with dry age-related macular degeneration (AMD). The atrophied tissue thins and loses pigment, causing the person to see a blur or blank spot.
HORIZON	A 2-year open-label, multicentre extension study of 853 patients who had completed one of the three 2-year, randomised, controlled trials of monthly intravitreal ranibizumab treatment (MARINA, ANCHOR, or FOCUS trial).
ICG angiography	A method to examine the deeper choroidal blood flow using indocyanine green dye.
Inject and Extend	An injection regimen involving an induction phase with three monthly injections with following visits individually adapted, extending or shortening the interval by 1 or 2 weeks according to the presence or absence of subretinal fluid. The inject and extend schedule has shown better efficacy in terms of visual acuity gain, with an almost equal number of injections, compared to PRN treatment.
Juxtafoveal CNV	Well-demarcated CNV that is between 1 and 199 microns from the centre of the foveal zone but does not reach its centre.
LogMAR chart score	Logarithm of the minimum angle of resolution (logMAR) charts to measure visual acuity are now strongly preferred to the traditional Snellen chart (see below), because they are more sensitive to small changes, have an ordered progression of letter size (five equally readable letters per line), are more reproducible and are able to compare with published trial data. Non-geometric progression of letter size, and a variable number of letters per line also prevent Snellen measures being easily equated to letters or lines of change in visual acuity.
Macula	The fovea plus the surrounding area on the retina.
Macular degeneration	A leading cause of blindness in the elderly. In the wet or neovascular form of macular degeneration there is a leaking neovascular membrane in the choroid that damages the macula and affects vision.
MARINA	Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab (formerly, RhuFab) In the treatment of Neovascular AMD is a Phase III study of 716 patients in the United States with minimally classic or occult wet AMD.

Minimally classic CNV	Area of CNV occupying <50% of the entire lesion area. Usually progresses at a slower rate of vision loss than classic CNV but faster than occult (see also Classic CNV, Predominantly classic CNV, and Occult CNV).
Occult CNV	Angiographic findings characterised by a fibrovascular retinal pigment epithelial detachment and/or late leakage of an undetermined source. Of the forms of neovascular AMD, it progresses at the slowest rate of vision loss (see also Classic CNV, Predominantly classic CNV, and Minimally classic CNV).
PIER	A Phase IIIb, Multicentre, Randomised, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in 187 Subjects with Subfoveal Choroidal Neovascularisation with or without Classic CNV Secondary to Age-Related Macular Degeneration. In this trial, Lucentis is administered once per month for the first three doses followed thereafter by doses once every three months for two years.
Photodynamic therapy (PDT)	A treatment for age-related macular degeneration. A photosensitive dye (verteporfin) is given intravenously and accumulates in the neovascular membrane of the choroid. The PDT laser then activates the dye, thrombosing the membrane.
Predominantly classic CNV	Area of CNV occupying $\geq 50\%$ of the entire lesion area. This is the most aggressive form of neovascular AMD, leading to faster vision loss than the other subtypes (see also Classic CNV, Predominantly classic CNV, and Minimally classic CNV).
PRN	<i>Pro re nata</i> . As needed. In the context of MD treatment, injections of anti-VEGF drug given as needed, typically based on pre-determined criteria such as retinal thickness, presence of bleeding or swelling.
PrONTO	A 2-year prospective, uncontrolled study of 37 wet AMD patients to assess the long-term efficacy of a variable dosing regimen of ranibizumab using Optical Coherence Tomography (OCT) Imaging to determine the need for retreatment.
QALY	Quality Adjusted Life Years. This is a measure of disease burden allowing for both the quantity and quality of life. It measures the number of years that would be added due to a particular intervention.
Retina	The light sensitive tissue lining the inside surface of the back of the eye. Light impulses hitting the retina are converted to electrical signals which are transmitted to the brain for interpretation.

Retinal angiomatous proliferation (RAP)	Exudative AMD is the late form of neovascular AMD (late AMD) and is commonly known as wet AMD. This is characterised by the formation of new blood vessels that have originated from the choroid. These breach Bruch's membrane and invade the sub-pigment epithelial and or sub-retinal spaces. Neovascular AMD can also occur in the macular retina, which is known as retinal angiomatous proliferation (RAP). RAP can establish contact with choroidal vessels to form chorioretinal anastomoses (CRA).
Sclera	The white, fibrous outer coating of the eye.
Snellen value	Visual acuity can be measured using the Snellen eye chart. Patients are asked to identify letters of standard sizes at a specified distance. A visual acuity measurement of 6/60, for example, indicates the smallest letter identified by the patient at a distance of six meters that could be seen by a healthy eye at 60 metres.
Subfoveal CNV	CNV that underlies the centre of the foveal zone.
SUSTAIN	A 12-month, phase III, multicentre, open-label, single-arm study of 513 ranibizumab-naïve patients receiving three initial monthly injections of ranibizumab (0.3 mg) and thereafter pro re nata (PRN) retreatment for 9 months based on pre-specified retreatment criteria.

Executive Summary

Age-related macular degeneration (AMD) is the most common cause of visual impairment in people over the age of 50 years in developed countries (Coleman et al, 2008). In Australia, it is the most common cause of blindness contributing to 50% of all blindness. AMD progressively destroys the macula (the central portion of the retina), impairing central vision and affecting quality of life and independence.

Generally, AMD can be classified into the early (typically not visually impairing) and late (visually impairing) stages. Late AMD can be further divided into 'wet' (neovascular) and 'dry' (atrophic) forms. Population studies indicate that two-thirds of late cases are neovascular and one-third are atrophic. However, over time, cases that are initially neovascular also develop atrophic signs.

- 'Early' AMD, defined by the development of large drusen or pigment changes at the macula may be associated with either no vision loss or early changes in reading/ central vision.
- 'Late' AMD includes both neovascular AMD and geographic atrophy, in a ratio of about 2:1.
 - Neovascular ('wet' or exudative) AMD is characterised by the appearance of blurring of the central vision and distortion with straight lines appearing crooked or wavy, with or without a dark or blank patch. Perception of colours is also often affected.
 - Geographic Atrophy ('dry' AMD) reduces capacity for near visual tasks as central vision becomes severely impaired. Note that some people include 'early AMD' within the category of 'dry AMD'. In this report, 'dry AMD' refers only to the late, atrophic stage.

Prevalence

The prevalence of AMD increases sharply with age, particularly from the age of 65 years (Wong et al, 2008). Demographic ageing will cause the prevalence of AMD to increase.

It is estimated that in 2010, there were 1.023 million Australians with AMD, equivalent to one in seven people over the age of 50. This comprises 856,000 with early AMD (Table 3.5), plus nearly 167,000 with late AMD in at least one eye (Table 3.7).

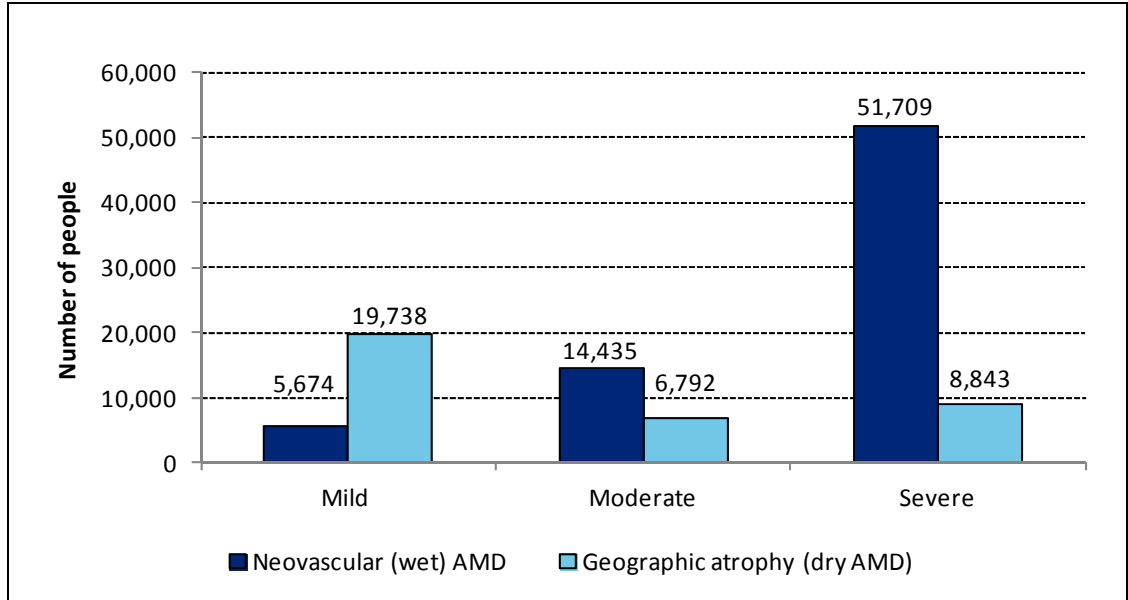
It is further estimated that by 2030, as a result of demographic ageing, the numbers with AMD would increase by over 70% to 1.77 million, in the absence of effective prevention and treatment efforts. This comprises 1.44 million with early AMD and 329,000 with late stage AMD in at least one eye.

- In the absence of prevention and treatment efforts, the number of Australians visually impaired in both eyes due to AMD would double from 107,000 in 2010 to over 215,000 by 2030 (Table 3.9).
- Estimates for the number of people who were legally blind due to AMD in 2010 range between 39,000 and 73,000¹ of whom about two-thirds have neovascular AMD.

¹ Estimates vary due to different models and assumptions. See section 3.1.5.3.

Chart i, shows the numbers of people with visual impairment from wet and dry AMD, by severity, in 2010. Chart ii, compares the prevalence of AMD to multiple sclerosis, dementia and diabetes.

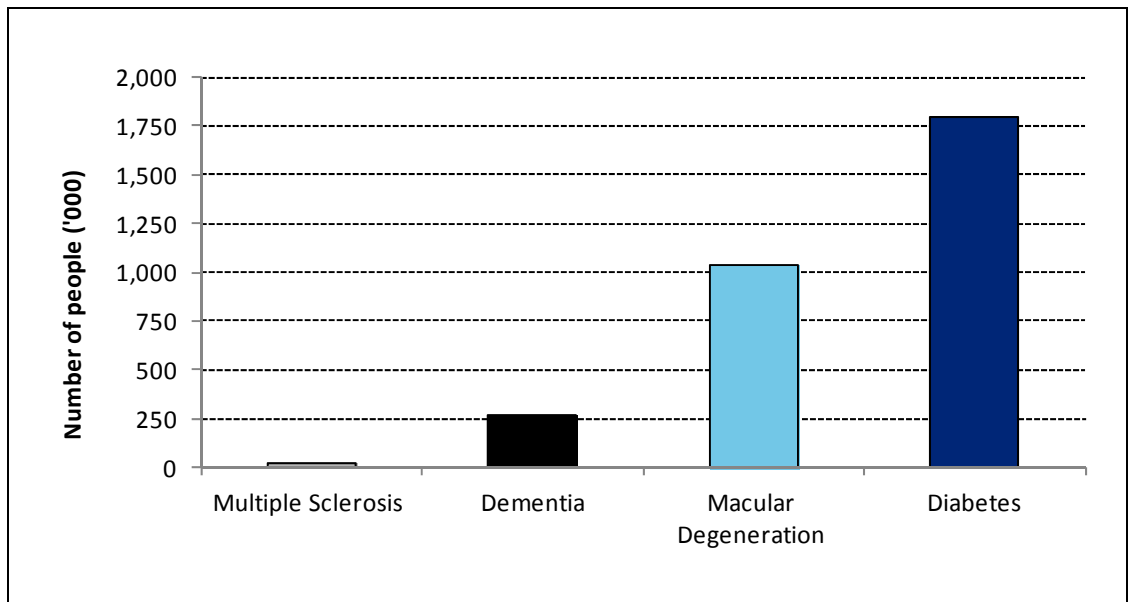
Chart i: Prevalence of visual impairment from AMD by severity of vision loss



Source: Deloitte Access Economics calculations.

Mild - worse than 6/12 and better or equal to 6/18; Moderate - worse than 6/24 but better or equal to 6/60; Severe - worse than 6/60 (blindness).

Chart ii: Prevalence of some key chronic diseases - Australia, 2010



Source:

Multiple Sclerosis: www.msaustralia.org.au/aboutms-faq.asp, Accessed 16/9/11

Dementia: www.alzheimers.org.au/understanding-dementia/statistics.aspx, Accessed 16/9/11

Diabetes: www.diabetesaustralia.com.au/en/Understanding-Diabetes/Diabetes-in-Australia/, Accessed 16/9/11. This figure is comprised of 1 million diagnosed, and an estimated 800,000 undiagnosed.

The Macular Degeneration figure includes 167,000 with late stage disease (vision impairment) and 856,000 with early disease.

Progression and prevention

Progression from early to late AMD can occur rapidly in some people, and more slowly in others (Wang et al, 2007). On average, about 4% of people with early AMD progress to late AMD each year. The progression rate from mild to moderate visual impairment is around 32% and from moderate to severe visual impairment around 46% over 2-3 years, without treatment (Wang et al, 2007).

Epidemiological studies have identified several risk factors that can increase the risk of developing AMD and increase the speed at which the disease progresses. Age, genetic factors and ethnicity are important non-modifiable risk factors. Cigarette smoking is a major lifestyle risk factor predicting the presence and development of AMD. Dietary antioxidants also play an important role in the occurrence, prevention and treatment of AMD. Some foods such as leafy greens (e.g., spinach), fish and nuts can decrease risk by at least 65% (Tan et al, 2008; Tan et al, 2009). Olive oil may also reduce risk (Chong et al, 2009). There is also recent evidence to suggest that diets with lower than average dietary glycaemic index (dGI) may reduce the risk of developing early and late AMD. Since there is currently no effective treatment for dry AMD, prevention is the first approach to reducing vision loss and the associated burden on society (Coleman et al, 2008).

Treatment of neovascular AMD

For neovascular AMD, substantial progress has been made in the development of new and effective treatments. Ranibizumab (Lucentis® - Novartis), an anti-VEGF agent, is a recent therapy that can halt the progression of neovascular AMD and may also provide some improvement. The MARINA and ANCHOR studies showed that around 95% of the eyes treated with ranibizumab (0.5 mg) at monthly intervals maintained stable vision within 15 letters (compared to 62%-64% of sham or PDT group) at one year. Between 34%-40% of the treated eyes improved by more than 15 letters of vision (compared to 4%-6% in the PDT or sham group).

Lucentis gained reimbursement for neovascular AMD on the Pharmaceutical Benefits Scheme (PBS) in August 2007 based on results from the ANCHOR, MARINA, and PIER trials. The listing was recommended at the price proposed in the submission on the basis of an average incremental cost per extra quality adjusted life-year (QALY) gained across all lesion types of between \$15,000 and \$45,000 (Table 6.2).

In patients who do not qualify for PBS reimbursed Lucentis, the closely related bevacizumab (Avastin® - Roche) is sometimes used "off-label". Avastin has been shown to provide similar visual acuity outcomes to Lucentis at 12 months, although small differences in retinal thickness, favouring Lucentis, have been shown. There is also some suggestion that relatively uncommon, but serious adverse events may be more common with Avastin. Further research is still needed to clarify the longer-term efficacy and safety of Avastin.

The anti-VEGF agents have essentially superseded older treatments such as photodynamic therapy (PDT) using verteporfin, laser photocoagulation and the injection of steroids such as triamcinolone.

Cost of AMD

This report updates results of an earlier study for the Centre for Eye Research (CERA) – *Centrally Focused: The Impact of Age-Related Macular Degeneration: a dynamic economic model and report* (Access Economics, 2006a). The cost of AMD is estimated based on health system data from the Australian Institute of Health and Welfare, and adding more recent cost estimates of Lucentis expenditure on the PBS. Other financial costs comprise primarily low vision aids, the cost of care, and the deadweight efficiency losses from welfare and taxation transfers, as well as a small component of productivity losses for people with AMD. The largest proportion (85%) of the economic cost of AMD results from the loss of quality of life associated with visual impairment, known as the ‘burden of disease’. This is measured in disability adjusted life years (DALYs) and converted to dollars using the value of a statistical life year of \$166,603 from the Department of Finance and Deregulation. Table i shows the total cost of vision loss associated with AMD in 2010.

In 2010, the total cost of vision loss associated with AMD was estimated to be \$5.15 billion (\$48,028 per person), of which the financial cost was \$748.4 million (\$6,982 per person).

Table i: Total cost of vision loss associated with AMD in 2010 by cost type

Cost type	Total cost (\$m)	Per person with AMD (\$)
Health system costs (a)	359.1	3,350
Productivity losses	18.7	175
Carer opportunity costs	47.5	443
Other indirect (aids/modifications/other carer and bring forward of funeral)	158.6	1,480
Dead Weight Losses	164.4	1,533
Total other financial costs (b)	389.2	3,631
Total financial costs (a) + (b)	748.4	6,982
Loss of wellbeing (c)	4,399.8	41,047
Total economic cost (a) + (b) + (c)	5,148.2	48,028

Source: Deloitte Access Economics calculations.

Benefits from AMD prevention and treatment

Comparing the overall savings to the cost of Lucentis, the social benefit cost ratio was estimated to be over 2:1, and the \$/DALY averted is estimated as \$41,792.

Even though there is currently no effective treatment for dry AMD, controlling for modifiable risk factors could prevent or delay the onset to the more advanced stages of AMD, suggesting substantial benefits through the possibility of alleviating some of these costs. For example, if cigarette smoking was halved, reducing the number of cases of AMD by one sixth over time, the total savings would be in the order of \$247 million per annum, in 2010 dollars.

From MARINA trial evidence, Lucentis improves average visual acuity by 17.6 letters over the treatment period of one year. The savings potentially associated with Lucentis are estimated to be \$887.5 million in 2010, if all neovascular AMD were treated. The largest savings is related to the reduction in the burden of AMD, but financial savings in 2010 would be worth some \$142.9 million, including fewer productivity losses from informal care, reduced need for low vision aids, and less downstream or alternative treatment for visual impairment (e.g., PDT).

Remaining barriers to treatment

Although the cost savings from using Lucentis are relatively large, there can be further improvements made through the removal of remaining treatment barriers. In unpublished research carried out by the Macular Degeneration Foundation in March 2010, it was found that the key reason people with neovascular AMD did not commence treatment was that they were diagnosed too late. The lack of early detection was most likely caused by a lack of awareness. It has also been shown that treatment of smaller lesions has a better visual prognosis, further emphasising the importance of early diagnosis (and the value of improved awareness). Adherence to therapy is also a significant barrier. Treatment for neovascular AMD should generally be continued in order to have ongoing therapeutic benefit. However, many people receiving treatment discontinue or have their treatment interrupted, for various reasons.

There are several recognised barriers to treatment, including out of pocket expenses (notably patient co-payments and travel costs), workforce supply and professional development constraints, demographic and socioeconomic disadvantage, and compliance and adherence issues. In this regard, it is recommended that:

- measures are adopted to maintain the work undertaken in awareness raising, to continue increasing population awareness of AMD in the 50+ age group beyond 83% awareness in 2010, and any gaps in awareness are addressed;
- awareness programs are increased to convey the importance of daily use of an Amsler grid in people with established AMD. This is the best way for the patient to pick up any sudden changes in vision which may indicate a progression to neovascular disease, and hence the need for immediate treatment;
- greater assistance is provided to meet patient co-payments, and travel costs for regional and disadvantaged Australians, since 15% of people receiving treatment for neovascular AMD consider discontinuing treatment due to out of pocket costs, and 3% do discontinue, despite the high priority they accord to their sight;
- workforce constraints are addressed, including increasing opportunities for Fellowship places for ophthalmologists;
- professional development to further the education of eye health professionals and specifically optometrists and general practitioners, to improve their understanding of the clinical sequelae of AMD, treatment options and referral guidelines and rates;
- measures are taken to improve the availability of free/bulk billed public treatment, either in public hospitals or via an alternate model; consideration be given to the addition of a Medicare item number for OCT scans, when performed as part of the management of AMD;
- measures are introduced to support the patient to help maintain and improve adherence with therapy. The issue of “injection fatigue” can be a major problem which

can lead to a desire by both patients and doctors to increase the time intervals between injections, potentially leading to under treatment, which can negatively impact outcomes;

- implementation of programs to improve communication between patients and their eye and health care professionals. The introduction of intra-vitreous injections has dramatically increased the demand for the ophthalmologist's services and access to these services can be limited. The time available with the specialist for discussion, explanation and questions can also be severely restricted; and
- careful review of effective best practice models which overcome some of these challenges would assist, along with a closer analysis of the supply and location of ophthalmologists, to aid future planning to meet the needs of the Australian community in the next 20 years.

Rehabilitation

Except for the effectiveness of managing risk and protective factors, there is no 'cure' for late stage AMD. While most people with neovascular AMD can now obtain highly effective treatment with anti-VEGF agents, some still experience a significant loss of vision. Many others have lost vision before effective treatments became available. For people with dry AMD, there is currently no treatment that can restore lost sight. Loss of vision affects quality of life and levels of independence. The emotional, social and economic impact on quality of life from visual impairment can be severe. Low vision rehabilitation is considered the best option for mitigating the impacts if medical treatment is unsuccessful in restoring an appropriate level of vision. Rehabilitation services can improve the capacity to read, provide opportunities for using low vision aids and technologies, increase confidence, address issues related to depression, increase daily living activities, improve mobility and functional ability and maintain and support workforce participation.

It has been estimated that 90% of people with vision impairment have useful residual vision, and could benefit from rehabilitation services, however, it is further estimated that only 20% of Australians that could benefit from rehabilitation services actually use the services. Several barriers to accessing rehabilitation services have been identified, such as a lack of awareness about services offered or their capacity to help, confusion with the referral process and problems with using transport. Personal factors can also act as barriers, such as culture and co-morbidities. There are also systemic barriers, such as poor communication with healthcare professionals and a reluctance to refer patients to low vision providers, especially in the earlier stages of vision loss. Patients may have to access more than one low vision service provider as many providers do not provide a comprehensive service. In some regional and rural communities, certain services may not even be available or accessible.

To improve uptake of rehabilitation services, it is recommended that:

- rehabilitation services are better tailored to client needs and preferences and there is regular assessment of services to ensure they are flexible to adapt to changing needs;
- adequate information and practical training is provided to people requiring low vision devices immediately or slightly in advance of requirement;
- access to rehabilitation services is enhanced by encouraging the development of additional services within the public hospital system and with private optometrists;

- referral pathways are strengthened by improving knowledge of AMD and low-vision rehabilitation services among health professionals, and encouraging health professionals to promote rehabilitation as an effective tool for reducing the impact of vision loss;
- rehabilitation should also be offered in the earlier stages of vision loss when patients are better able to learn new strategies; and
- national standards for low vision services are established to ensure the quality of services and facilitate comparison and choice.

Deloitte Access Economics

1 Background

Deloitte Access Economics was commissioned by the Macular Degeneration Foundation to update findings from work previously undertaken for the Centre for Eye Research in 2005-06 – *Centrally Focused: The Impact of Age-Related Macular Degeneration: a dynamic economic model and report* (Access Economics, 2006a). Within that report, several cost effective interventions were modelled to inform ongoing policy formulation and best practice treatment, including a quit smoking campaign, hypothetical research that delays disease progression, and the use of pegaptanib (an anti-angiogenesis treatment which has not been marketed in Australia).

This report updates knowledge of the epidemiology of age-related macular degeneration (AMD) in 2011 (prevalence, incidence, risk and protective factors), reviews prevention and treatment protocols, determines the impact of these on costs and the burden of disease (in particular, the cost benefit of Lucentis treatment), and evaluates barriers to treatment and to rehabilitation services. The report is structured as follows.

- **Chapter 2** - Describes and defines AMD. It includes the classification of AMD according to progression as detailed in the Age Related Eye Disease Study (AREDS). The severity of neovascular AMD is also classified based on the proximity of the new vessel to the centre of the fovea.
- **Chapter 3** - Explores the natural history and progression of AMD and presents updated estimates on the prevalence of AMD in Australia using data from the Blue Mountains Eye Study (BMES) and the Melbourne Visual Impairment Project (MVIP), supplemented with data from the Beaver Dam Eye Study (BDES) and other studies where appropriate.
- **Chapter 4** - Reviews the risk and protective factors using the latest international and domestic studies.
- **Chapter 5** – Estimates the costs of AMD, including health system expenditures, other financial costs, and value of the loss of healthy life.
- **Chapter 6** - Evaluates the treatments used for dry and wet AMD, and explores the new developments in treatment of wet AMD, particularly with anti-VEGF (vascular endothelial growth factor) agents, including associated costs and savings.
- **Chapter 7** - Summarises findings regarding barriers to treatment from the MD Foundation Research Surveys on neovascular AMD in Australia in 2009 and 2010 and changing awareness levels from the 2011 National Galaxy Poll research.
- **Chapter 8** - Explores the benefits of rehabilitation. It also describes the barriers to accessing rehabilitation services and suggestions for improving the uptake of these services in Australia.

2 Description of AMD

AMD is the most frequent cause of major visual impairment in people aged over 50 years in developed countries (TEDPR, 2004). In Australia, it has been shown to be the most common cause of legal blindness contributing to half of all blindness cases (Wang et al, 2005; Taylor et al, 2005; Access Economics, 2006). This chapter presents a formal definition of AMD and categorises AMD into four distinct categories based on the clinical presentation and severity of AMD features.

2.1 Definition of AMD

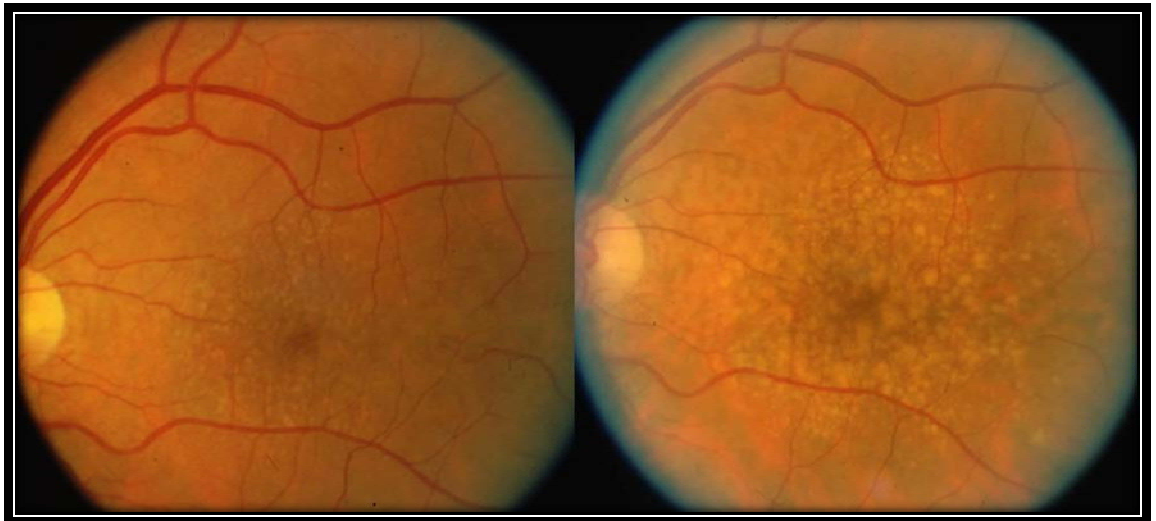
AMD is an eye disease that usually develops in people aged 50 years and older. It progressively destroys the macula (the central portion of the retina) and thereby impairs central vision. Changes to the central area of the macula responsible for detailed vision are often rapid, impacting severely on day to day life. Other less common forms of macular disease include inherited dystrophies such as Stargardt's disease, Best's disease and Sorsby's macular dystrophy, which can affect much younger people.

AMD can be classified as either 'early stage AMD' or 'late stage AMD', depending on the stage of disease progression and characteristics of the disease within the eye. In the early stages of AMD, typically pale spots caused by distinct lesions consisting of lipid and protein deposits from the retinal pigment epithelium (RPE), that are termed drusen, accumulate as deposits within Bruch's membrane² and beneath the RPE³. A second sign is the presence of subtle RPE changes (either increased or decreased pigmentation or both). People with early stage AMD, which poses a future risk to vision, either have drusen at least 125 microns in diameter present in the central retina, or have RPE abnormalities (Mitchell et al, 1995; Van Newkirk et al, 2000), or both signs (Figure 2.1). The presence of only drusen that are smaller (i.e., 63 to <125 microns in diameter) is classified as very early AMD (AREDS, 2001).

Figure 2.1, Left: shows a large drusen (>125 microns) present in a participant from the Blue Mountains Eye Study with Early AMD. Right: Progression in both the size of the drusen and of the area involved during a 5-year follow-up period.

² Bruch's membrane is the innermost layer of the choroid. The choroid is the layer between the white of the eye (sclera) and the inner surface of the eye (retina).

³ The retinal pigment epithelium (RPE) is the pigmented cell layer just outside the retina next to Bruch's membrane.

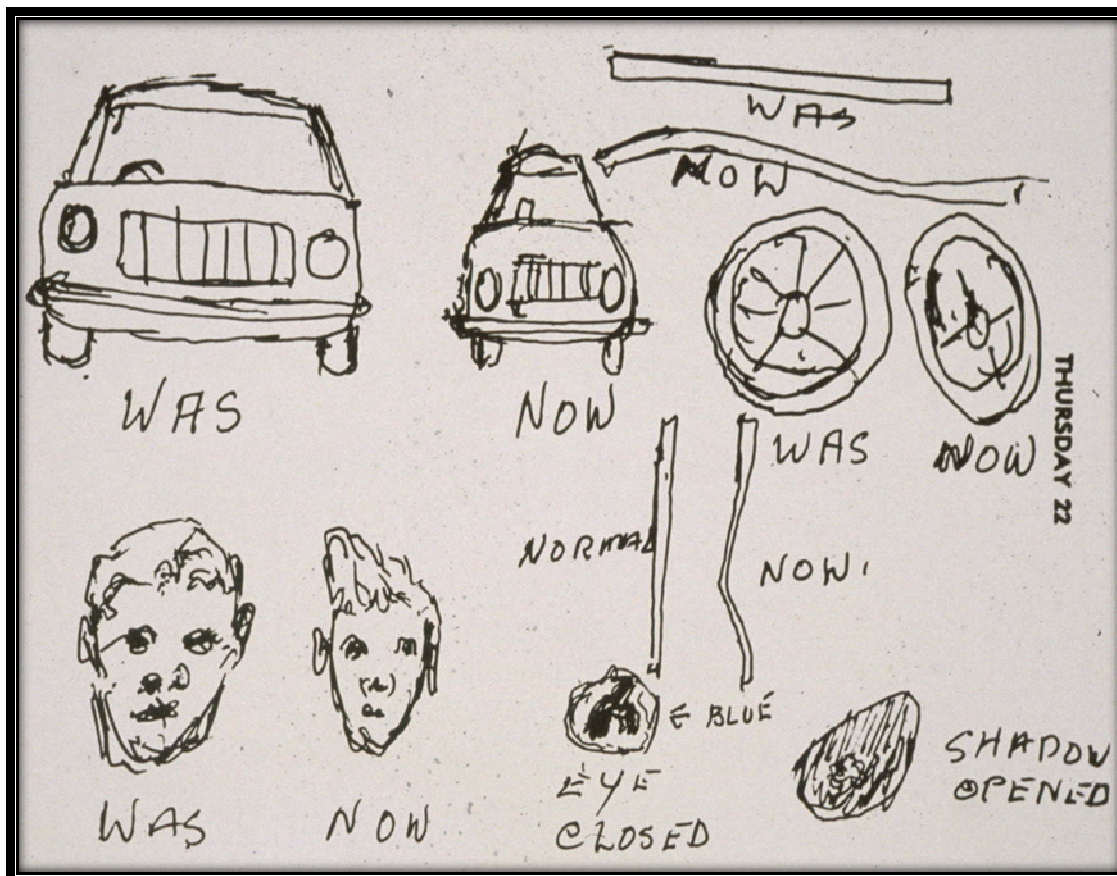
Figure 2.1: Early AMD

Source: Photos courtesy of Professor Paul Mitchell.

A person with early stage AMD may experience no visual difficulties. Only a proportion of those with early AMD will progress to the late form of the disease, which includes either neovascular (“wet”) AMD or geographic atrophy (“dry”) AMD (Cook et al, 2008). This progression is mostly associated with visual symptoms including distortion of straight lines (metamorphopsia), a dark or grayish patch in the central visual field (scotoma), a sudden change in vision or a significant decrease in visual acuity in the affected eye.

Figure 2.2, shows the distortion experienced by a patient with neovascular AMD. There is a consistent buckling of each of the images to the left and superiorly. This corresponds to the area of elevation or swelling in the retina at the macula.

Figure 2.2: Appearance of distortion drawn by a patient presenting with recent neovascular AMD



Source: Photos courtesy of Professor Paul Mitchell.

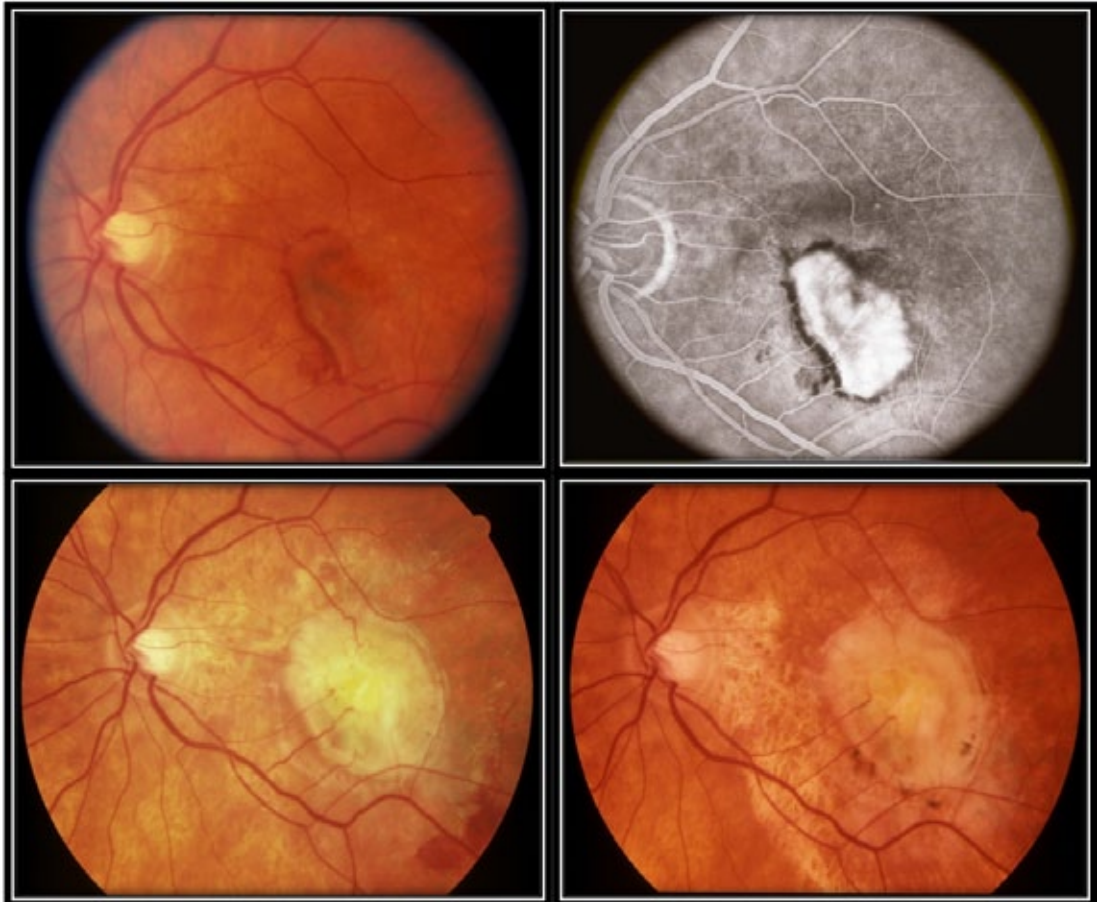
Progressive changes in Bruch's membrane and the RPE (e.g., fading drusen and pigmentary abnormalities) may lead to the development of abnormal blood vessels growing from the existing choroidal capillary bed (Cook et al, 2008), leading to neovascular AMD in a process termed choroidal neovascularisation (CNV) (Mitchell et al, 1995; AAO, 2008). In this process, these new vessels, which are not helpful, actually leak or bleed into the underlying retinal layers, damaging the retina, including the central macula region leading to detachment of either the RPE or sensory retina by blood and fluid, and subsequently leading to scarring (fibrosis) and eventual atrophy, mostly with severe vision loss or blindness.

Figure 2.3, shows neovascular AMD at various stages in the same person:

- **Top left:** an oval, grayish area with surrounding haemorrhage represents the choroidal new vessels lying under the sensory retina. This is a stage eminently treatable with newer anti-VEGF therapy.
- **Top right:** appearance on fluorescein angiography. The white area represents the choroidal new vessel staining with fluorescein dye.
- **Bottom left:** appearance after 1 year, showing the development of dense subretinal fibrosis at the site of the previous choroidal new vessel. This represents an untreatable stage of the disease, which could now have been prevented or ameliorated if anti-VEGF therapy were instituted when neovascularisation first developed.

- **Bottom right:** appearance after 3 years, showing enlargement of the lesion, due to the development of atrophic areas surrounding the original new vessel. In this case, the size of the scotoma (dark patch in the central visual field) will have enlarged considerably, causing major visual disability.

Figure 2.3: Neovascular AMD shown in a clinical photograph



Source: Photos courtesy of Professor Paul Mitchell.

In neovascular AMD, the CNV typically first develops just outside the centre of the fovea (termed extrafoveal CNV). However, it soon spreads to involve the edge of the fovea (juxtafoveal CNV), and then the central foveal region (subfoveal CNV). The fovea is the central portion of the macula, responsible for detailed, central vision. Neovascular AMD is characterised by the appearance of central visual blurring or distortion (metamorphopsia), with straight lines appearing crooked or wavy with or without blank areas (scotoma) (AAO, 2008). Colour perception can also be affected. When neovascular AMD occurs in only one eye, often no symptoms may be reported by the person due to compensation by the brain using the non-affected eye (Chorrenky et al, 2007). Symptoms are typically noticed prominently once the second eye becomes affected.

Geographic atrophy, the alternate form of late AMD, is characterised by light-sensitive cells in the macula slowly breaking down (located directly above the RPE) and becoming atrophic with complete loss of the RPE and of adjacent choroidal elements with marked choroidal thinning. People with geographic atrophy usually also have extensive medium-sized

drusen, often with a crystalline or calcified appearance, and at least one or more large drusen (125 microns in diameter) in one or both eyes (AAO, 2008).

Figure 2.4, shows a rounded light coloured zone involving the central macula that has a sharp edge, with visible choroidal vessels within the zone, which in this case, just spares the very central foveal zone. There are also surrounding crystalline (calcified) large drusen present. The atrophy will progressively enlarge to involve these more peripheral areas over time, with a concomitant enlargement of the scotoma.

Figure 2.4: Typical appearance of geographic atrophy, with loss of the retinal pigment epithelium



Source: Photos courtesy of Professor Paul Mitchell.

Geographic atrophy may exist with relatively good distance vision but a substantially decreased capacity for near visual tasks. This is because the centre of the fovea usually or eventually becomes affected by the loss of retinal cells, thereby deteriorating central vision (Cook et al, 2008), and also because in many cases, geographic atrophy surrounds the central macula before finally spreading to involve it.

2.2 Classification of AMD

The accurate diagnosis and classification of AMD using recommended criteria is critical to ensuring proper treatment. According to Mitchell et al (2010), assessment of AMD should include:

- history, duration and characteristics of visual symptoms;
- stereoscopic bio-microscopic slit-lamp fundus examination (using a 78D or similar lens);
- fluorescein angiography (FA) if a choroidal new vessel is suspected; and
- optical coherence tomography (OCT) to evaluate whether fluid is present within or beneath the layers of the retina.

FA is deemed mandatory for initial diagnosis, if CNV is suspected, in order to exclude non-AMD causes, such as neovascularisation secondary to myopia, pseudo-xanthoma elasticum, birdshot choroidopathy, previous trauma, infections or other causes (Mitchell et al, 2010). OCT is recommended to define the extent and level of retinal thickening.⁴

A number of classification schemes for AMD have been developed. Most have been based on the Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS). Given the WARMGS' complexity and multiple scales, some simplifications were made to develop the International ARM Classification System, which distinguishes both early features of AMD, such as drusen and pigmentary irregularities (Bird et al, 1995), as well as late features (neovascular AMD or geographic atrophy). Both the WARMGS and the International ARM Classification System provide detail on the size and surface features of drusen and the presence of pigmentary abnormalities (RCO, 2009).

More recently, the Age Related Eye Disease Study (AREDS) defined different stages of AMD using participants enrolled in this large randomised clinical trial (RCT). This classification incorporated many of the features, sign descriptions, and measured grading characteristics from the WARMGS. Many current treatment recommendations have been based on the AREDS classifications (AAO, 2008). The AREDS was a long term prospective multicentre RCT designed to assess the natural course and risk factors for both AMD and age-related cataract and the effects of an antioxidant vitamin and mineral supplement on these conditions, compared to placebo. The study categorised AMD into four stages, as outlined in Table 2.1.

⁴ OCT can also determine the localisation and qualitative pattern of extracellular fluid accumulation. Indocyanine green angiography can be useful when polypoidal choroidal vasculopathy or retinal angiomatous proliferation (RAP) is suspected, or the degree of CNV in occult lesions is unclear (Mitchell et al, 2010).

Table 2.1: Classification scale used to define four stages of AMD

Stage	Classification	Characteristics
No AMD	AREDS category 1	None or a few small drusen (<63 microns in diameter).
Early AMD	AREDS category 2	Any or all of the following: multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.
Early AMD	AREDS category 3	Any or all of the following: extensive intermediate drusen, and at least one large drusen (≥ 125 microns in diameter), or geographic atrophy not involving the centre of the fovea.
Late AMD	AREDS category 4	Is characterised by one or more of the following (in the absence of other causes) in one eye: <ul style="list-style-type: none"> • geographic atrophy of the RPE and choriocapillaris involving the centre of the fovea • Neovascular maculopathy such as the following: <ul style="list-style-type: none"> ○ CNV ○ Serous and/or hemorrhagic detachment of the sensory retina or RPE ○ Retinal hard exudates (a secondary phenomenon resulting from chronic leakage from any source) ○ Subretinal and sub-RPE fibrovascular proliferation ○ Disciform scar

Source: Deloitte Access Economics and AREDS (2001).

2.3 Visual impairment

Visual impairment can be broadly defined as a limitation in one or more functions of the eye or visual system, most commonly impairment of visual acuity (sharpness or clarity of vision), visual fields (the ability to detect objects to either side, or above or below the direction of vision) and colour vision.

According to the Snellen scale, normal vision is recorded as 6/6, (20/20 in Imperial/US measures), which means that a person can see at six metres what a person with normal vision can see at six metres. Degrees of visual impairment are measured similarly, where the first number is the furthestmost distance at which the person can clearly see an object, and the second number is the distance at which a person with normal vision could see the same object. For example, 6/12 vision means that the person can clearly see at six metres (but not more), an object that a person with unimpaired vision could see at 12 metres (but not more) (Taylor et al, 2005).

LogMAR is an improved scale which is expressed as the logarithm of the minimum angle of resolution. It measures visual acuity, where positive values indicate vision loss, while negative values denote normal or better visual acuity. This scale is most frequently used in statistical calculations (and cost savings calculations) because it provides a more scientific equivalent for the traditional clinical statement of 'lines lost' or 'lines gained', which is valid when all steps between lines are equal. Each increase of 0.1 units on the logMAR scale indicates a one line loss on the visual acuity chart. (Mallah et al, 2000). LogMAR charts are now increasingly preferred to the traditional Snellen chart because they are more sensitive to small changes, have an ordered progression of letter size (with five equally readable letters per line), are more reproducible and enable close comparisons with published trial data.

While typical severity stages of visual impairment have been defined and mapped to the AREDS classification of AMD and visual acuity in Table 2.2, many individuals have different levels of visual impairment (or even no impairment) at different AREDS levels.

In general, people with no AMD or with early stage AMD will continue to maintain normal vision and therefore the cost of AMD to the person and society is relatively low.

However, people with signs of early stage AMD have a much greater risk of developing late stage AMD (Wang et al, 2007). If and when this occurs, the impact of AMD on visual acuity will become pronounced. Late stage AMD is often first characterised by mild visual impairment for a short period but as the disease progresses within this stage, vision loss may increase and can eventually lead to blindness. It is the vision loss associated with late stage AMD however that imposes substantial personal distress to people with AMD as well as leading to significant costs to society. These costs are estimated in Chapter 5.

Table 2.2: Comparison of AMD stages with alternative measurements of visual impairment

Classification	Severity	Snellen (6 m)	Snellen (20 ft)	Decimal notation	Visual Angle	LogMAR	Letter count
No AMD and early stage AMD (AREDS categories 1,2 and 3)	Normal	6/3.0	20/10.0	2.00	0.50	-0.3	-
		6/3.8	20/12.5	1.60	0.63	-0.2	110
		6/4.8	20/16	1.25	0.80	-0.1	105
	6/6.0	20/20	1.00	1.00	0	100	
	6/7.5	20/25	0.80	1.25	+0.1	95	
	6/9.5	20/32	0.63	1.6	+0.2	90	
	Mild	6/12	20/40	0.50	2.0	+0.3	85
		6/15	20/50	0.40	2.5	+0.4	80
		-	-	-	-	-	-
	Late stage AMD (AREDS category 4)	Moderate	6/19	20/63	0.32	3.2	+0.5
6/24			20/80	0.25	4.0	+0.6	70
6/30			20/100	0.20	5.0	+0.7	65
6/38		20/125	0.16	6.3	+0.8	60	
6/48		20/160	0.125	8.0	+0.9	55	
6/60		20/200	0.10	10.0	+1.0	50	
Severe (Blindness)		6/75	20/250	0.08	12.5	+1.1	45
		6/95	20/320	0.06	16.0	+1.2	40
		6/120	20/400	0.05	20.0	+1.3	35

Source: Deloitte Access Economics and Holladay (1997). Note that the categorisation of AMD stages is not based on visual acuity. Many individuals have different levels of visual impairment (or even no impairment) at different AREDS levels.

3 Epidemiology, Risk Factors and Natural History of AMD

This chapter provides information on current estimates for both the prevalence and incidence of AMD worldwide⁵, together with data on the known risk factors for this condition. It includes Australian data based on the Blue Mountains Eye Study (BMES) and the Melbourne Visual Impairment Project (MVIP). It also outlines the natural progression of AMD from early to late stages, and the typical levels of visual impairment associated with AMD.

3.1 Prevalence of AMD

3.1.1 Definitions

In the past, there were few internationally agreed definitions of early AMD, so prevalence comparisons were difficult (Bird et al, 1995). However, this paper that included investigators from all the recent prevalence studies, was the first to define an international classification. It was based largely on the Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS), and defined the following lesions as comprising early AMD (Mitchell et al, 1995).

- Large drusen, which sometimes have a 'soft' or occasionally a 'reticular' appearance. Large indicates a size of at least 125 microns, which is equivalent to the typical diameter of retinal venules at the edge of the optic disc.
- Retinal pigmentary changes, either hyper-pigmentation (observed as clumps of visible pigment) or hypo-pigmentation - 'de-pigmentation' due to thinning of the retinal pigment epithelium (RPE), but not sufficient loss to be classified as geographic atrophy.

Early AMD has been defined as the presence of large (>125 microns) drusen and/or retinal pigmentary changes in many studies, including the Rotterdam Study (Vingerling et al, 1995), the Beaver Dam Eye study (BDES) (Klein et al, 2002) and the MVIP (vanNewkirk et al, 2000). It was also used, together with a more advanced definition, in the BMES (Mitchell et al, 1995). This definition has been used in providing prevalence rates for early AMD from the BMES and other studies in this report.

The second, more severe definition of early AMD, used in the BMES (Mitchell et al, 1995), was defined as the presence of: a) large (>125 microns), indistinct or 'soft' drusen, or b) the presence of any large drusen with associated retinal pigmentary abnormalities.

⁵ Prevalence relates to the total number of people in a population with a disease at any point in time, whereas incidence describes the number of new cases occurring during a defined period, typically over one year.

Late AMD is defined to include both neovascular AMD and atrophic AMD, also termed geographic atrophy (Bird et al, 1995).

The definition of neovascular AMD is generally consistent across studies, and is generally considered to include the following lesions (Mitchell et al, 1995 and VanNewkirk et al, 2000):

- Detachment of the neurosensory retina or RPE;
- Subretinal or sub-RPE haemorrhage;
- Retinal hard exudate deposition (from chronic leakage); and/or
- Subretinal fibrosis, previously termed disciform scar.

The definition of geographic atrophy is also generally consistent across studies as comprising the central areola zone of RPE atrophy with visible choroidal vessels, at least 175 microns in diameter and without any signs indicating neovascular AMD (Mitchell et al, 1995; Klein et al, 2002).

3.1.2 Prevalence of AMD - International Studies

Many epidemiological studies of AMD have been conducted worldwide during the past 30 years. In a large meta-analysis of several population-based studies in the US, Australia and Europe, the prevalence of early AMD was estimated to be 6.83%, and that for late AMD (neovascular AMD and/or geographic atrophy) estimated to be 1.47% among persons 40 years and older (Smith et al, 2001). Many other studies, including those from countries outside the US and Europe, have also reported relatively similar results in Caucasian populations.

In recent years, population-based data on AMD in many other racial/ethnic groups have also been provided. An Asian meta-analysis that included data from studies conducted in China, Japan, India, Taiwan, Singapore and other countries demonstrated that the age-specific prevalence of AMD in Asian populations was relatively similar to that in white populations (Kawasaki et al, 2010). More important has been the emerging evidence that in Asian populations, a polypoidal dilatation of the inner choroidal vasculature, termed polypoidal choroidal vasculopathy (PCV), appears to account for up to 50% of all cases of neovascular AMD, particularly in ethnic Japanese and Chinese populations (Maruko et al, 2007). In various AMD series reported from Western countries, the PCV subtype of neovascular AMD lesions is estimated to only make up 8-13% of neovascular AMD (Maruko et al, 2007; Laude et al, 2010; Lafaut et al, 2000; Yannuzzi et al, 1997; Yannuzzi et al 1999; Sho et al, 2003). The significance of PCV is that it does not respond as well to standard management of neovascular AMD (see Treatment of AMD, Section 6).

3.1.3 Prevalence of AMD - Australian Studies

The BMES, 1992-1994, reported in 1995, provided the first Australian estimates of the prevalence for early and late stages of AMD in residents of a 2-postcode area of the Blue Mountains region, west of Sydney. This area had a demographic distribution very similar to that of the Australian population, and could be considered representative of Australia as a whole. The study was conducted on 3,654 urban residents aged 50 years or older, and a further 123 nursing home residents. Its population was older than the MVIP (below), but it

did not, however, include a specifically rural sample (Mitchell et al, 1995) as was included in the MVIP.

The MVIP study, 1995-1996, reported in 2000, provided estimates of the prevalence of early and late stage AMD in residents of the state of Victoria, Australia. Considered to be representative of the Victorian population and of Australia as a whole, the study was conducted on 5,147 urban and rural residential adults aged 40 years and older (VanNewkirk et al, 2000).

A greater proportion, 3428 (91%) to 3505 (93%) of the 3777 BMES participants, including nursing home residents had gradable retinal photographs for assessment of AMD signs (Mitchell et al, 1995, Mitchell et al, 1997), than the 4345 (84%) with gradable photographs of the 5147 MVIP participants (van Newkirk et al, 2000).

Prevalence rates for early AMD, geographic atrophy and neovascular AMD derived from the BMES are shown in Table 3.1. The prevalence of early AMD was estimated to be around 13.0%, increasing from around 6% in participants aged 50-59 years to around 35% of participants aged 90 years and older. The prevalence of neovascular AMD and geographic atrophy were 1.38% and 0.65%, respectively. While there were some gender differences in prevalence for subgroups, most of these were not statistically significant.

Table 3.1: Estimated early and late AMD prevalence rates, BMES

Age group	Early AMD*		Neovascular AMD		Geographic atrophy	
	Male	Female	Male	Female	Male	Female
50-59	8.5 (1.2)	3.6 (0.4)	0	0	0	0
60-69	11.4 (3.1)	10.1 (3.1)	0.34	0.57	0	0
70-79	20.1 (8.2)	19.1 (8.5)	1.82	1.67	0.78	1.11
80-89	24.2 (11.9)	26.1 (15.0)	4.03	10.00	2.42	2.78
90+	37.5 (25.0)	31.8 (13.6)	12.50	13.64	12.50	22.73
All ages (50+)	13.9 (4.7)	12.4 (5.0)	0.98	1.69	0.46	0.80
Combined (50+)	13.0 (4.8)		1.38		0.65	

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

*Defined as presence of large drusen (>125 microns) and/or retinal pigment epithelial abnormalities (hyperpigmentation or hypopigmentation). Values in parentheses represent the prevalence of the more severe BMES Early AMD definition (large indistinct soft drusen or large distinct soft drusen with accompanying retinal pigment epithelial abnormalities).

The overall prevalence rate for late AMD was higher in the BMES, compared with the BDES and Rotterdam studies, and lower in the MVIP (Table 3.2). For early AMD, the estimates were quite similar for the BMES, MVIP and BDES, using a similar definition (large drusen and/ or retinal pigment epithelial changes). Published BMES data (Mitchell et al, 1995) gave an overall lower rate (5.8%), due to the use of a more advanced definition. Table 3.2 incorporates some unpublished age-specific prevalence data from the baseline BMES examination. Adjusting the MVIP definition to coincide with the more severe alternate definition used in the BMES, gave a prevalence of early AMD that was slightly lower at 4.4% for males (compared to 5.7% in the BMES) and 5.4% for females (compared to 5.9% in the BMES) (VanNewkirk et al, 2000).

Table 3.2: Comparison of AMD prevalence in various population based studies of predominantly European Caucasian samples

Study	Age standardised prevalence % (95% confidence interval)		
	Early AMD	Late AMD	Any AMD
Blue Mountains Eye Study (BMES) *	12.1** (10.9, 13.3)	2.2 (1.7, 2.8)	14.3 (13.0, 15.6)
Visual Impairment Project (MVIP)	4.2 *** (3.6, 4.9)	0.68 (0.30, 1.1)	15.7 (14.4, 17.1)
Beaver Dam Eye Study (BDES)	15.1 (13.7, 16.4)	1.1 (0.85, 1.4)	15.3 (14.2, 16.4)
Rotterdam Study (RS)	-	1.1 (0.90, 1.4)	-

Sources: Mitchell et al (1995) and additional BMES data; VanNewkirk et al (2000); Klein et al (2002); Vingerling et al (1995).

* Age-standardised to Australian 50+ population in 2010, using the following definitions of 'Early AMD'.

** Presence of large drusen and/ or retinal pigment epithelial abnormalities in at least one eye.

*** Presence of large indistinct soft drusen or large distinct soft drusen with retinal pigment epithelial abnormalities in at least one eye).

Smith et al (2001) pooled data from Australia, Europe and North America on AMD and reported relatively similar prevalence rates for geographic atrophy and neovascular AMD across these populations (Table 3.3). The pooled (3-continent) data included population-based cohort studies in North America (the BDES), Europe (the Rotterdam Study) and Australia (the BMES).

The prevalence of geographic atrophy in the BDES, Rotterdam Study and BMES was 0.44%, 0.66%, and 0.45% respectively, while prevalence of neovascular AMD was estimated to be 0.88%, 0.72%, and 1.20% respectively (shown in Table 3.3). An age-related increase in the prevalence of both these late AMD lesions was evident in the three studies. Some individual cases were excluded from each study in the pooled analysis, after strict adjudication, or because of slightly poorer photographic quality, hence the small differences from the numbers in Table 3.2 above.

Using the BDES and the BMES, a ratio of roughly two to one was estimated for the prevalence of neovascular AMD compared with geographic atrophy (Smith et al, 2001). This indicates that atrophic AMD (here termed 'dry' AMD) is only around half as prevalent in European Caucasian populations as neovascular AMD. This, however, does not apply to the commonly used description of 'dry' AMD which also includes cases with early AMD signs.

In this document, 'dry' AMD is confined to cases of geographic atrophy, and does not include early AMD cases.

Table 3.3: Estimated prevalence of late AMD across three large scale population studies

Age	BDES		Rotterdam Study		BMES		Combined	
	NV	GA	NV	GA	NV	GA	NV	GA
	%	%	%	%	%	%	%	%
<55	0.00	0.00	0.00	0.00	0	0.00	0	0
55-64	0.31	0.08	0.09	0.04	0.17	0.00	0.17	0.04
65-74	1.05	0.32	0.30	0.34	0.50	0.17	0.54	0.29
75-84	3.41	2.07	1.7	1.26	3.33	1.58	2.52	1.54
85+	5.41	5.41	3.86	4.41	11.57	3.31	5.76	4.22
All ages	0.88	0.44	0.72	0.66	1.20	0.45	0.89	0.54

Source: Smith et al (2001).

Note: GA = Geographic atrophy NV = Neovascular AMD.

3.1.4 Prevalence of early AMD

The prevalence of early AMD was derived from prevalence rates of these signs bilaterally (i.e., based on the better eye) as shown in Table 3.4 or in one or both eyes (i.e., based on the worse eye) in Table 3.5. Demographic ageing over the coming decades will result in an increase in the proportion of people in older age groups. As the proportion of people aged 65 years or over is projected to increase from 13% in 2010 to 23% by June 2050 (IGR, 2010), the numbers of people with AMD is also projected to increase.

Table 3.4: Prevalence estimates for bilateral Early AMD (based on the better eye)

Age	2010	2015	2020	2025	2030
50-54	12,887	13,797	13,792	14,793	14,598
55-59	10,066	11,040	11,831	11,839	12,700
60-64	33,073	35,588	39,112	41,967	42,039
65-69	46,991	60,638	65,504	72,164	77,528
70-74	48,883	59,216	76,838	83,358	92,059
75-79	59,494	69,088	84,552	110,377	120,261
80-84	68,069	70,445	83,133	102,863	135,072
85-89	35,699	41,072	43,295	51,922	65,057
90+	22,202	30,252	37,033	41,206	49,238
Total	337,364	391,135	455,091	530,488	608,552

Source: BMES data based on Mitchell et al (1995) and later; Australian Bureau of Statistics (ABS) population projection series B.

Table 3.5: Prevalence estimates for Early AMD in at least one eye (based on worse eye)

Age	2010	2015	2020	2025	2030
50-54	84,057	89,991	89,960	96,491	95,216
55-59	75,492	82,800	88,733	88,790	95,252
60-64	110,848	119,278	131,091	140,660	140,899
65-69	110,556	142,664	154,112	169,782	182,401
70-74	130,355	157,911	204,902	222,287	245,491
75-79	116,221	134,963	165,172	215,620	234,928
80-84	101,088	104,617	123,460	152,760	200,594
85-89	83,316	95,855	101,044	121,177	151,833
90+	44,392	60,485	74,045	82,386	98,446
Total	856,324	988,563	1,132,517	1,289,954	1,445,058

Source: BMES data based on Mitchell et al (1995) and later; ABS population projection series B.

Table 3.4 and Table 3.5 show that the number of Australians with early AMD in at least one eye exceeds those with early AMD in both eyes. This is because a large proportion of people who have mild pigmentary changes at the macula, have it in just one eye, in the absence of large drusen. In the BMES, there were around as many persons with macular pigmentary changes in either the right or left eye only as those with this sign in both eyes. However, the symmetry of large drusen was considerably greater. It is known that there are many non-AMD causes of pigmentary disturbance (previous infection, trauma, central serous retinopathy etc), causes that cannot be identified separately with ease in a large prevalence study.

This finding highlights a potential shortcoming of the International AMD Classification. It was one of the reasons a more advanced definition for early AMD was developed for the BMES, and which is also reported in this document. More advanced early AMD signs are known to be more symmetrical (i.e., tend to affect both eyes at any time).

The number of Australians with early AMD in at least one eye is projected to increase by almost 70%, from around 855,000 in 2010 to around 1.44 million in 2030.

The number of Australians with early AMD in both eyes is projected to increase from around 340,000 in 2010 to over 600,000 in 2030, due to demographic ageing.

3.1.5 Prevalence of late AMD

Prevalence rates for bilateral or unilateral late AMD by age group, in the better or worse eye respectively, are shown in Table 3.6. The economic cost of visual impairment is based on the prevalence of bilateral AMD (i.e., when it affects both eyes) as this has the greatest impact on visual acuity. However, the cost of treating AMD, for example by using Lucentis, depends on the prevalence of AMD regardless of whether the disease is affecting the best or worse eye. Consequently, both prevalence estimates are described.

Table 3.6: Estimated prevalence rates (%) for late stage AMD in Australia

Age	Bilateral (better) eye	At least one (worse) eye
	%	%
<55	0	0
55-59	0	0
60-64	0	0.32
65-69	0.15	0.61
70-74	0.76	1.15
75-79	2.25	4.75
80-84	5.14	7.01
85-89	11.11	17.78
90+	26.67	33.33

Source: BMES data based on Mitchell et al (1995) and later.

The number of prevalent cases of late AMD affecting at least one (worse) eye is presented in Table 3.7. It is estimated that in 2010 in Australia there were around 167,000 people with late AMD affecting at least one eye.

Table 3.7 : Prevalence estimates for late AMD affecting at least one (worse) eye

Age	2010	2015	2020	2025	2030
<55	0	0	0	0	0
55-59	0	0	0	0	0
60-64	3,877	4,171	4,585	4,919	4,928
65-69	5,555	7,168	7,744	8,531	9,165
70-74	8,183	9,913	12,862	13,954	15,410
75-79	26,288	30,527	37,360	48,771	53,139
80-84	30,945	32,025	37,793	46,762	61,405
85-89	47,617	54,783	57,749	69,255	86,776
90+	44,392	60,485	74,045	82,386	98,446
Total	166,855	199,072	232,137	274,579	329,267

Source: BMES data based on Mitchell et al (1995) and later; ABS population projection series B.

Note: These data are not additionally adjusted for the competing risk of mortality. These projections have assumed no effective intervention (e.g., such as Lucentis for neovascular cases).

The number of prevalent neovascular AMD cases affecting at least one (worse) eye is presented in Table 3.8. It is estimated that in 2010 in Australia, there were around 108,000 people with neovascular AMD affecting at least one eye.

Table 3.8: Prevalence estimates for neovascular AMD in at least one eye (worse eye)

Age	2010	2015	2020	2025	2030
<55	0	0	0	0	0
55-59	0	0	0	0	0
60-64	3,877	4,171	4,585	4,919	4,928
65-69	5,555	7,168	7,744	8,531	9,165
70-74	4,056	4,913	6,375	6,916	7,638
75-79	17,987	20,887	25,562	33,370	36,358
80-84	22,690	23,482	27,711	34,288	45,024
85-89	35,699	41,072	43,295	51,922	65,057
90+	17,754	24,190	29,613	32,950	39,372
Total	107,617	125,884	144,886	172,896	207,543

Source: BMES age specific data based on Mitchell et al (1995) and later; ABS population projection series B.

Note: These data are not additionally adjusted for the competing risk of mortality. These projections have assumed no effective intervention (e.g., such as Lucentis).

The number of prevalent cases of bilateral late AMD (affecting the better eye) is presented in Table 3.9. It is estimated that in 2010 in Australia, there were around 107,000 people with late AMD affecting both eyes.

Table 3.9: Prevalence of bilateral late AMD (better eye)

Age	2010	2015	2020	2025	2030
<55	0	0	0	0	0
55-59	0	0	0	0	0
60-64	0	0	0	0	0
65-69	1,366	1,763	1,904	2,098	2,254
70-74	5,408	6,551	8,500	9,222	10,184
75-79	12,452	14,460	17,697	23,102	25,171
80-84	22,690	23,482	27,711	34,288	45,024
85-89	29,754	34,232	36,085	43,275	54,223
90+	35,521	48,399	59,249	65,924	78,774
Total	107,191	128,886	151,146	177,908	215,630

Source: BMES data based on Mitchell et al (1995) and later; ABS population projection series B.

Note: These projections have assumed no effective intervention (e.g., such as Lucentis).

The number of prevalent bilateral neovascular AMD cases (affecting both eyes) is presented in Table 3.10. It is estimated that in 2010 in Australia, there were around 62,000 people with neovascular AMD in both eyes.

Table 3.10: Prevalence of bilateral neovascular AMD (better eye)

Age	2010	2015	2020	2025	2030
<55	0	0	0	0	0
55-59	0	0	0	0	0
60-64	0	0	0	0	0
65-69	1,366	1,763	1,904	2,098	2,254
70-74	1,352	1,638	2,125	2,305	2,546
75-79	6,918	8,033	9,832	12,835	13,984
80-84	18,584	19,233	22,697	28,084	36,878
85-89	20,836	23,971	25,269	30,304	37,970
90+	13,319	18,147	22,216	24,718	29,537
Total	62,375	72,786	84,043	100,344	123,168

Source: BMES aged specific data based on Mitchell et al (1995) and later; ABS population projection series B.
 Note: These projections have assumed no effective intervention (e.g., such as Lucentis).

Table 3.11 summarises the estimated prevalence rates for late AMD in Australia in 2010, by subtype (neovascular or atrophic), as either bilateral cases or those with late AMD lesions in at least one eye. This is relevant as only neovascular AMD is currently treatable.

The first estimate assumes that 67% of late stage AMD is primary neovascular AMD and that 33% is primary geographic atrophy (Smith et al, 2001). However, the second estimate (in parentheses) assumes that 58% of late stage AMD consists of neovascular AMD and 42% consists of geographic atrophy, as found in the BMES (Mitchell et al, 1995). Given the relatively small number of late AMD cases in any particular population study (such as BMES), the first estimate (using the pooled data from '3 continents') is likely to be more accurate and hence is shown as the total of late AMD cases in Australia in at least one or in both eyes.

Table 3.11: Estimated prevalence of late stage AMD in 2010, by type (based on BMES data)

	Bilateral (better) eye	At least one (worse) eye
Neovascular AMD	71,818 (62,375)	111,793 (107,617)
Geographic atrophy	35,373 (44,816)	55,062 (59,238)
Total late stage AMD	107,191	166,855

Source: BMES data based on Mitchell et al (1995) and later; ABS population projection series. Note: the estimate in parentheses takes neovascular AMD and geographic atrophy assumptions from BMES (Mitchell et al, 1995)

It is estimated that in 2010, there were 1.023 million Australians with AMD, equivalent to one in seven people over the age of 50. This comprises 856,000 with early AMD (Table 3.5), plus nearly 167,000 with late AMD in at least one eye (Table 3.7).

It is further estimated that by 2030, as a result of demographic ageing, the numbers with AMD would increase by over 70% to 1.77 million, in the absence of effective prevention and treatment efforts. This comprises 1.44 million with early AMD and 329,000 with late stage AMD in at least one eye.

3.1.5.1 Prevalence of vision impairment associated with late AMD

Estimates of vision loss associated with AMD can be based on the prevalence of bilateral late AMD (in the better eye). However, estimating the number of Australians with vision loss due to neovascular AMD or geographic atrophy, particularly bilateral blindness, is difficult, as none of the surveys included such persons.

One approach to estimating the severity of vision loss from neovascular AMD is to use the proportions of patients who would be likely to progress to different visual acuity levels, after 3 years, as calculated in the large natural history study by Wong et al (2000). Using this approach, it can be estimated (shown in Table 3.12) that of people with neovascular AMD, by 3 years, 7.9% would be likely to have mild visual impairment, 20.1% would be likely to have moderate visual impairment and 72% would be likely to have severe visual impairment (Australian 'legal' blindness). Table 3.12 assumes no effective therapeutic intervention.

Table 3.12: Likely impact of neovascular AMD on vision (and proportion with blindness)

Visual acuity lines lost	% total at 36 months	Visual classification
> 20/50	7.9	Mild
< 20/50, ≥20/100	9.6	Moderate
<20/100, ≥20/200	10.5	Moderate
<20/200, ≥20/400	23.7	Severe (blindness)
<20/400	48.3	Severe (blindness)

Source: Deloitte Access Economics calculations based on Wong et al (2008). This table assumes no effective therapeutic intervention.

The severity of visual impairment associated with geographic atrophy was approximated using vision loss proportions derived from Access Economics (2006). It used DISMOD II⁶ to project the prevalence by severity based on data from the MVIP and Australian Institute of Health and Welfare (AIHW) disability weights. Using these data it is estimated that in 2010, approximately 56% suffer from mild visual impairment, 19% from moderate visual

⁶ DISMOD II is a publicly available software tool developed by the World Health Organization (WHO) to help estimate the epidemiology of a disease. It exploits the fact that disease incidence, prevalence, remission, case fatality, and mortality are not independent variables and can therefore be estimated from one another. For more information see http://www.who.int/healthinfo/global_burden_disease/tools_software/en/index.html, accessed 19 April 2010.

impairment and 25% from severe visual impairment associated with geographic atrophy in the better eye.

Using these proportions, the following assumptions were used to estimate the number of Australians with vision impairment and blindness from late AMD:

1. 58% of late stage AMD consists of neovascular AMD and 42% consists of geographic atrophy, as found in the BMES (Mitchell et al, 1995) – Table 3.13.
2. 67% of late stage AMD consists of neovascular AMD and 33% consists of geographic atrophy (Smith et al, 2002) – Table 3.14

Table 3.13: Estimated prevalence of bilateral visual impairment due to late AMD, 2010

	Mild ¹	Moderate ²	Severe ³	Total
Neovascular AMD	4,918	12,556	44,901	62,375
Geographic atrophy	24,995	8,624	11,197	44,816
Total	29,913	21,180	56,098	107,191

Source: Access Economics (2006); Mitchell et al (1995); Wong et al (2005).

- 1- worse than 6/12 but better than or equal to 6/24, in the better eye.
- 2- worse than 6/24 but better than or equal to 6/60, in the better eye.
- 3- worse than 6/60 in the better eye (bilateral blindness).

Note: assumes 58% NV and 42% GA split (62,375 NV + 44,816 GA = 107,191 total); and assuming no effective therapeutic intervention.

Table 3.14: Estimated prevalence of bilateral visual impairment due to late AMD, 2010

	Mild ¹	Moderate ²	Severe ³	Total
Neovascular AMD	5,674	14,435	51,709	71,818
Geographic atrophy	19,738	6,792	8,843	35,373
Total	25,412	21,227	60,552	107,191

Source: Access Economics (2006); Smith et al (2002); Wong et al (2005).

- 1- worse than 6/12 but better than or equal to 6/24, in the better eye.
- 2- worse than 6/24 but better than or equal to 6/60, in the better eye.
- 3- worse than 6/60 in the better eye (bilateral blindness).

Note: assumes 67% NV and 33% GA split (71,818 NV + 35,373 GA = 107,191 total); and assuming no effective therapeutic intervention.

3.1.5.2 Limitations of using natural history estimates

It is possible and even likely that the approach of incorporating natural history projections over 3 years could lead to an overestimate of the number of persons at any point in time with neovascular AMD causing bilateral blindness, as it is based on future projections rather than actual data.

An alternative approach is to use the actual proportion of persons with prevalent bilateral neovascular AMD (and geographic atrophy), who were blind in both eyes in the baseline BMES, even accounting for the major limitation from the relatively small number of such cases in any population study.

This approach provides a further, possibly more realistic, estimate of the number of Australians in 2010 with bilateral blindness due to neovascular AMD of between 22,954 and 26,429 persons, respectively, using either the Smith et al (2001) estimates for neovascular AMD versus geographic atrophy, or the actual BMES proportions of these two late stage lesions. These estimates rose to between 30,487 and 34,255 Australians, respectively, when those bilaterally blind people with a non-AMD cause of blindness in their first eye and neovascular AMD as the cause of blindness in their second eye were also included (disparate cases).

The corresponding estimated prevalence of Australians in 2010 with bilateral blindness due to geographic atrophy was between 10,400 and 13,176, respectively, using either the two approaches above. These estimates rose to between 19,485 and 20,709 Australians, respectively, when those bilaterally blind people with a non-AMD cause of blindness in their first eye and geographic atrophy as the cause of blindness in their second eye were also included (disparate cases). None of these estimates has assumed any effective therapeutic intervention, as this was relatively true at the time the BMES and MVIP studies were conducted.

Neovascular AMD may be subfoveal, juxtafoveal or extrafoveal; the location depends mainly on the likely duration of symptoms. If symptom duration is quite short, patients may be seen while the new vessel is still outside the foveal centre (i.e., juxtafoveal, meaning involvement of the foveal edge), or extrafoveal, meaning that the new vessel is still outside the foveal area. Within a few weeks, most new vessels spread to involve the fovea. Of patients presenting with neovascular AMD, studies have indicated that only around 8-9% were extrafoveal, around 18-19% juxtafoveal and the remaining 72-74% were subfoveal (Beaumont et al, 2007; Zawinka et al, 2005).

Another classification that was used in the past to describe the characteristics of neovascular AMD, was to describe the new vessels as predominantly or minimally 'classic', meaning well defined on fluorescein angiography (FA), or 'occult', meaning poorly defined on FA. This was particularly used to help identify patients who had the best response to photodynamic therapy (PDT) – those with classic lesions (Bressler, 2001), but this subdivision has much less prognostic value now that anti-VEGF therapy is available and has been shown to be fairly similarly effective in both classic and occult neovascular AMD lesions. The proportion of patients presenting with neovascular AMD who have occult disease has ranged from around 60% (Zawinka et al, 2005) to higher proportions in different studies.

Classic or occult patterns of neovascular AMD, however, have not been shown to predict any particular level of vision loss.

3.1.5.3 Prevalence of late AMD summary

It is estimated that without effective treatment, up to 61,000 Australians could have been legally blind (i.e., in both eyes) associated with late AMD in 2010. Of these, most (around 52,000) would have been legally blind from neovascular AMD, for which a highly effective treatment is now available (Table 3.14). Using the actual BMES proportions of persons with neovascular AMD who were bilaterally blind provided a lower figure, i.e., between 30,000 (lowest estimate) and 34,000 (Section 3.1.5.2).

The true estimate of prevalent bilateral blindness from neovascular AMD in Australia in 2010 is likely to lie between 30,000 and 52,000 persons, assuming no effective therapeutic intervention.

Table 3.14 shows that around 9,000 would have been legally blind from geographic atrophy. Using the actual BMES proportions of persons with geographic atrophy who were bilaterally blind, provided a higher figure, i.e., between 19,000 and 21,000.

The true estimate of prevalent bilateral blindness from geographic atrophy in Australia in 2010 is likely to lie between 9,000 and 21,000 persons.

Overall, the true estimate for bilateral blindness from any late AMD in Australia in 2010 is thus likely to lie between 39,000 and 73,000 persons. Without effective therapeutic intervention, the number of Australians with bilateral visual impairment due to AMD would thus be projected to increase from 107,000 in 2010 to 215,000 by 2030; two-thirds of these cases would be due to neovascular AMD (Table 3.10).

Future analyses will also estimate the number of Australians whose blindness from neovascular AMD has been avoided by the use of ranibizumab (Lucentis) therapy, since the Pharmaceutical Benefits Scheme (PBS) listing in late 2007.

The projected rise in the number of people with AMD will lead to an increasing importance of the disease as the population ages. Visual impairment and blindness from AMD have important socio-economic implications, of which the costs of care and rehabilitation are the most apparent (Bonastre et al, 2003), with other impacts from increasing dependency (Wang et al, 1999; Ivers et al, 2003). Equally important are the indirect costs resulting from the loss of quality of life (Chia et al, 2004). Actively addressing risk and protective factors will help reduce the burden of the disease as well as socio-economic costs. Later chapters discuss these issues.

3.2 Incidence and Progression of AMD

3.2.1 Incidence of AMD

Overview of International Studies

The U.S. Beaver Dam Eye Study reported a 14.3% 15-year cumulative-incidence (i.e., new cases) for early AMD and 3.1% for late AMD, with increasing age as the strongest risk factor (Klein et al, 2007b). Similar findings were made from the Australian Blue Mountains Eye Study (BMES); a 14.1% cumulative incidence for early AMD and 3.7% for late AMD (Wang et al, 2007). The Los Angeles Latino Eye Study reported a 4-year incidence of AMD of 2.5%, with 2.2% showing progression over the same period (Choudhury et al, 2011). Data from Asian populations have been somewhat comparable. The Hisayama study reported an age-standardised 9-year cumulative incidence of early AMD of 10.0%, with late AMD in 1.4% (Yasuda et al, 2009).

Australian Studies

Australian incidence rates for AMD have most recently been estimated using the BMES (Wang et al, 2007), with cumulative 10 year rates reported for early and late stage AMD.

Table 3.15: Estimated cumulative 10 year incidence rates of AMD, by age, using BMES data

Age	Geographic atrophy	Neovascular AMD	Any late AMD ^(a)	Early AMD ^(b)	Indistinct/reticular drusen	Pigmentary abnormality
<60	0.17	0	0.17	4.2	3.4	13.2
60-69	1.0	2.0	3.0	14.7	11.3	24.8
70-79	4.9	4.9	9.1	28.7	26.0	36.7
80 +	17.5	12.4	24.3	32.5	31.6	44.1
All ages	1.7	2.2	3.7	14.1	11.7	23.3

Source: Wang et al (2007). Note: (a) Any late AMD was defined by the new appearance of either neovascular AMD or geographic atrophy in either eye. (b) Early AMD was defined by the new appearance of either indistinct soft or reticular pseudodrusen or the new appearance of both distinct soft drusen and retinal pigmentary abnormalities (more severe AMD definition).

The cumulative 10-year incidence of early AMD is naturally much greater than late AMD across all age groups. The incidence of early AMD for all ages is 14.1%, ranging from 4.2% for those aged 60 years and younger to 32.5% for those aged 80 years and older. In comparison, the incidence of late AMD for all ages is 3.7%, ranging from 0.17% in the youngest group to 24.3% in the oldest group. Across all ages the incidence of geographic atrophy is lower than neovascular AMD, at 1.7% and 2.2% respectively, but higher in the 80+ group (17.5% compared to 12.4%).

Wang et al (2007) compared the incidence rates from BMES with those in the BDES⁷, finding some differences but none that were substantially significant. Since the BMES is believed to be representative of the Australian population, incidence rates from Wang et al (2007) were used to estimate the incidence of early and late AMD (along with Australian population forecasts from Access Economics Demographic Model⁸ (AE-DEM)). The number of incident cases (number of people) of early and late stage AMD is shown in Table 3.16.

Table 3.16: Estimated incident cases of early and late stage AMD in 2010, by age

Age	Geographic atrophy	Neovascular AMD	Early AMD
<60	569	0	14,045
60-69	2,102	4,204	30,900
70-79	6,150	6,150	37,277
80 +	14,649	10,380	27,206
Total	23,470	20,734	109,428

Source: Access Economics calculations based on Wang et al (2007) and AE-Dem population projections.

Overall, it can be estimated that in 2010, there were 20,734 new cases of neovascular AMD, 23,470 new cases of geographic atrophy and 109,428 new cases of early AMD in Australia.

3.2.2 Natural history and progression of AMD lesions

The progression to late AMD from signs of early AMD has been reported to range from 1.1% to 5.4% over five years (Mitchell et al, 2002, Wang et al, 2002). Over 15 years, this range has been reported at 4.7% to 16.3% (Klein et al, 2007).

Data based on the AREDS Classification

People with no AMD (AREDS category 1) generally have no signs of the characteristics associated with AMD, although they mostly have prevalent small ('hard') drusen (AAO, 2008). According to Mitchell et al (2005) and Cook (2008), over 90% of the population aged 40 years or over will have one or two small hard drusen (<63 microns in diameter) in the macular region of at least one eye with no definite risk of progression to advanced AMD. In eyes with more than 8 small hard drusen (<63 microns in diameter), there is a three-fold increased risk of developing large soft drusen (≥125 microns in diameter) and pigmentary changes after 10 years (Cook, 2008).

⁷ Methods and grading used in the BMES were almost identical to those used in the BDES (Klein et al, 2002).

⁸ AE-DEM uses a combination of fertility, mortality and migration rates forecasts to project the future Australian population. Base fertility and mortality profiles for each age and gender (for mortality) were sourced from Productivity Commission (2005), and adjusted over time to match the projection for the total value.

Early AMD

AREDS category 2 is characterised by multiple small drusen, single or non-extensive intermediate drusen (63–124 microns) and/or pigment abnormalities in one or both eyes. People in this category generally have a central visual acuity similar to those with normal maculae. People with category 2 AMD have a relatively low (1.3%) risk of progressing to advanced AMD within five years in either eye (AREDS, 2001).

AREDS category 3 is defined as the presence of extensive medium-sized drusen or one or more large drusen (>125 microns in diameter) in one or both eyes, or geographic atrophy not involving the foveal centre (AREDS, 2001). In the AREDS, progression from category 3 to category 4 over five years was approximately 18%. For people with large drusen in at least one eye, around 6% of people developed late stage AMD after five years, while around 26% of people with bilateral large drusen developed late stage AMD over that period (AAO, 2008).

Three morphological or lesion factors were identified to be associated with an increased risk of progressing from early stage AMD to late stage AMD. They include:

- the presence of large drusen (>125 microns in diameter);
- retinal pigment epithelial abnormalities; and
- presence of late AMD in one eye (AREDS, 2001).

Late stage AMD

AREDS category 4 is defined by the presence of neovascular AMD and/or geographic atrophy. The recognition of late stage AMD in one eye is a moderate predictor of the future development of late AMD in the other eye. In the Beaver Dam Eye Study (BDES), approximately 22% of people had developed AMD in their remaining good eye after five years (Klein et al, 1997).

The BDES (Klein et al, 1997), BMES (Mitchell et al, 2002) and Rotterdam study (Van Leeuwen et al, 2003) followed participants five years from the initial baseline examinations. Klein et al (2002) and Wang et al (2007) followed participants again 10 years from baseline. Wang et al (2007) used the BMES to estimate the risk of progressing to late AMD over 10 years. These results are summarised in Table 3.17.

Table 3.17: The 10 year risk of developing late stage AMD in the BMES associated with different early AMD lesions and their characteristics

Early AMD lesion characteristics	Late stage AMD incidence		Relative risk (95% C.I.)
	5 year follow-up	10-year follow-up	
	%	%	%
Drusen size			
None or <125 microns	0.55	1.07	1.0
≥125 microns	11.11	21.3	9.3 (5.4-16.1)
Drusen type			
None or small drusen <125 microns	0.54	1.0	1.0
Distinct soft drusen	1.01	4.76	1.8 (0.6-4.9)
Indistinct soft drusen	19.47	44.44	19.2 (9.8-37.8)
Drusen location			
None or <63 microns with an area <250 microns	0.27	0.73	1.0
1500-3000 microns from the foveal centre	0.82	1.30	1.2 (0.3-4.3)
500-1500 microns from the foveal centre	9.16	14.29	8.6 (4.1-18.2)
Within a 500 microns radius of the foveal centre	17.60	36.36	26.5 (13.3-52.7)
Drusen area			
None or <375 microns in diameter	0.53	0.94	1.0
≥375 microns in diameter to <0.5 of the disc area	8.22	20.51	10.6 (5.2-21.7)
>0.5 of the disc area	23.94	62.50	26.7 (11.5-62.0)
Retinal pigment abnormality			
Absent	0.30	1.19	1.0
Present	11.26	12.18	11.8 (7.0-20.0)

Source: Wang et al (2007).

Note: Conditional on early AMD characteristics at baseline examination.

The progression of neovascular AMD is variable, so that in some people, no definite change in vision is noticed as the disease becomes more severe. This is particularly evident when AMD occurs in only one eye. Understanding disease progression is crucial to compare the outcomes from new therapies, and to determine the stage of AMD progression where the initiation of treatment is appropriate (Wong et al, 2008).

In patients with neovascular AMD, a systematic review and meta-analysis of 4,362 untreated neovascular AMD patients, showed that visual loss was progressive and rapid, with the number of lines of acuity lost between 1-3 lines at 3 months and between 3-4 lines by one year (Wong et al, 2008). Other recent data corroborate the findings of this meta-analysis. For The MARINA, VISION (Gragoudas et al, 2004) and PIER (Regillo et al, 2008) trials reported rapid falls in acuity in their control groups, with 2.5 (in MARINA) to 3.3 (in PIER) to 3.5 (in VISION) lines lost by the 12 month follow up.

As neovascular AMD accounts for around two-thirds of late AMD (Smith et al 2001; Guyer et al 1986), and is the only late stage currently amenable to treatment, there has also been interest in progression of early to neovascular AMD. A systematic literature review of the natural history of neovascular AMD from major randomised clinical trials and observational studies by Wong et al (2008) showed that after the onset and diagnosis of neovascular AMD, progression to severe central vision loss is reasonably rapid on average (Table 3.18).

Table 3.18: Proportion of visual acuity lines lost over time due to neovascular AMD

Visual acuity lines lost	3 months	6 months	12 months	24 months	36 months
< 3	76.0	65.0	49.3	43.4	43.6
3 to 6	14.1	15.4	27.0	25.4	18.2
> 6	10.1	19.8	28.3	39.0	43.3

Source: Wong et al (2008).

Wong et al (2008) found that the average visual acuity change associated with neovascular AMD progressed from one line lost at three months to 2.7 lines lost after 12 months and four lines lost after 24 months. The proportion of patients who developed severe vision loss (greater than six lines) compared to baseline, increased from 21.3% at six months to 41.9% by three years. These findings concur with findings from the MARINA and PIER randomised control trials of ranibizumab (Lucentis), where sham-treated eyes lost an average of two (in MARINA) or three (in PIER) lines by one year and three lines by two years (Rosenfeld et al, 2006; Mitchell et al, 2010).⁹ This matched findings from the VISION trial (Gragoudas et al, 2004), in which three lines were lost in the sham/PDT group at one year.

Wong et al (2008) also reported that the proportion of patients with visual acuity worse than 6/60 increased from 19.7% at baseline to 50.3% within three months and to 75.7% within three years. The changing proportions of patients in different visual acuity groups are shown in Table 3.19.

Table 3.19: Proportions of patients in different visual acuity groups

Visual acuity lines lost	3 months	6 months	12 months	24 months	36 months
> 20/50	2.1	4.0	2.7	2.2	8.5
< 20/50, >20/100	18.4	13.9	8.8	5.0	10.4
<20/100, >20/200	23.3	23.3	19.6	14.0	11.3
<20/200, >20/400	26.8	21.5	30.6	35.7	25.5
<20/400	23.5	33.8	35.4	49.4	52.1

Source: Wong et al (2008).

⁹ Minimally classic/occult trial of Anti- VEGF antibody ranibizumab in the treatment of Neovascular Age- related macular degeneration (MARINA) study

In order to estimate the risk of progressing from early stage AMD to late stage AMD, the AREDS research group developed a simplified clinical scale based on:

- the strong association of maximum drusen size and drusen area;
- the low frequency of RPE depigmentation and/or geographic atrophy in the absence of increased retinal pigment; and
- the presence of large drusen in both eyes as a strong risk factor for progression to late stage AMD compared to the presence in only one eye (AREDS, 2005).

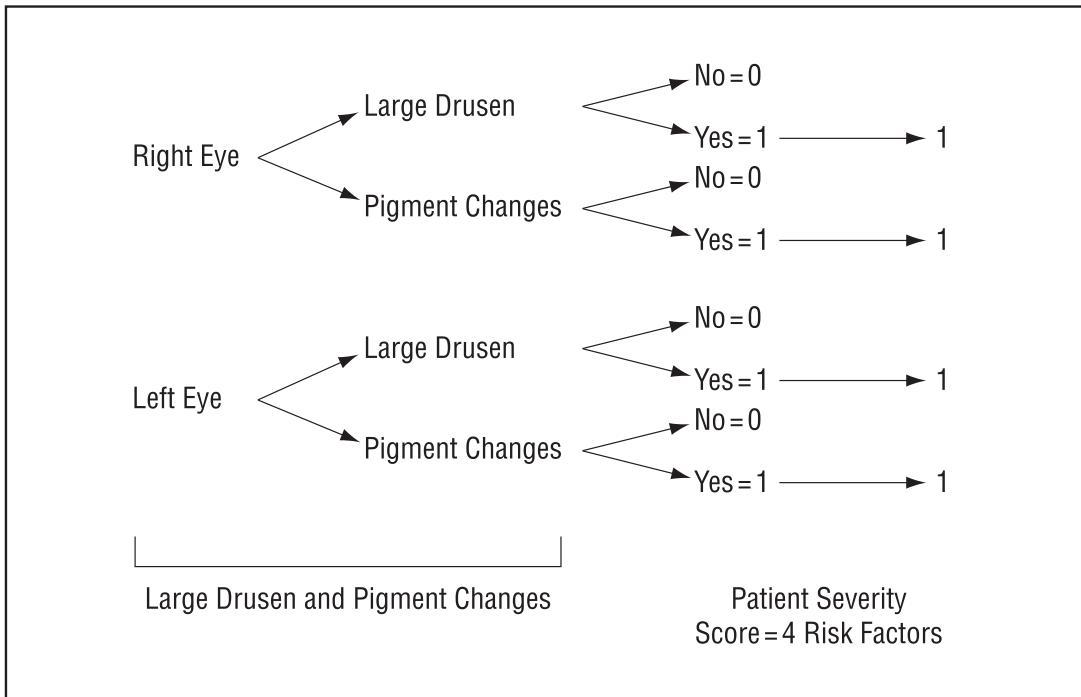
The clinical scale defines risk categories for the development of late AMD in people with early AMD. The scale was constructed using a grading of fundus photographs and cross-tabulations of presence or absence in each eye of drusen and pigment abnormalities (AREDS, 2005).

In order to estimate the risk of developing late AMD, clinicians first determine the number of risk factors present. The process to achieve this task is shown in Figure 3.1. The grading system assigns to each eye one risk factor for the presence of one or more large drusen (125 microns, width of a large vein at disc margin) and one risk factor for the presence of any pigment abnormality. Risk factors are summed across both eyes, yielding a five score scale (zero to four) on which the approximate five year risk of developing advanced AMD in at least one eye increases. For people with no large drusen, the presence of intermediate drusen in both eyes is counted as one risk factor.

Once the number of risk factors has been identified, the risk of developing late stage AMD can be determined by referring to estimated risk calculated by the AREDS research group. The number of risk factors and their associated risks are shown in Table 3.20.

The five-year risk of advanced AMD in at least one eye increases in a non-linear fashion as the number of risk factors increases from zero to four. However, the rate of increase in risk decreases, suggesting that the largest change in risk occurs with fewer risk factors. For example, the risk of progressing to advanced AMD from zero to one risk factor increases by around 2.5% compared to 25% from three to four risk factors. The former represents a five-fold increase in risk while the latter represents a doubling of risk.

Figure 3.1: Process to compute the number of risk factors associated with late stage AMD using AREDS data



Source: AREDS (2005).

Table 3.20: Estimated five year risk of progressing to late stage AMD using AREDS data

Number of risk factors	Five year risk (%)	Change in risk (%)
0	0.5	n/a
1	3	500
2	12	300
3	25	108
4	50	100

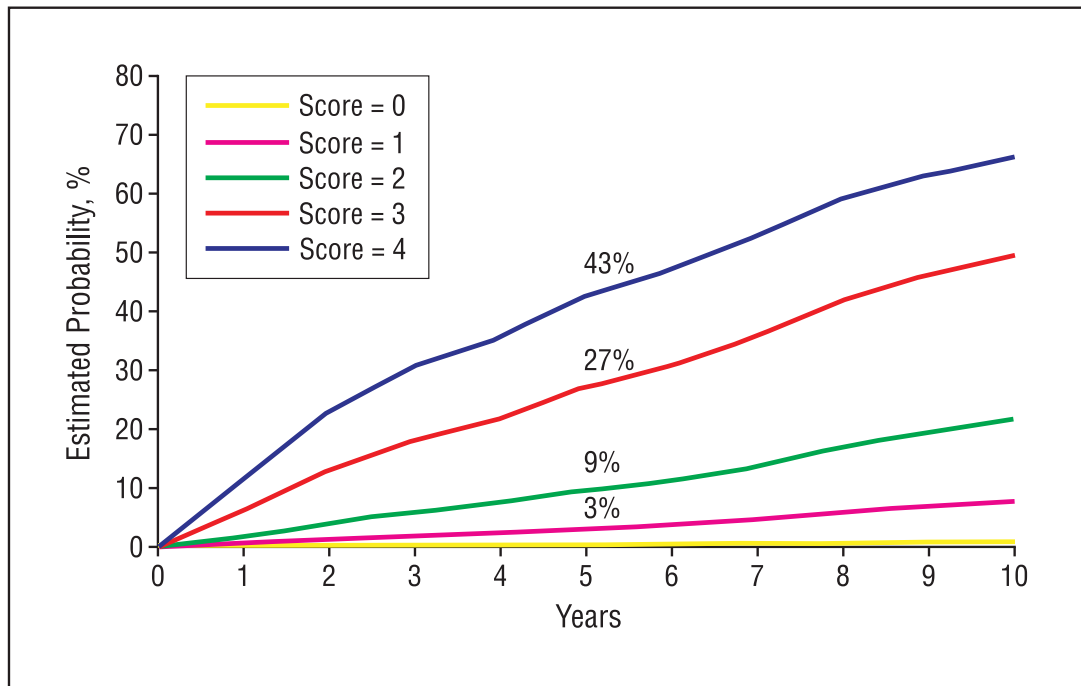
Note: In at least one eye in patients with both eyes at risk. Source: AREDS (2005).

The prevalence of drusen and pigment abnormalities can be used to determine the risk of progressing to late stage AMD. However, other modifiable risk factors, such as smoking, may influence these risks, as discussed in Chapter 4.

Since the AREDS research group initially developed the simplified clinical scale, there have been a number of studies that have sought to validate their scalar metric. The AREDS research group estimated the event rates for all AREDS participants using the simplified clinical scale through 10 years of follow-up. Chart 3.1 shows the risk of developing late stage AMD based on the number of risk factors present within each participant at the baseline examination. It shows that after five years the estimated risk presented in the clinical scale (Table 3.20) concurs well with the five year risk found in the AREDS. For example, using the clinical scale the estimated risk of developing late stage AMD after five years for a person with four risk factors is 50%, whereas in the AREDS the risk is 43%.

Across all scores, the average progression from early to late was 20.2% over five years in the AREDS, or around 4% per annum.

Chart 3.1: The risk of progressing to late stage AMD in the AREDS associated with different baseline severity scores



Note: In at least one eye in patients with both eyes at risk. Source: AREDS (2005).

Using BMES data, Wang et al (2007) found the scale to be robust in terms of predicting the risk of developing late stage AMD, although the five year risk (in Australia) tends to be slightly lower when compared to the simple clinical scale developed by the AREDS research group. This can be seen in Table 3.21, which shows the five year risk of developing late stage AMD based on the number of risk factors as determined by the simple clinical scale identified within the baseline examination.

Table 3.21: Five year risk of developing late stage AMD in the BMES

Number of risk factors	Five year risk (%)
0	0.11
1	1.69
2	9.72
3	10.26
4	35.29

Source: Wang et al (2007).

Currently there is no natural remission of AMD signs. However, intravitreal ranibizumab (Lucentis) has been found to stop the decline in visual acuity, and in many cases improve visual acuity, for people presenting with neovascular AMD. This is further explored in Chapter 6.

The Age Related Eye Disease Study (AREDS) measured the rate of progression from early stage¹⁰ AMD to late stage AMD. After five years, the AREDS reported that 20.2% of all those with early AMD progressed to advanced AMD, equivalent to around 4% per year. This rate of progression was relatively similar to rates reported from the Rotterdam Study (Klaver, 2000)¹¹ and the Blue Mountain Eye Study (BMES) Study (Mitchell, 2002)¹².

The progression rates for mild to moderate visual impairment and moderate to severe visual impairment have been measured within the Treatment of AMD with Photodynamic therapy (TAP) study and the MVIP. The rate of progression reported for mild to moderate visual impairment was 32% and for moderate to severe visual impairment was 46% over 2-3 years (Access Economics, 2006a).

3.3 Mortality associated with visual impairment from AMD

Many past studies have shown that the presence of visual impairment is a predictor of mortality, including data from the BMES (Wang, et al 2001). As AMD is the main cause of visual impairment in older people, this finding presents a paradox, as late AMD is a condition that typically occurs in people who have often survived to a relatively older age. Recent data from the BMES has contributed further to this question. In Cugati et al (2007), AMD was found to predict a 60% increase in mortality risk over an average 11-year period, independent of visual impairment or cataract, both of which have been associated with mortality. This was evident particularly among those aged under 75 years at the baseline examination. In a later assessment of 13-year mortality by Karpa et al (2009), the mortality risk associated with visual impairment and AMD was over 2-fold in persons aged under 75 years at baseline, and was predicted by both direct and indirect pathways.

Mortality associated with AMD is not caused by the disease itself but by the higher risk of other complications such as accidental falls, social isolation and depression. The attributable fraction previously estimated (Centre for Eye Research Australia and Access Economics, 2004) was updated for this report to reflect more recent data. Mortality data for the years 2003 to 2008 (ABS, 2010a) for 'diseases of the eye and adnexa' as the 'underlying cause' and as 'one of multiple causes of death' were used to derive an attributable fraction for mortality from vision loss of 1.38%. Applying this to the total number of deaths for people with vision loss in 2010 and the proportion of 'loss of well being' from severe visual impairment caused by AMD to all other eye diseases, it is estimated that 565 deaths are attributable to vision loss associated with AMD in 2010.

¹⁰ AREDS definition of Early Disease Stage (6/10) differs slightly from that used in this report (6/12).

¹¹ The Rotterdam Study was conducted during the period 1990–1993 in Rotterdam, The Netherlands, and included 7983 of 10,275 eligible residents aged 55 to 106 years (response, 77.7%) identified from the municipal registers. Klaver (2000) found a 5-year risk of developing AMD from Stages 2 and 3 (early stages) of 12.5% and 24%, respectively.

¹² Mitchell (2002) found 25 subjects who developed visual impairment from late AMD over the course of the study (5 years) from 115 who initially had early AMD, suggesting a progression rate from early to late AMD of approximately $4.3\% = (25/115)/5$.

Table 3.22: Deaths associated with vision loss associated with AMD, 2010

Age group	Deaths in the vision loss population	Deaths attributable to vision loss associated with AMD
40-49	123	0
50-59	1,210	0
60-69	3,080	7
70-79	12,589	89
80-89	52,359	331
90+	12,707	138
Total	82,068	565

Source: Access Economics using ABS 3303.0 (2010a) mortality data, AE-Dem population 2010 estimates, MVIP mortality rates and the relative burden of AMD in total burden from all eye diseases.

4 Risk and protective factors, and pathogenesis

Age is the strongest risk factor for both dry and wet AMD, a universal finding in all AMD studies (Mitchell et al 1995; Smith et al, 2001; Bird et al, 1995; Klein et al, 1992; Klein et al, 2004; Wong et al, 2006; Schmidt et al, 2006). Over 10% of people aged 80 years or older have late AMD (Bressler, 2004; Chakravarthy, 2006; Jager et al, 2008; Cruickshanks et al, 1997). Female gender has been variously identified as either a risk factor for AMD in people aged over 75 years (Smith et al, 2001), or unrelated to AMD (Mitchell, et al, 2002).

Epidemiological studies have also identified several other factors that can either increase or decrease the risk of developing AMD and increase the speed at which the disease progresses, or affect its age of onset. This chapter highlights those factors and also discusses preventive factors that could reduce an individual's likelihood of developing AMD.

4.1 Risk and protective factors

Risk factors can be both modifiable and non-modifiable. Modifiable risk factors mostly relate to lifestyle choices, and include tobacco smoking, suboptimal diet, alcohol consumption, and high body mass index (weight gain). Control of modifiable risk factors can potentially reduce the risk of developing AMD. Non-modifiable risk factors are those factors that cannot be changed (are immutable), such as genetic factors, age, sex, and ethnicity.

Although people may have one or more risk factor, this does not mean they will develop AMD. Conversely, AMD can arise even in the absence of known risk factors. In general, however, the more risk factors a person has, and the greater severity of each risk factor, then there is an increased likelihood of developing AMD.

4.1.1 Lifestyle factors

By eliminating or reducing modifiable risk factors, (smoking, alcohol, high body mass index, suboptimal diet), the likelihood of developing AMD may be reduced or its age of onset delayed, along with the risk of developing many other debilitating conditions that share these risk factors, such as cardiovascular disease.

Several studies have investigated the role of potential protective factors to reduce the likelihood of developing AMD, or to reduce the speed of progression. The potential role of diet and vitamin supplements stems from the hypothesis that oxidative stress is one pathogenetic mechanism by which AMD develops, and that diet high in antioxidant micronutrients can protect against this oxidative stress (Finkel et al, 2000).

Tobacco smoking

Tobacco smoking includes packet cigarettes, roll-your-own cigarettes, pipes and cigars. The mechanism by which smoking affects the retina is not fully established. It has been hypothesised that smoking can increase AMD risk by depressing serum antioxidant levels, altering choroidal blood flow and the retinal pigment epithelium (RPE) drug detoxification pathways, or by decreasing the dietary absorption of luteal pigments needed at the macula, thereby allowing the macula to sustain light and oxidative damage (Klein et al 2002; Smith et al, 1996; Thornton et al 2005; Seddon et al 2006; Coleman et al 2008).

Smoking is the main modifiable risk factor for AMD (Klein et al, 1993; Smith et al, 1996; Vingerling et al, 1996; Klein, 2007), and is the only modifiable risk factor consistently identified to increase the risk of developing AMD in large scale population based studies (Tomany et al, 2004).

A dose response relationship has been observed in many studies whereby increasing odds are associated with a greater number of pack-years¹³ smoked (Klein et al 2002; Tan et al 2007). This and other data suggest that cessation of smoking may be associated with a reduced subsequent risk. Some studies (Mitchell et al 2002; Tan et al 2007; Klein et al 2002), have also shown that current smokers develop late AMD 5 to 10 years earlier than never (or past) smokers.

In the BMES Australian population-based study, current smokers at the study baseline had a cross-sectional four-fold increase in the risk of developing late AMD over 10 years compared to people who had never smoked (Tan et al, 2007). Furthermore, past smokers (those who had stopped smoking tobacco for more than a year) were found to have a three-fold increase in the risk of developing geographic atrophy. The longitudinal relationship between smoking and AMD over 19 years reported by Tan et al (2007) was consistent with the baseline findings reported by Smith et al (1996), who reported that current smokers in the BMES had a statistically significant odds ratio of 3.8 for the presence of late AMD and a statistically significant odds ratio of 1.75 for the presence of early AMD.

The link between smoking and late AMD was also found in other large scale population-based studies. For example, in the BDES, Klein et al (2002) found that smoking was related to the incidence (new development) of large (≥ 250 microns in diameter) soft drusen, pigmentary abnormalities, and lesions that defined early AMD. However, dose response was evident between the amount of tobacco smoked and the incidence of late AMD. The Rotterdam Study reported that current smokers had around a 6.2-fold greater likelihood of developing neovascular AMD, and past smokers were also significantly more likely to develop neovascular AMD, when compared with non-smokers (Tomany et al, 2004).

Tobacco smoking can also increase the likelihood that AMD will develop earlier in life. For example, current smokers in the BMES were found to develop AMD between 5 and 10 years earlier than those who had never smoked (Mitchell et al, 2002; Tan et al 2007). Klein et al (2002) also reported that participants in the BDES developed AMD five years earlier on average than people who had never smoked. This is an important finding, as it suggests

¹³ The total time smoked (years) by the usual daily cigarette-equivalent intake, divided by 20.

that cessation of smoking could delay the onset and impact on visual function from late AMD. The greatest increase in odds for AMD has been consistently shown for people who currently smoke. Although past smokers have also been shown to have a greater risk of developing AMD than non-smokers, this has not been consistent across all studies. Moreover, the level of risk in past smokers has been shown to decline with increasing duration of smoking cessation. For example, Khan et al (2006) demonstrated that among people who had given-up smoking for over 20 years, their risk was comparable to that of non-smokers.

Many other studies have examined and supported both cross-sectional and longitudinal relationships between smoking and AMD (Hyman et al, 1983; Seddon et al, 1996; Eye Disease Case-Control Study Group, 1992; Delcourt et al, 1998; McCarty et al, 2001). Two meta-analyses confirming the strong link between smoking and AMD have recently been reported (Thornton et al, 2005; Chakravarthy et al, 2010).

Public health initiatives, such as introducing campaigns of public advice about this link, including cigarette pack warnings, have also been proposed (Mitchell et al, 1999; Kelly et al, 2003). The recently proposed 'plain paper' cigarette packaging legislation in Australia will continue to include as one of its warnings 'Smoking causes blindness'.

Smoking has many other effects on the eye, including increasing the likelihood of developing cataract, and lowering the age at which it develops (Tan et al, 2008), as well as exacerbating thyroid eye disease, and ocular inflammatory conditions.

The relationship between smoking status and the risk of developing AMD suggests that smoking tobacco imposes a substantial risk of increased burden of disease through visual impairment. This is especially the case given that a substantial number of older people are smokers, or were smokers at one stage of their life. For example, Table 4.1 shows the estimated prevalence of tobacco smoking in Australia in 2010, with the proportion of ex-smokers above 40% for those aged 55 years and older.¹⁴ Furthermore, around 16% of people aged 55-64 years remain current smokers, even though prevalence of current smoking declines as people get older. Around 9.5% of people aged 65-74 years and 4.7% of people aged 75 years and over are still current smokers.

Table 4.1: Estimated prevalence rate of tobacco smoking in Australia, 2010

Age group	Per cent of population		
	Never smoked ^(a)	Ex-smoker ^(b)	Current Smoker ^(c)
25-34	47.1	27.5	26.4
35-44	49.5	26.7	24.1
45-54	44.6	32.4	23.1
55-64	43.4	40.7	16.2
65-74	47.8	42.8	9.5
75 and over	52.0	43.3	4.7

Source: ABS (2003; 2006; 2009) and Deloitte Access Economics calculations.

Note: (a) Never smoked more than 100 cigarettes or the equivalent tobacco in their life (b) Smoked at least 100 cigarettes or the equivalent tobacco in their life and no longer smoke (c) At the time of survey smoked daily, weekly or less than weekly.

¹⁴ Prevalence of tobacco smoking by age and smoking status for 2010 was estimated by applying the average annual growth determined from the 2001 NHS (ABS, 2003), 2004-05 NHS (ABS, 2006) and 2007-08 NHS (ABS, 2009) to the prevalence reported in the 2007-08 NHS.

Alcohol consumption

The relationship between alcohol and AMD is not firmly established (DoHA, 2008).

It has been hypothesised that alcohol consumption may be both beneficial and detrimental to the risk of developing AMD. Heavy alcohol consumption (defined as four or more standard alcoholic drinks per day) was thought to potentially increase the risk of developing AMD by increasing the oxidative stress or affecting mechanisms that protect against oxidative damage, such as serum carotene, vitamin E and zinc (Klein et al, 2002). Moderate alcohol consumption, particularly through wine, was thought to reduce the risk of developing AMD through decreased platelet aggregation, lower serum fibrinogen levels, lower C-reactive protein concentrations and higher high density lipoprotein levels. Chong et al (2008) investigated the potential J-shape relationship between alcohol consumption and AMD risk, but could not determine a significant relationship between moderate alcohol consumption and reduced risk of developing AMD.

Moreover, although an increased risk of developing early AMD was found in the BMES, with a relative risk of 1.6 (Smith et al, 1996), this was only found in cross-sectional data. In the 10-year follow-up study reported by Tan et al (2007), there was no significant evidence that heavy alcohol consumption was associated with either early or late AMD, except for a significant positive association between consumption of spirits and early AMD. The authors noted there was only a small number of heavy drinkers and outcomes so that the power to find a significant relationship was low.

Heavy alcohol consumption was associated with an increased risk of developing neovascular AMD in the BDES, although the confidence interval on the relative risk was large and therefore non-significant (Klein et al, 2002). However, people who were heavy drinkers at baseline were significantly more likely to develop late AMD compared to those who had never been heavy drinkers (Klein et al, 2002).

Knudtson et al (2007) investigated alcohol consumption as a risk factor for 15-year cumulative incidence and progression of AMD in the BDES, finding a higher risk among participants of developing pure geographic atrophy¹⁵ among heavy drinkers at baseline compared to non heavy-drinkers.

A recent systematic review and meta-analysis using five cohort studies with a total sample size of 136,946 persons (1,513 developed early AMD and 410 developed late AMD) showed that heavy alcohol consumption (defined as more than three standard drinks per day) predicted a 47% significant increase in the risk of developing early AMD. The change in risk increased to 67% after excluding two studies with low alcohol consumption cut-offs used to define heavy drinking. Although three studies identified a positive relationship between heavy alcohol consumption and late AMD, this was not statistically significant, as late AMD was relatively infrequent in the studies included (Chong et al, 2008).

¹⁵ Pure geographic atrophy lesions can be classified into 3 configurations based on the number of atrophic areas and appearance of the atrophy. They include “classic”, “multifocal” and “merged”.

Excessive alcohol consumption is not only a risk factor for AMD, but it can also lead to many other health problems including stroke, cardiovascular disease, hypertension, cancer, and pancreatitis (Irving et al, 2009). Table 4.2 shows that consumption of alcohol in Australia has been relatively stable since 1993. The proportion of people consuming alcohol on a daily and weekly basis has only changed slightly, while the proportion consuming alcohol less than weekly has increased by 3.2%. This suggests the AMD risk from excessive alcohol consumption, even if confirmed, is unlikely to change substantially through self-motivated action.

Table 4.2: Trend in the consumption of alcohol in Australia

	1993	1995	1998	2001	2004	2007	2010 ^(a)
	%	%	%	%	%	%	%
Daily	8.5	8.8	8.5	8.3	8.9	8.1	8.3
Weekly	39.9	35.2	40.1	39.5	41.2	41.3	40.1
Less than weekly	29.5	34.3	31.9	34.6	33.5	33.5	32.7
Ex-drinkers ^(b)	9	9.5	10	8	7.1	7	8.5
Never a full serve	13	12.2	9.4	9.6	9.3	10.1	10.6

Source: Access Economics calculations and AIHW (2010).

Note: (a) Estimated using a linear trend for data relating to 1993-2007 (b) Ex-drinkers are those who consumed at least a full serve of alcohol in their lives but not in the last 12 months.

4.1.2 Suboptimal nutrition

Many consistent studies now support the concept that suboptimal nutrition is an important, modifiable, risk factor for the development of AMD, and a large randomised clinical trial has confirmed benefits of reducing AMD progression from a high dose zinc and antioxidant supplement (AREDS 2001).

Research confirms a role for dietary antioxidants, particularly for zinc, but also potentially for Vitamin C, vitamin E and β carotene (van Leeuwen et al 2005), though β carotene was found to be possibly harmful in the BMES (Tan et al 2008). Dietary antioxidants play an important role in the occurrence, prevention and treatment of AMD. Some foods such as spinach, fish and nuts potentially decrease AMD risk by at least 65% (Tan et al, 2008; Tan et al, 2009). One study has also shown that olive oil ($\geq 100\text{mL}$ per week) may decrease risk (Chong et al, 2009).

A potentially strong role for lutein/ zeaxanthin has also been identified by an increasing number of studies, including the BMES (Tan et al 2008). A new supplement that includes lutein/ zeaxanthin is now being evaluated in AREDS2.

Meta-analysis has highlighted potential benefits from dietary intake of omega-3 fatty acids, or regular consumption of fish (Chong et al 2008). Higher levels of fish consumption were also found associated with reduced AMD development in the BMES (Tan et al 2009).

Finally, lower glycaemic index of foods consumed has also been reported to be protective for AMD progression by 2 groups (Chiu et al 2007, using AREDS data, and Kaushik et al 2010 using BMES data).

These increasing reports suggest considerable potential benefit to patients with early AMD stages, by addressing suboptimal nutrition, which is now probably the most modifiable risk factor for AMD. More research is required, e.g., from AREDS2, with respect to the relationship between AMD and dietary intake of carotenoid, omega-3 fatty acids and low glycaemic index foods.

There is also considerable potential to address gene-environment interaction with diet (see below).

Intake of antioxidants from diet and supplements

A major randomised clinical trial (RCT), the Age-Related Eye Disease Study (AREDS, 2001) was undertaken in the US to investigate whether high dose antioxidants (given as a supplement) could prevent or reduce the development of AMD. This RCT involved 3,609 participants selected from AREDS clinical centres across the U.S. who were photographically assessed for AMD, and randomly assigned either to high doses of antioxidants (five to 15 times the daily recommended doses) of zinc, vitamin C, vitamin E and β carotene, or to placebo. The trial showed that patients with intermediate AMD treated with high dose antioxidant supplements (vitamins C and E, zinc, and β carotene) plus zinc had a 28% reduction in the risk of progression to intermediate AMD or to advanced AMD in either eye,

compared with placebo. There was also a reduction in the risk of developing advanced AMD with zinc and antioxidants alone, of 25% and 20%, respectively. The risk of developing moderate visual acuity loss was also reduced by around 27% for people assigned to receive antioxidants in addition to zinc.

Based on these findings, the AREDS group recommended that people with intermediate AMD who were at high risk of progression (those with monocular intermediate AMD, binocular intermediate AMD, and those with either monocular vision loss from AMD or monocular advanced AMD with a fellow eye at risk) should consider taking high doses (as defined within the AREDS trial) of zinc, vitamin C, vitamin E and β carotene.

Subsequent analysis of the AREDS sample has confirmed that diets with high intakes of these nutrients can reduce the risk of developing drusen and advanced AMD (Chiu et al, 2009). Results from many other studies are also consistent with the AREDS findings. For example, van Leeuwen et al (2005) found that dietary zinc was inversely associated with incident AMD in the Rotterdam Study. The hazard ratio per standard deviation increase of intake for zinc was 0.91, suggesting a reduced risk of around 9%.

The AREDS sample population included a large proportion of persons who already had signs of intermediate AMD or more advanced levels. AREDS could not determine whether high dose antioxidant supplements and zinc could protect against the development of early AMD, or whether they could slow, or stop, the progression of early stage AMD to later stages. This study may have been underpowered to assess these questions for the earliest stages.

Other studies have investigated the role of dietary antioxidants in reducing the risk of developing AMD and slowing progression, with some conflicting results. For example, other clinical trials have failed to conclude that vitamin E and β carotene can reduce the risk of developing AMD (Taylor et al 2002; Christen et al 2007; Evans et al 2008, Christen et al 2010). Further research by the AREDS group also failed to establish that individual dietary intakes of vitamin A, retinol, vitamin C, or alpha-tocopherol or its equivalent, could alter the long-term risk of developing intermediate or large drusen, geographic atrophy or neovascular AMD (AREDS, 2007).

In Australia, the relationship between dietary antioxidants and the long term risk of developing AMD has been investigated in BMES participants, and includes both assessments of the use of dietary supplements and nutrient consumption (Tan et al, 2008). Although the study was not designed to assess the role of high dose supplements or the overall antioxidant patterns shown in the Rotterdam Study (van Leeuwen et al, 2005), a significant relationship between dietary components at baseline and the 10-year longitudinal risk of developing AMD was reported.

Summary of significant findings from the BMES 10-year study:

- people consuming the highest decile of zinc had a significantly reduced risk of developing any AMD (relative risk 0.56) and a reduced risk of developing early AMD (relative risk 0.54), when compared to the rest of the sample;
- people consuming the highest tertile of vegetables were less likely to develop AMD when compared to the rest of the sample;

- increased dietary intake of β carotene predicted a significantly greater risk of developing neovascular AMD (relative risk 2.68, comparing the highest to lowest tertile); and
- increased dietary intake of vitamin E predicted a significantly greater risk of developing late AMD (relative risk 2.83 comparing highest to lowest tertile) (Tan et al, 2008).
- increased dietary intakes of lutein and zeaxanthin were protective (see below)

The positive relationship between the consumption of zinc and AMD was inconsistent with earlier 5-year BMES data that did not confirm a significant relationship (Flood et al, 2002). Tan et al (2008) concluded that a high intake of zinc from diet and supplements combined could protect against early AMD and any AMD.

The positive relationship between β carotene and vitamin E with the risk of developing AMD, however, was inconsistent with findings from AREDS and the Rotterdam Study. The authors suggested that as there is known to be competitive absorption of carotenoids in the gut, higher intakes of β carotene could thereby inhibit the absorption from the diet of larger quantities of the more valuable lutein and zeaxanthin (see below). They also drew on findings from Miller et al (2005) to suggest high doses of vitamin E could increase oxidative effects and displace other fat-soluble vitamins.

As increased consumption of zinc could reduce risk of developing AMD, the risk of developing AMD may be modified by diet. Foods rich in zinc are generally protein based and include meat (e.g., beef, lamb, pork, chicken) and various types of seafood (e.g., crab, lobster, salmon and oysters). However, high concentrations of zinc are also found in non-meat foods, such as nuts (e.g., cashews, pine nuts and brazil nuts), whole grains (e.g., branflakes, oats, and barley), legumes (e.g., lentils, chickpeas and dried beans), seeds (e.g., sunflower seeds) and dairy products (e.g., milk and yoghurt).

Intake of other dietary carotenoids (lutein/zeaxanthin)

Research has also investigated the relationship between dietary carotenoid intake more broadly, and the risk of developing AMD. It has been hypothesised that lutein and zeaxanthin, which are found in a wide variety of green leafy plants such as spinach and kale and in some animal products such as egg yolks, can protect the retina from the harmful effects of free radicals released by visible light (O'Connell et al, 2006). It has also been suggested that lutein and zeaxanthin can repair systems that defend oxidative stress and the effects of chronic inflammation (AREDS, 2007).

In the AREDS, a significant inverse relationship was found between dietary intake of lutein and zeaxanthin and the risk of developing AMD (AREDS, 2007). Participants reporting the highest intake of these carotenoids were less likely to develop large or extensive intermediate drusen compared to those reporting the lowest intake, with a reduced risk of 27%. They were also less likely to develop neovascular AMD and geographic atrophy, with reduced risks of 35% and 55%, respectively. Similar results were found by Snellen et al (2004), who found the prevalence of AMD in patients attending a hospital with low antioxidant intake and low lutein intake was around 70% and 140% greater, respectively, than in patients with a high intake.

Using the BMES, Tan et al (2008) assessed the relationship between baseline dietary and supplement intakes of lutein and zeaxanthin, and found participants in the top percentile of

intake had a 65% lower risk of developing incident neovascular AMD and those with above median intakes had a 34% lower risk of developing indistinct soft or reticular drusen (the main precursor of late AMD identified in the BMES). The authors concluded that a high dietary carotenoid intake (particularly of lutein/ zeaxanthin) may protect against long-term incident neovascular AMD and indistinct soft or reticular drusen.

Dietary intakes of omega-3 fatty acids and consumption of fish

It has been hypothesised that a relationship exists between the consumption of omega-3 fatty acids and the risk of developing AMD through protecting the retina by reducing inflammation (Ikram et al, 2003). This could occur because the retina contains high levels of the omega-3 fatty acid known as docosahexaenoic acid (DHA), particularly in the disc membranes of the photoreceptors, and accounts for over half the total fatty acyl groups present in the phospholipids of rod outer segment membranes (Hodge et al, 2006). It is thought DHA plays an important role in photoreceptor membrane anatomy and physiology.

It has also been hypothesised that the omega-3 fatty acid known as eicosapentaenoic acid (EPA) can affect lipoprotein metabolism and decrease the production of other compounds that can lead to inflammation through the increased production of collagenase and expression of adhesion molecules necessary for leukocyte extravasation (Hodge et al, 2006).

Two major systematic reviews have been reported on the potential benefits of omega-3 fatty acids in preventing or reducing AMD risk (Hodge et al 2006; Chong et al 2008).

Hodge et al (2006) reviewed six observational studies (none of which were RCTs) and found significant variation in the results, both within and across studies. One study which included a sufficiently large sample and appropriate multivariate analysis, reported that the consumption of tuna and five or more fish servings per week had a protective role on the development of AMD. However, when the same analysis was undertaken on sardines and mackerel (fish known to have high concentrations of DHA and EPA), the protective effect was not significant. Hodge et al (2006) concluded that the variation in results across studies was too great to draw any firm conclusions on the relationship between omega-3 fatty acid intake and the risk of developing AMD.

The second systematic review (Chong et al, 2008) identified nine relevant studies of dietary intake of omega-3 fatty acids and AMD. Higher dietary intake of omega-3 fatty acids (comparing the highest with the lowest omega-3 fatty acids intake) was associated with a 38% reduction in the risk of developing late AMD. Fish consumption at least twice per week was associated with a 24% reduced risk of early AMD and a 33% reduced risk of late AMD. The authors suggested that both high dietary intakes of omega-3 fatty acids and consumption of fish were associated with a reduced risk of both early and late AMD. However, they noted that these findings could not be used to justify a routine recommendation of increased omega-3 fatty acids and fish intake as their review did not contain any RCTs and there may be bias in the observational data. It seems very unlikely, however, that any major RCTs will be conducted to assess fish consumption, with the only major trial underway being the AREDS II, which will investigate, among other aims, whether an omega-3 fatty acid (fish oil) supplement, reduces progression of AMD signs.

Studies have also been conducted on dietary fatty acids in preventing the development of AMD in Australia. Chua et al (2006) undertook a 5-year follow-up of BMES participants and found that regular consumption of fish was associated with a reduced risk of both early and late AMD. Participants with the highest quintile of dietary intake of omega-3 fatty acids had a 59% decrease in risk of developing early AMD, and those who reported consuming fish at least once per week had a reduced risk of 40%. Fish consumption at least three times per week was found to significantly reduce the development of late AMD by 75%.

Tan et al (2009) undertook a 10-year follow-up of BMES participants and found similar results, with fish consumption at least once a week reducing the risk of early AMD and pigmentary abnormalities by around 31% and 29%, respectively, although the effect was not significant in people with high levels of linoleic acid intake. The authors also found that one or more serving of nuts per week was associated with a reduced risk of developing early AMD, indistinct soft or reticular drusen, or pigmentary abnormalities.

Long-chain fatty acids such as DHA and EPA are generally found in oily fish, such as tuna, sardines, salmon, trout and mackerel. By increasing the dietary intake of omega-3 long-chain polyunsaturated fatty acid through greater fish consumption, there may be beneficial effects in preventing AMD, and a potential reduction in the likelihood of progression from drusen to late stage AMD.

Some studies have shown the beneficial effect of fish could be lower in persons consuming higher levels of linoleic acid (Mares-Perlman et al, 1995, Seddon et al, 2001, 2004, 2006; Cho et al, 2001). In the CAREDS study (Parekh et al, 2009) of women only, where the consumption of omega-3-fatty acids (including fish) was moderately associated with the consumption of omega-6 fatty acids, greater intakes (high vs low quintiles) of omega-3-fatty acids were associated with around a 2-fold higher prevalence of intermediate (early) AMD. This finding, however, contrasts with those from most other studies. Higher intakes of omega-6 fatty acids, primarily from vegetable fats (e.g. salad dressing, mayonnaise, and margarine) were also associated with higher early AMD prevalence.

Similar associations with overall omega-6 fatty acid intake, and in particular linoleic acid, were observed in 5 previous U.S. reports, although in some the association was only in women (Mares-Perlman et al, 1995; Cho et al, 2001). In other American (SanGiovanni et al, 2007), Australian (Smith et al, 2000; Chua et al, 2006) and French (Delcourt et al, 2007) studies, an increased risk of AMD was not seen in persons with high intake of omega-6 fatty acids or linoleic acid compared with low intake. Nevertheless, more studies than not suggest a possible association between greater vegetable fat intake and AMD. Omega-6-fatty acids are thought to be pro-inflammatory in contrast to omega-3 which tend to be anti-inflammatory, suggesting a possible mechanism.

The close correlation between the consumption of different types of fats, their biochemical interactions, the variability of the source of the fats in different populations together with the major difficulties in estimating fats in food frequency questionnaires has led to conflicting results and stresses the need for more research, and data pooling where appropriate.

Dietary glycaemic index

There is now evidence to suggest that diets with lower than average dietary glycaemic index (dGI)¹⁶ may reduce the risk of developing early and late AMD (Kaushik et al 2008; Chiu et al 2007). Foods with a lower dGI include most fruits and vegetables, whole grain breads, pasta, milk and yogurt.

Chiu et al (2007) conducted a study to test the association between dGI and the risk of developing AMD in non-diabetic elderly populations, including information on dietary habits collected from participants in the AREDS. They reported a 49% increase in the risk of developing geographic atrophy or neovascular AMD among people with a dGI higher than the median for each gender. They also estimated that 20% of prevalent AMD cases could have been eliminated if the AREDS participants consumed diets with a dGI below the median.

Kaushik et al (2008) examined the association between dGI and the development of AMD in the BMES population. After adjusting for covariates such as age, smoking and other dietary parameters, higher mean dGI was associated with an increased 10-year risk of developing early AMD. Consistent with this finding, the consumption of cereal fibre and breads and cereals was independently significantly associated with a reduced risk of developing early AMD by 32% and 33%, respectively.

New Studies - AREDS2

The AREDS is the only large scale RCT to show a positive effect associated with high doses (five to 15 times the daily recommended doses) of zinc, vitamin C, vitamin E and β carotene and the risk of developing AMD (AREDS, 2001). Given some encouraging results on the relationship between other dietary factors and the prevention of AMD progression, the Age-Related Eye Disease Study 2 (AREDS2) trial was commenced in 2006 to evaluate the effects of oral supplementation of carotenoid and lipid intake on the risk of developing to late stage AMD.

AREDS2 is a multi-centre randomised trial being conducted across the United States that aims to collect data on approximately 4,000 participants aged 50 to 85 years who at the time of enrolment have either bilateral large drusen or large drusen in one eye and geographic atrophy or neovascular AMD in the other eye. The objectives are to:

- study the effects of high supplemental doses of the dietary xanthophylls (lutein and zeaxanthin) and omega-3 LCPUFAs (DHA and EPA) on the development of advanced AMD and cataract and moderate vision loss (doubling of the visual angle or the loss of 15 or more letters on the ETDRS chart);
- study the impact of eliminating beta-carotene in the original AREDS formulation on the development and progression of AMD;
- study the effects of reducing zinc in the original AREDS formulation on the development and progression of AMD; and

¹⁶ The Glycemic Index is a way of scoring different foods according to the effect they have on blood sugar levels, or more accurately, how quickly the sugars (carbs) in foods are absorbed. Carbohydrates that break down quickly during digestion and release glucose rapidly into the bloodstream have a high GI; carbohydrates that break down more slowly, releasing glucose more gradually into the bloodstream, have a low GI.

- validate the fundus photographic AMD scale developed from the AREDS (AREDS2, 2010).

Enrolment concluded in June 2008 and participants will be followed between five and six years. To date there has been no published literature on the results from AREDS2 on the relationship between dietary intake of carotenoids and lipids on the risk of developing late stage AMD.

4.1.3 Genetic risk factors

AMD results from the interaction of genetic predisposition and environmental factors. The relationship between the risk of developing AMD and genetics is well established from family and twin studies. For example, heritability of up to 70% has been estimated (Scholl et al 2007; Fajnkuchen and Cohen 2008).

The proportion of variation in AMD across populations appears to be influenced more by genes than environmental (non-genetic) factors. Genetic factors hypothesised to increase the risk of developing AMD include: genes associated with the complement cascade; the chromosome 10q locus; other major genetic loci; gene-environment interactions; and pharmacogenetic relationships.

The two confirmed AMD-related gene loci polymorphisms with the greatest magnitude of effect are Y402H in CFH and A69S in LOC387715.

These are further discussed below. In general, although some significant relationships have been found, there are inconsistencies in findings and further research needs to be undertaken.

Genes associated with the complement cascade

The complement system provides an innate immune defence mechanism. When complement regulatory proteins are defective, uncontrolled complement activation can lead to inadvertent tissue damage. Genetic studies have revealed very strong associations between AMD and variants of several complement pathway-associated genes including: complement factor H (CFH), complement factor H-related 1 and 3 (CFHR1 and CFHR3), complement factor B (CFB), complement component 2 (C2), and complement component 3 (C3) (Anderson, 2010).

Mutation in complement factor H (CFH) is strongly associated with risk of AMD (Edwards et al 2005; Haines et al 2005; Klein et al 2005).

A common coding variant in the gene encoding complement factor H on chromosome 1q31 has been identified. In individuals carrying the Y402H polymorphism (CFH) gene, where histidine is substituted for tyrosine at amino acid position 402, the risk of developing AMD is increased between two and seven fold (Edwards et al 2005; Klein et al 2005), with the greatest risk occurring in people with both genes of the pair defective. Research has estimated that having one particular form of this gene explains approximately 43% of AMD cases (Haines et al, 2005).

Using BMES data, Pai et al (2009) reported that the presence of the CFH CC (Y402H polymorphism) genotype increased the likelihood of bilateral compared with unilateral involvement with any soft drusen by around 2.5 times, increased the likelihood of bilateral distinct soft drusen by around 2.8 times, and bilateral pigmentary abnormalities by around 1.7 times, thereby concluding the CFH CC genotype increased the risk of developing early AMD lesions. The authors however, did not find that this genotype was related to higher risk of developing late AMD in both eyes, compared to only one eye.

An earlier study by Xing et al (2008) using the BMES found an association between the CFH CC genotype and the risk of developing early and late AMD after adjusting for age and sex, with a population attributable risk (PAR) of 0.22. They concluded that the small PAR suggests the CFH CC genotype does not cause AMD alone, but does facilitate its development in combination with other genetic and environmental factors.

The discovery of the relationship between genes associated with the complement cascade and the risk of developing AMD has redefined AMD as a disease of complement dysregulation in roughly 50% of patients (RCO, 2009).

However, a common haplotype in CFH has also been found to be associated with a decreased risk of AMD. Deletions of CFHR1 and CFHR3 close to the CHF locus have been found to be responsible for some protective effect against AMD. Hughes et al (2006) found that this deletion was present on 20% of chromosomes of controls and 8% of chromosomes of individuals with AMD.

Polymorphisms in complement C3 have been shown to be predictors of risk for AMD. Compared with the common CC genotype, the odds ratio was 1.7 for CG heterozygotes and 2.6 for GG homozygotes (Yates et al, 2007). Other activators of the same biological pathway as CFH, i.e. complement factor B (BF) and complement component 2 (C2) have also been found to be associated with AMD. These two genes are located on chromosome 6p within the major histocompatibility complex class III region. Haplotype analyses confer a common risk haplotype (H1) and two protective haplotypes; the L9H variant of *BF* and the E318D variant of C2 (H10) as well as a variant in intron 10 of C2 and the R32Q variant of BF (H7). Specifically, the odds ratios were 1.32, 0.45 and 0.36, respectively.

Chromosome 10q locus

The association of AMD with two distinct polymorphisms within chromosome 10q26 has been identified as independent risk factors for the development and progression of AMD (DeWan et al, 2006). The first is a single nucleotide polymorphism A69S identified in the coding region of the LOC387715/ARMS2 (age-related maculopathy susceptibility 2) gene (Rivera et al, 2005), and the second single is a nucleotide polymorphism located in the promoter region of HTRA1 (high temperature requirement factor A1) (Yang et al, 2006). It is currently unclear whether either of the polymorphisms is causally associated with increased risk for development of AMD (Brantley et al, 2009) and represents the true genetic risk variant at this locus (RCO, 2009). Nevertheless, possession of the risk-associated genotype is estimated to have an up to 10-fold increase in the likelihood of developing AMD (DeWan et al, 2006).

Other major genetic loci

Genome-wide linkage studies in AMD have revealed a number of putative candidate regions for susceptibility genes. Evidence for linkage to regions on chromosomes 1q (CFH locus) and 10q (discussed above) has been consistent in showing strong association with AMD. Other chromosomal regions exhibiting significant evidence for linkage are 2p, 3p and 16q (Fisher et al 2005; Zhang et al 2008). Refinement of these candidate regions will assist in revealing undiscovered variants.

More recently, a susceptible locus near TIMP3 on chromosome 22 which encodes the enzyme metalloproteinase inhibitor 3, has been identified to be associated with increased risk of AMD (Chen et al, 2010). In the same study, two other loci were found to exhibit evidence for association. They are near hepatic lipase on chromosome 15 (Neale et al, 2010) and near cholesterylester transfer protein on chromosome 16. Both are involved in the HDL metabolism pathway and are associated with high-density lipoprotein cholesterol (HDL-c) levels in blood (Chen et al, 2010) although association between HDL cholesterol levels in the blood and AMD remains unclear.

Gene-environment interactions

Some postulated gene-environment interactions are between carrier of a susceptibility gene for AMD and:

- smoking;
- past infection;
- body mass index (BMI);
- fish and omega-3 fatty acid consumption; and
- antioxidant intake.

To date, there is suggestive, but not yet conclusive evidence that cigarette smoking exerts a greater effect on AMD risk in people carrying the risk alleles of either the two confirmed AMD-related gene loci polymorphisms – Y402H in CFH and A69S in LOC387715, compared to people homozygous for the non-risk alleles. Schmidt et al (2006) documented a synergistic effect between history of cigarette smoking and carriage of LOC387715 variant. Similarly, Despret et al (2006) found that the combined effect of homozygosity for the Y402H variant in CFH and smoking exceeded the sum of the independent effects. Findings from an analysis of the BMES cohort also found joint effects with long-term late AMD risk to be 10-fold higher among subjects who currently smoked and possess the CHF CC/CT genotype compared to current non-smokers without the risk genotypes (Wang et al, 2009). However several other studies were not able to demonstrate significant statistical interaction at a multiplicative scale (Rivera et al 2005; Conley et al 2006; Seddon 1996). Nevertheless, population studies have consistently shown greater late AMD risk to be associated to cigarette smoking (Tomany et al, 2004). This suggests that joint effects from multiple, independent risk factors are likely to be strongly involved in the pathogenesis of AMD.

Seddon (1996) reported that higher BMI was independently related to AMD after controlling for genotype. The association between AMD and BMI also varied dependent on genotype. The CHF TT genotype was found to confer a non-significant to marginally

protective effect while for the CT and CC genotype a moderately high 2.2-fold increased risk and a high 5.9-fold increased risk, respectively was found (Seddon, 1996).

The BMES found that weekly fish consumption was associated with reduced late AMD risk among persons with the higher risk CHF CC genotype but not with the lower risk CHF TT genotypes (Wang et al, 2009).

Pharmacogenetic relationships

Pharmacogenetic relationships have been observed between the genetic risk factors associated with AMD and response to treatment. Visual acuity loss after PDT was found to be greatest in patients with the CFH TT genotype compared to those with the TC and CC genotypes (Brantley et al 2009; Goverdhan et al 2008). Similarly, intravitreal injection of the anti-VEGF antibody Avastin was associated with poorer post-treatment response in patients with the CFH CC genotype compared to TC and TT genotypes (Brantley et al, 2007). These findings suggest altered local inflammatory mediator response by the various CFH genotypes, impacting on response to treatment. Further data are expected on this topic from the large Lucentis (ranibizumab) studies in which genetic samples have been collected.

Oxidative stress plays an important role in pathogenesis of AMD. Consequently, ways to upregulate the anti-oxidant defence response to defend against oxidative stress have been subject to investigation. Nuclear factor erythroid-2 related factor 2 (Nrf2) is a transcription factor that has been implicated as the central protein that regulates the expression of several antioxidant enzymes and maintains cellular redox homeostasis (Reddy et al 2007; Nguyen et al 2003) which in turn protects the cell from oxidative injury. It has been postulated that the impact of cigarette smoke induced oxidative stress increases with age due to the declined Nrf2 signalling response with increasing age (Cano et al, 2010). Consequently, pharmacologic induction of Nrf2 suggests a new avenue for treating age-related oxidative stress.

4.1.4 Medical factors

Several medical conditions have revealed statistically significant associations with the development of AMD. Three of these, obesity, hypertension, and high cholesterol levels, are also risk factors for cardiovascular disease. Cardiovascular disease itself (and prior history of stroke) has been identified as a contributor to the development of AMD, although findings have not been entirely consistent. The potential contribution of these medical conditions to the development of AMD within a person, and the estimated prevalence of each medical condition in Australia, is discussed below.

Overweight and obesity

Overweight and obesity is a condition of excess deposition of body fat (adipose tissue) that results from a sustained energy imbalance. This occurs when dietary energy intake exceeds energy expenditure over a period of time. There are a number of methods used for measuring overweight and obesity (such as waist measurements and waist to hip ratios)

although body mass index (BMI) is the most frequently used measure.¹⁷ A BMI score greater than or equal to 20 but less than 25 is considered to reflect normal body mass. BMI scores greater than or equal to 25 but less than 30 indicate overweight, and BMI scores of 30 or more indicate obesity (WHO, 2000).

The pathway that leads from obesity to AMD has not been confirmed, although some studies have hypothesised that oxidative stress could be one mechanism (Zarbin 2004; Kopitz 2004). Several population based studies have investigated the link between AMD and obesity. In general, most have found that an increased risk of developing AMD is associated with a relatively high BMI and abdominal obesity.

Peters et al (2008) examined the association between changes in waist-hip ratio, a measure of abdominal obesity, and AMD, in the Atherosclerosis Risk in Communities Study population-based cohort. This study included 12,515 people aged 45 to 64 years, undertaken between 1987 and 1989 and followed over six years. The average change in waist-hip ratio was an increase of 2%, ranging from a decrease of 44% to an increase of 102%. A decrease in waist-hip ratio of 3% or more was associated with 29% lower odds of developing any AMD. People who experienced the greatest reduction in the risk of developing AMD with a decrease in waist-hip ratio were obese participants at baseline, with a 59% lower odds. Peters et al (2008) concluded that a reduction in waist-hip ratio in middle-aged people, particularly in those who were initially obese, may be associated with a decrease in the likelihood of developing AMD.

A relationship between BMI and the risk of developing AMD was also investigated in the BMES. Smith et al (1998) found that a BMI score lower than normal (BMI<20) was associated with a statistically significant increased odds ratio of 1.9 for developing early AMD when compared to a person with a normal BMI. They also found being overweight or obese also imposed an increased risk of developing early AMD, with significant odds ratios of 1.4 and 1.8, respectively. However, Tan et al (2007) could not confirm this association either at the five-year or 10 year follow up of this population sample.

Being overweight may also increase the rate of progression to the advanced stages of the condition. For example, Seddon et al (2003) found in a survey of 261 participants in a hospital-based retinal practice that being overweight was associated with a relative risk in progressing to advanced stage AMD of around 2.3. For obese people, the relative risk was 2.4. A higher waist circumference was also associated with an increased risk of progression, with a relative risk of 2.0 when comparing the highest with the lowest tertile.

However, some studies have failed to find a relationship between BMI and the risk of developing late stage AMD. For example, Tomany et al (2004) used pooled data from the BMES, BDES and Rotterdam Eye Study and found neither a low BMI score (<22) or a high BMI score (≥30) was significantly associated with the risk of developing geographic atrophy, neovascular AMD, or late stage AMD.

¹⁷ BMI is calculated as the weight in kilograms divided by the square of the person's height in metres. Excessive body-weight gain results in abnormalities in blood lipids, leading to an increased risk of developing Coronary Heart Disease. However, BMI is a crude measure of obesity and does not take into account the distribution of body fat. Furthermore, BMI does not allow for differences across individuals and populations with different body builds, such as those of different racial backgrounds. Welborn et al (2003) proposed that the waist-hip ratio (a measure of abdominal obesity) is an important determinant of the risk of coronary disease and death and is a better predictor than BMI.

There is growing evidence of a relationship between excess body mass and AMD, but more research is required as this is a potentially important modifiable risk factor.

The prevalence of overweight or obesity continues to grow in Australia (AIHW, 2010). The most recent data available to estimate the prevalence of being overweight and obese are from the 2007-08 National Health Survey (NHS), which found that around 61% of adults had a BMI that indicated they were either overweight or obese (ABS, 2009). Table 4.3 shows that across all ages, males are estimated to have higher prevalence of being overweight or obese than females. For both males and females, the prevalence of obesity peaks between 55-64 years, when it then starts to decline as age increases. For overweight males, the greatest prevalence is for those aged 75 years and over, while for females the prevalence of being overweight peaks between 65-74 years.¹⁸

Table 4.3: Estimated prevalence rate of overweight and obesity in Australia^(a), 2010

Age group	Per cent of population			
	Males		Females	
	Overweight	Obese	Overweight	Obese
25-34	42.4	19.5	26.5	18.0
35-44	44.2	26.6	32.5	22.8
45-54	47.0	29.8	32.5	26.4
55-64	40.0	34.9	34.7	33.2
65-74	45.1	33.8	41.9	29.3
75 years and over	52.8	21.5	32.5	24.2

Note: (a) Overweight = $25 \leq \text{BMI} < 30$, Obese = $\text{BMI} \geq 30$. Based on measured data and age standardised to the 2001 Australian population. Source: Access Economics calculations and AIHW (2009b)

Hypertension

National Heart Foundation of Australia (2008) guidelines define high blood pressure as systolic pressure at or above 140 mmHg or diastolic pressure at or above 90 mmHg. Hypertension is thought to increase the risk of AMD due to its effects on the choroidal circulation (Bischoff and Flower, 1983). Some studies have found an association between systemic hypertension and the risk of developing AMD, while others have not.

Hyman et al (2000) used a case-control study design with 2,067 people to evaluate the relationship between AMD, hypertension and cardiovascular disease. They found that people with diastolic blood pressure greater than 95 mmHg were around four times more likely to develop neovascular AMD, and found a much higher risk for people with this condition who were also using antihypertensive medication. Furthermore, persons with self-reporting use of potent antihypertensive medication (regardless of their blood pressure), or people with a physician reported history of hypertension, were also at significantly increased risk, with odds ratios of 2.1 and 1.8, respectively.

¹⁸ To estimate the prevalence of overweight and obesity for 2010, linear trends were established for overweight and obesity by age and gender using the 2001 NHS (ABS, 2003), 2004-05 NHS (2006) and 2007-08 NHS (ABS, 2009) and applied to measured BMI data contained within the 2007-08 NHS.

A positive relationship between systolic blood pressure and an increased risk of developing early AMD lesions and neovascular AMD was found in the BDES. Klein et al (2003) noted that an increase of systolic blood pressure by 10mm Hg at baseline was associated with an increased risk of around 10% in developing retinal pigment epithelial depigmentation over ten years, and around a 20% increase of developing neovascular AMD. No relationship between diastolic blood pressure and the development of AMD lesions was found.

Using data from the BMES, Smith et al (1998) also did not find a relationship between hypertension and the risk of developing AMD. This was a cross-sectional study. However, Tan et al (2007) also did not find a significant relationship between hypertension (defined in people using antihypertensive medication or with systolic blood pressure greater than 160 mm HG or diastolic blood pressure greater than 95 mm HG at baseline) and the 10 year incidence of either early or late AMD.

Given conflicting results regarding the relationship between hypertension and the development of AMD, the Royal College of Ophthalmologists has concluded that there is no definitive finding regarding the association between hypertension and AMD, nor is there any evidence that antihypertensive medication or treatments can prevent the development or progression of AMD (RCO, 2009).

The most recent measured national data to report the prevalence of high blood pressure is the Australian Diabetes, Obesity and Lifestyle (AusDiab) study conducted in 1999-2000 (Dunstan et al, 2001). Table 4.4 shows that the prevalence of high blood pressure was estimated to increase with age, both on average and within gender. Significant increase in high blood pressure occurs across all age groups, although the greatest increases are between 25-34 years and 35-44 years, with more than double the prevalence for males and females.¹⁹

Table 4.4: Estimated prevalence rate of high blood pressure in Australia, 2010

Age group	Population (%)		
	Males	Females	Persons
25-34	5.0	2.9	4.1
35-44	10.0	6.6	8.5
45-54	21.8	20.6	21.5
55-64	35.1	38.9	37.2
65-74	49.6	58.8	54.2
75 years and over	56.9	66.2	61.4

Source: AIHW (2009b), Mathur (2002) and Access Economics calculations.

Note: High blood pressure is defined as systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm HG or more or receiving medication for high blood pressure.

¹⁹ To estimate the prevalence of high blood pressure in 2010, an exponential trend in blood pressure between 1980 and 1999 for males and a logarithmic trend in blood pressure between 1980 and 1999 for females was fitted to data presented in Mathur (2002) and applied to AusDiab data.

High cholesterol

Cholesterol is a fatty metabolite produced by the liver and carried by the blood to the rest of the body. Blood cholesterol can be described as either high-density lipoprotein (HDL) cholesterol or low-density lipoprotein cholesterol. HDL is often known as 'good' cholesterol with high levels shown to have a protective effect against heart disease by helping to reduce plaque. HDL is also required to make cell membranes, corticosteroids, certain hormones and bile acids which assist in the proper functioning of the nervous system. Low-density lipoprotein cholesterol is often known as 'bad cholesterol' with excess levels contributing to plaque build-up.

Problems occur when too much cholesterol forms an accumulation of plaque on blood vessel walls, which impedes blood flow to the heart and other organs. For most people, saturated fat in the diet is the main factor that raises blood cholesterol levels. Genetic factors can also affect blood cholesterol levels, more so in some people than others (AIHW, 2009a).

Cholesterol is hypothesised to increase the risk of developing AMD through its contribution to drusen and its involvement in the pathogenesis of atherosclerosis (van Leeuwen et al, 2004). Several studies have investigated the relationship between cholesterol and the development of AMD, with mixed results.

In the BMES, Smith et al (1998) did not find an association between increased serum cholesterol levels and the development of AMD. However, the authors noted that this result could have been due to statistical power constraints and survivor cohort effects. In the 10-year follow-up of the BMES, Tan et al (2007) also did not find a significant relationship between high density lipoprotein (HDL) and the development of early AMD, or a relationship between the ratio of total cholesterol and HDL cholesterol to early or late AMD. However, there was a significant inverse relationship between HDL cholesterol and the long-term development of late AMD.

An inverse relationship between HDL cholesterol and AMD is inconsistent with other studies. In a 10 year follow-up of BDES participants, Klein et al (2003) found a significant relative risk of 1.29 in developing geographic atrophy per 10 mmol/l increase of serum HDL cholesterol, but no relationship with neovascular AMD, late AMD, or the progression of AMD. van Leeuwen et al (2004) found in the Rotterdam Study that serum HDL cholesterol was directly associated with an increased risk of developing geographic atrophy, with a one standard deviation increase in HDL cholesterol associated with an approximate 20% increase in risk. Furthermore, using pooled data that included the BMES, BDES and Rotterdam Study studies, Tomany et al (2007) reported that higher levels of total serum cholesterol were associated with a significantly increased risk of developing geographic atrophy, but a significantly decreased risk of developing neovascular AMD. No relationship was found between serum HDL cholesterol and the development of geographic atrophy, neovascular AMD, or late stage AMD.

Tan et al (2007) suggest the discrepancy between the inverse relationship between HDL cholesterol and late AMD and other studies may be due to their study measuring cholesterol from fasting blood samples, rather than non-fasting blood samples as in the

BDES and Rotterdam Study. They concluded that further longitudinal studies are required in order to clarify the relationship between cholesterol and the development of AMD.

There is some conflicting evidence of a relationship between high serum cholesterol or low HDL and AMD; more research is required, given that this is also a potentially modifiable factor.

The most recent data available to estimate the prevalence of high cholesterol in Australia is the 1999-2000 AusDiab study (Dunstan et al, 2001). Table 4.5 shows the prevalence of high cholesterol is predicted to be greatest in males aged between 55 and 64 years, where prevalence starts to decrease.²⁰ For females, the prevalence of high cholesterol peaks within the age group 65 to 74 years and then starts to decline. Males are expected to have a higher rate of high cholesterol than females up until the age of 54 years, after which females are more likely to have high cholesterol.

Table 4.5: Estimated prevalence rate of high cholesterol in Australia, 2010

Age group	Percent of population		
	Males	Females	Persons
25-34	27.7	27.3	27.7
35-44	49.5	33.0	41.5
45-54	54.7	51.4	53.4
55-64	54.8	65.0	60.3
65-74	47.1	67.7	58.7
75 years and over	45.9	59.1	54.1

Source: AIHW (2009b), Mathur (2002) and Access Economics calculations.

Note: High cholesterol is defined as total blood cholesterol levels over 5.5mmol/L.

Cardiovascular disease (CVD) and chronic kidney disease (CKD)

It has been suggested that a relationship may exist between the prevalence of cardiovascular disease (CVD) and the development of AMD through a similar pathogenesis to atherosclerosis and arteriosclerosis (Snow and Seddon 1999; Friedman 2000). Accumulation of lipids in the sclera and Bruch's membrane is thought to increase hydrostatic pressure of the choroidal vasculature and impair choroidal perfusion, thereby depositing extracellular proteins and lipids (Tan et al, 2007). It is also thought that oxidative stress and inflammation could link CVD and AMD (Snow 1999; Beatty et al; 2000; Bok 2005).

A relationship between CVD and AMD has been inconsistently found in the BMES. Using a cross sectional study, Smith et al (1998) investigated the association between stages of AMD and previous diagnosis of CVD, including angina, acute myocardial infarction, stroke and hypertension. Although a positive relationship was found, there was no significant association between early or late AMD and CVD. In contrast, using the 10-year follow-up of

²⁰ To estimate the prevalence of high cholesterol in 2010, a linear trend in high cholesterol between 1980 and 1999 for males and females was fitted to data presented in Mathur (2002) and applied to AusDiab data.

BMES participants, Tan et al (2007) found that any CVD (prior stroke, acute myocardial infarction or history of angina) increased the risk of developing early AMD and indistinct or reticular soft drusen, with a statistically significant relative risk of 1.6 (the model controlled for other CVD risk factors, such as diabetes, hypertension, and the total/HDL cholesterol ratio). Furthermore, the authors found that stroke alone increased the risk of developing early AMD, with a relative risk of 2.0. No significant relationship was found between CVD and development of late AMD.

The relationship between CVD and AMD has been inconsistent across international studies. In a 5- and 10-year follow-up of BDES participants, Klein et al (1997; 2003) did not find a relationship between heart attack or stroke and development of AMD. In a case control study, Hyman et al (2000) did not find a relationship between specific cardiovascular diseases and the development of neovascular or non-neovascular AMD. Furthermore, in the Women's Health Initiative Sight Examination (WHISE) study that included 4,288 women aged 63 years or older, Klein et al (2007) did not find a history of myocardial infarction or stroke significantly increased the risk of developing early AMD, presence of soft drusen, increased retinal pigment, depigmentation of the RPE, neovascular AMD, geographic atrophy or late AMD.

However, other international studies have found a relationship between CVD and AMD. Vingerling et al (1995) using data from the Rotterdam Eye Study, found that people aged between 55-85 years with plaques at the carotid bifurcation had around 4.7 times increased odds of developing late AMD (on the same side), compared to people without these plaques. Furthermore, people with plaques in the common carotid artery, and those with lower extremity arterial disease had 2.5-fold increased odds of developing AMD. The authors concluded that atherosclerosis may cause AMD. Klein et al (1999) found in the Atherosclerosis Risks in Community Study that prevalent carotid artery plaques increased the risk of developing RPE depigmentation by around 1.8 times, and that early AMD was associated with an increased risk of experiencing a stroke. Pooling data from the BDES, BMES and Rotterdam Study, Tomany et al (2004) did not find a significant relationship between myocardial infarction and stroke with the development of either geographic atrophy or neovascular AMD.

It has also been hypothesised that statins may protect against AMD by reducing dyslipidaemia (Guymer et al, 2005). However, results have been mixed, with some studies finding a positive outcome (McGwin et al 2003; 2005) while large prospective cohort studies such as the BDES, BMES and Rotterdam Study have not found consistent relationships between statin use at baseline and the 5- or 10-year incidence of early AMD or neovascular AMD (Klein and Klein, 2004). A recent meta-analysis of observational studies concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing AMD (Chuo et al, 2007).

It has further been hypothesised that CKD may impact AMD by accelerating the progression of atherosclerosis and increasing susceptibility to oxidative stress. Liew et al (2008) investigated the relationship between CKD and risk of developing AMD in a 5-year follow-up of participants in the BMES. They found that people with moderate CKD ($eGFR_{CG}^{21} < 60$ ml/min/1.73m²) were three times more likely to develop early AMD compared to people with either mild CKD or no CKD. Furthermore, each standard deviation increase in $eGFR_{CG}$

²¹ Estimated glomerular filtration rate using the re-expressed Cockcroft–Gault equation.

was associated with a doubling of risk in developing early AMD, and was also associated with an increased risk of developing macular pigmentary abnormalities and indistinct soft or reticular drusen.

Relationships between CVD and CKD and risk for AMD have been inconsistent. More research is required, as these areas are also potentially modifiable.

4.1.5 Ocular factors

Research has also been conducted on the relationship between the risk of developing AMD and ocular indications, none of which is yet conclusive, including: refractive status; iris colour; and various types of cataract and cataract surgery.

Of these, the relationship of cataract surgery to the long-term risk of developing late AMD signs is the most consistent and requires more rigorous study.

There is some empirical evidence from several studies that hyperopic refraction (long-sightedness) is associated with an increase in the risk of developing AMD (Sandberg et al, 1993; Lavanya et al, 2010; Xu et al, 2010).

Wang et al (1998) found a weak association between early AMD and each dioptre of increase in mean spherical equivalent in the BMES (after adjusting for age, sex, family history of AMD and smoking status), indicating a possible positive relationship between moderate to high hyperopia and early AMD. The authors did not find a significant relationship between hyperopia and late AMD. This positive relationship is consistent with general conclusions drawn from the Rotterdam Study (Ikram et al, 2003), although it is inconsistent with the BDES (Klein et al, 1998).

The postulated mechanism behind this association has been that shorter hyperopic eyes have higher scleral rigidity which impairs the choroidal circulation.

It has also been hypothesised that ocular melanin, which is correlated to iris pigmentation, protects the retina from ARM both by light absorption and by protecting the retina from free radicals associated with photo-oxidation. The influence of iris colour on AMD has been widely investigated. In the BDES, no relationship was found between iris pigmentation and the incidence and progression and incidence and progression of AMD at five years (Klein et al, 1998). However, at the 10-year follow-up, people with brown eyes were significantly more likely to develop soft indistinct drusen compared to people with blue eyes, and were less likely to develop increased retinal pigment and RPE depigmentation.

Although iris colour was found to be associated with the 10-year incidence of pigmentary abnormalities in the pooled study, Tomany et al (2003) found no association between iris colour and the incidence of late AMD. In contrast, Mitchell et al (1998) found that blue iris colour was significantly associated with an increased risk of both early and late stage AMD in the BMES (Mitchell et al 1998). Temporal changes in eye colour were not assessed in either of the population studies. Holz and colleagues (1994) found that initial light iris

pigmentation was not associated with an increased risk of developing AMD, but that change in iris colour, which decreases over the course of an individual's lifetime, did indicate a higher risk.

Many studies have suggested that a relationship exists between the risk of developing AMD and cataract surgery. Reports from pooled BDES and BMES data found that cataract surgery was a consistent risk factor for the development of late stage AMD (Wang et al, 2003). A greater proportion of nonphakic eyes (i.e., with no lens or an artificial lens) developed either neovascular AMD or geographic atrophy compared with phakic eyes after a five year follow-up, with a significant odds ratio of 5.7. The authors suggested that cataract surgery, or the increased light exposure after surgery, could quicken the progression of AMD in those people where early stage AMD lesions are present at the time of surgery.

However, a relationship between cataract surgery and AMD has not been definitively established. In order to shed some light on the relationship the Australian Prospective Study of Cataract Surgery and AMD was implemented in 2008 to recruit around 2,000 cataract surgery patients aged 65 years or older in western Sydney (Cugati et al, 2007). Participants are interviewed to collect information on demographic, medical and ocular conditions and AMD risk factors, and undergo eye examinations to monitor the development of early and late AMD lesions. Participants will be followed up five years after their initial cataract operation. Final data are not yet available from this cohort study.

4.1.6 Other risk factors

Other risk factors associated with the development of AMD have been investigated through population cohort studies conducted around the world, including sunlight exposure; gender; immune response; and race. Of these, only race appears to impact AMD risk, with higher prevalence in whites than in blacks, and possibly Asians or Hispanics. For other ethnicities, although some significant relationships have been found, the findings are often inconsistent so that further research needs to be undertaken.

Sunlight exposure

The relationship between sunlight exposure and AMD is also inconsistent (Coleman et al, 2008). Delcourt et al (2001) reported that individuals who wore sunglasses regularly were less likely to develop soft drusen. Results from the BDES suggest that people who spent leisure time outdoors were at an increased risk of developing early AMD (Klein et al, 2001). A 10 year follow-up of the BMES participants found sun related skin damage was not associated with the risk of developing early or late AMD (Pham et al, 2009). However, those with very fair skin were found to have an increased risk of developing geographic atrophy when compared to people with fair skin, and those who reported that their skin was relatively resilient to the sun were found to have a reduced risk of developing neovascular AMD. Other epidemiological studies have shown little or no association between sunlight exposure and the risk of AMD (AREDS 2000; Klein et al 2007).

Gender

Exposure to oestrogen (either endogenous or exogenous) has been thought to reduce the risk of AMD, although this has not been proven. For example, in the Women's Health Initiative study (Haan et al, 2006), around 4,000 women aged 65 years and over were randomised to receive conjugated equine oestrogens alone or with progestin, or placebo. The average duration of treatment was five years after which the participants were evaluated for the presence of AMD. The results of the study showed that there was no association between oestrogen supplementation and development of AMD.

Race

Studies have evaluated the incidence and prevalence of AMD among alternative ethnic groups and found there is significant variation. For example, Klein et al (2003) reported higher prevalence of large drusen, pigmentary abnormalities, neovascular AMD and geographic atrophy in whites than in blacks. Similar results were found by the Eye Diseases Prevalence Research Group (2004b) with a much lower prevalence of geographic atrophy and neovascular AMD among black participants compared to whites across all age groups.

Asians have also been found to have a lower risk of developing AMD when compared to a sample consisting of white participants (Friedman et al 2004; Das et al 1994). Varma et al (2004) reported a similar prevalence of early signs of AMD in Hispanic people compared to whites, but a lower prevalence of AMD in general.

Immune response

There is some evidence to suggest that the immune system may play a role in the risk of developing AMD. Nussenblatt et al (2007) suggested that the decline of the ocular down-regulatory immune environment (DIE) could be the underlying factor responsible for the increased risk. The subsequent activation of the immune system could lead to T cell sensitisation. When combined with local anti-angiogenic therapy, several existing immunotherapies could be used to down-regulate the immune response and potentially lead to a more efficient inhibition of choroidal neovascularisation.

5 Economic costs associated with AMD

This chapter estimates the economic costs of vision loss associated with AMD in Australia for the year 2010. The calculations are based on visual acuity, rather than clinical grading, because vision loss is more closely related to disease burden and cost impacts. Early AMD is assumed to be associated with a normal visual acuity (equal to or better than 6/12), so has no associated costs of vision loss.

The costs comprise Australian health system expenditures and other financial costs such as low vision aids, the cost of care, and the deadweight efficiency losses from welfare and taxation transfers, as well as a small component of productivity costs for people with AMD. In addition, cost of the loss of healthy life is estimated. The methodology adopted in this report is consistent with that used in Access Economics (2010a).

5.1 Health system expenditure

Health expenditures comprise the costs of running hospitals and nursing homes, general practitioner (GP) and specialist services funded through Medicare and patient contributions, the cost of prescribed and over-the-counter pharmaceuticals, optometry and allied health services, research and 'other' direct costs (such as health administration).

5.1.1 Methodology

Top-down estimates of health system expenditure for 2004-05 from the Australian Institute of Health and Welfare (AIHW) were obtained by special request. While the prevalence data relate to vision loss specifically, the cost data refer to disorders of the eye and adnexa, so may also include expenditure for early AMD (although this is likely to be relatively small).

AIHW 2004-05 data were converted to 2009 prices using historical health cost inflation (AIHW, 2009):

- 4.0% for 2004-05 to 2005-06;
 - 3.3% for 2005-06 to 2006-07; and
 - 2.9% per annum for years thereafter.
- Additionally, adjustments were made for age-gender demographic changes and population growth between 2004-05 and 2008-09. AIHW estimates for 2004-05 did not include costs for:
- outpatients in hospitals;
 - over-the-counter pharmaceuticals;
 - other health professionals; or
 - aged care homes.

Hence, estimates for these categories were based on those from the Centre for Eye Research Australia and Access Economics (2004), inflated to 2009 dollars and adjusted for demographic change. The AIHW changed the methodology for allocating health expenditure by disease between 2000-01 and 2004-05.²² AIHW (2010b) provided the following breakdown for unallocated health system expenditures in 2004-05 (comprising a total of 30%):

- 9.2% for non-admitted patient expenditure;
- 4.0% for over-the-counter pharmaceuticals;
- 3.4% for other health professionals;
- 1.9% for ambulance;
- 3.5% for aids and appliances;
- 4.8% for community and public health; and
- 3.2% for administration.

For this report, the first three categories were incorporated in the health expenditure estimates by inflating the estimates from Centre for Eye Research Australia and Access Economics (2004). The residual unallocated health system expenditure (13.4%) was incorporated by factoring up health expenditure estimates by 1/0.866. Expenditure data were also supplemented to account for the cost of the recently-listed drug Lucentis for AMD.

5.1.2 Pharmaceutical spending on Lucentis

Health system expenditures were adjusted to account for the 1 August 2007 listing of the drug Lucentis (item 1382R) on the Pharmaceutical Benefits Scheme (PBS) for the treatment of neovascular AMD. A patient treated with Lucentis through the PBS is charged the standard co-payment of \$34.20 for general patients and \$5.60 for concessional patients. The dispensed price for maximum quantity is listed as \$1,976.36 (DoHA, 2007).

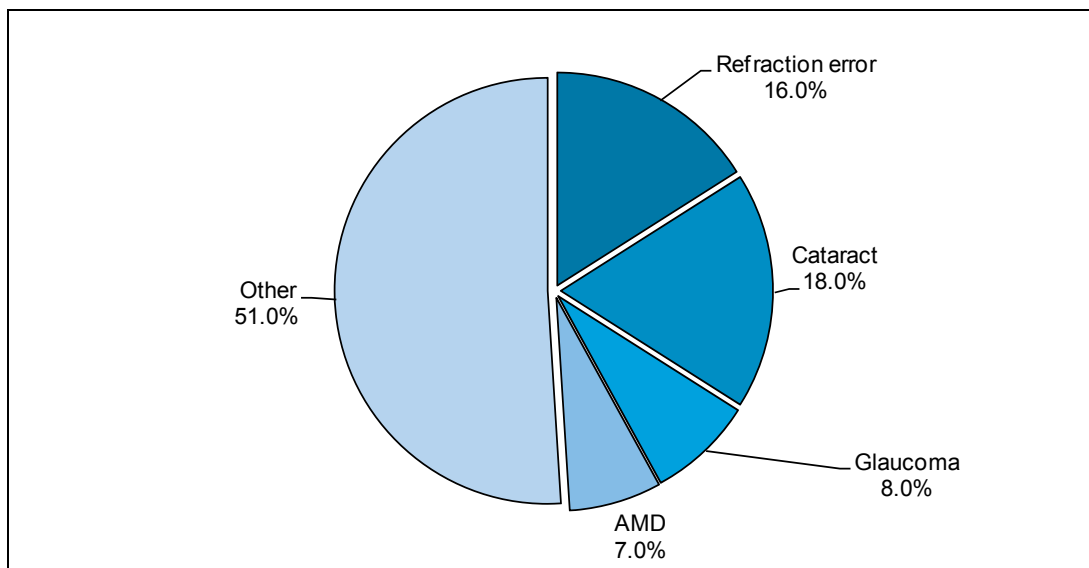
PBS statistics indicate that total government expenditure on Lucentis was approximately \$269.9 million in the 2010 financial year (Table 6.3).

5.1.3 Other health system costs

In 2009, total health system expenditure on disorders of the eye and adnexa was estimated at \$2.98 billion (\$2.58 billion being 'allocated' expenditure). In the same year, AMD's share of total allocated expenditure (\$174 million) was estimated at 7%, rising from 1% in 2004 (Chart 5.1). This was largely due to the addition of government expenditure on Lucentis in 2008-09, which contributed \$151 million to total AMD expenditure (Medicare, 2010).

²² For the older 2000-01 data from Clear Insight, 88% of total recurrent health system expenditure was included with excluded categories comprising capital expenditures, expenditure on community health, public health programs, health administration and health aids and appliances. The recent 2004-05 AIHW data allocated 70% of total recurrent health system expenditure to disease and injury groups. As noted by the AIHW (2010), this lower proportion was due to unallocated expenditures comprising capital expenditure and capital consumption, as well as expenditure on non-admitted patients, over-the-counter pharmaceuticals, patient transport (ambulance), other health practitioner services apart from optometrical services (out-of-hospital non-medical health services), health aids and appliances and health administration. In addition, the 2000-01 AIHW data used a different definition of health, which included high-level residential aged care (AIHW, 2010b).

Chart 5.1: Allocated health system expenditure in 2009 by condition ^(a)



Source: Deloitte Access Economics using AIHW 2004-05 and 2000-01 special request expenditure data, PBS data 2008-09 (Medicare, 2010), AIHW National Hospital Morbidity data for 2004-05 and 2007-08

(a) These data reflect expenditure on diseases of the eye and adnexa, including presbyopia, totalling \$2.64 billion.

Using total government expenditure on Lucentis in 2010 (\$269.9 million), we can put together the costs elements for AMD.

- Factoring up \$269.9 million to account for other AMD health costs (174/151) gives an estimate of total allocated health expenditure for AMD of \$311.0 million, of which \$41.1 million is the other allocated health costs. No adjustment was made for the cost of Visudyne (verteporfin) PDT for this report, because as of 2010, Lucentis is the primary treatment option for neovascular AMD.
- Factoring this up by a further 1/0.866 to account for unallocated health costs, gives total health costs of \$359.1 million, of which \$48.1 million is the unallocated component.

The total health costs associated with AMD is estimated to be \$359.1 million in 2010, with \$269.9 million being total government expenditure on Lucentis in 2010.

5.2 Other financial costs

5.2.1 Productivity losses

Productivity losses are estimated taking account of lower than average employment rates for people with vision loss from AMD, lost lifetime earnings due to premature death attributable to vision loss, and the 'bring forward' of employers' search and hiring costs resulting from premature death. Illness and disease more broadly may lead to productivity losses where they result in higher than average absenteeism, and lower than average productivity at work ('presenteeism costs'). These elements of potential productivity losses are typically difficult to measure and Australian studies with comparative data were not available for AMD for this report. Deloitte Access Economics adopts a human capital approach to the estimation of productivity losses in developed countries.

Employment participation

Vision loss can affect a person's ability to gain employment. Due to lower than average employment rates for people with vision loss, this loss in productivity represents a real cost to the economy, through a loss in earnings (and consequently, taxation revenue earned).

Centre for Eye Research Australia and Access Economics (2004) used MVIP data to estimate the impact of vision loss on employment rates, and these estimates are applied here. After adjusting for differences in the age and gender distribution of the MVIP sample, people with vision loss aged 40 to 64 years were 27.5% less likely to be employed than the general population and people with vision loss aged 65 or over were 4.5% less likely to be employed. A maximum working age of 74 was assumed, and thus the 4.5% employment difference was applied only to vision loss people aged 65 to 74. Average weekly earnings (AWE) data from 2008 (latest available) were inflated to 2010 dollars, using the labour price index (ABS, 2010).

Table 5.1: Productivity loss due to lower employment, 2010

Age	AWE (\$)	Prevalence of late AMD	Productivity loss (\$m)
65-69	1,206	1,366	3.85
70-74	1,176	5,408	14.88
Total		6,774	18.74

Source: Deloitte Access Economic calculations and ABS (2010a).

Table 5.1 shows the productivity losses reflecting the impact of vision loss associated with AMD on the likelihood of employment.

In 2010, the productivity loss due to lower employment was estimated to be \$18.7 million.

Premature death

From the calculations in Table 3.22, there were an estimated 565 deaths attributable to vision loss associated with AMD in 2010. Of these, there were an estimated 52 deaths attributable to vision loss associated with AMD in the 40 to 74 age group (assumed to be working age group in this report). Because of the low number of deaths, the lost productivity from premature death is insubstantial and therefore not included in the calculations.

5.2.2 Informal care costs

Informal carers are people who provide care to others in need of assistance or support on an unpaid basis. Most informal carers are family or friends of the person receiving care. Carers may take time off work to accompany people with vision loss to medical appointments, stay with them in hospital, or care for them at home. Carers may also take time off work to undertake many of the unpaid tasks that the person with vision loss would do if they did not have vision loss and were able to do these tasks.

Informal care is distinguished from services provided by people employed in the health and community sectors (formal care) because the care is generally provided free of charge to the recipient and is not regulated by the government. While informal care is provided free of charge, it is not free in an economic sense, as time spent caring is time that cannot be directed to other activities such as paid work, unpaid work (such as housework or yard work) or leisure. As such, informal care is a use of economic resources.

The informal care costs from vision loss associated with AMD in 2010 were estimated using the average informal care cost associated with all types of eye diseases. Access Economics (2010) estimated that in 2009 the total carer opportunity costs totalled \$251.2 million.

Adjusting for inflation and the proportion of vision loss associated with AMD, it is estimated that in 2010 the total care costs associated with AMD was \$47.5 million.

5.2.3 Deadweight losses from transfers

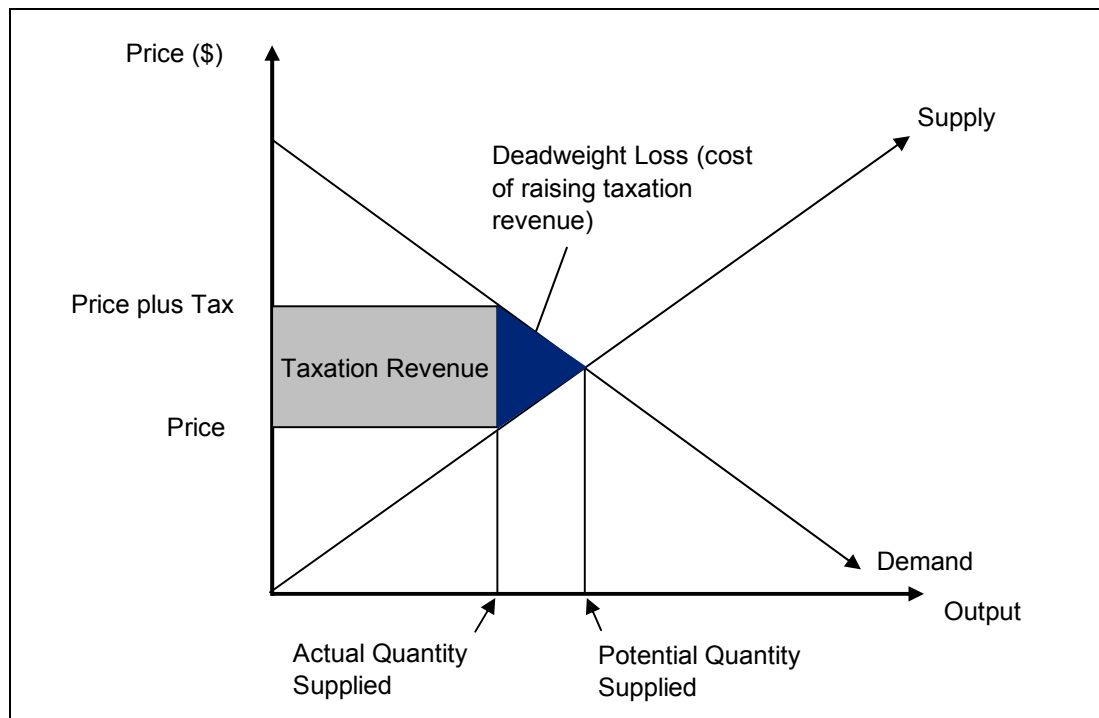
Deadweight loss (DWL) refers to the costs of administering welfare pensions and raising additional taxation revenues. Although disability and sickness benefits and forgone taxation are transfers, not real costs (so should not be included in the estimation of total costs), it is still worthwhile estimating them as that helps us understand how the total costs of low vision are shared between the taxpayer, the individual and other financiers.

Transfer payments (government payments/services and taxes) are not a net cost to society as they represent a shift of consumption power from one group of individuals to another in society. If the act of taxation did not create distortions and inefficiencies in the economy, then transfers could be made without a net cost to society. However, through these distortions, taxation does impose a DWL on the economy.

DWL is the loss of consumer and producer surplus, as a result of the imposition of a distortion to the equilibrium (society preferred) level of output and prices. Taxes alter the

price and quantity of goods sold compared to what they would be if the market were not distorted, and thus lead to some diminution in the value of trade between buyers and sellers that would otherwise be enjoyed (Chart 5.2).

Chart 5.2: DWL of taxation



Source: Deloitte Access Economics calculations.

The DWL from vision loss associated with AMD in 2010 was estimated using the average DWL associated with all types of eye diseases. Access Economics (2010a) estimated that in 2009 the total DWL totalled \$869.0 million.

Adjusting for inflation and the proportion of vision loss associated with AMD, it is estimated that in 2010 the DWL associated with people with AMD was \$164.4 million.

5.2.4 Other indirect costs: aids, home modifications and other carer

Aids and home modifications are those not captured in formal health sector or disability services costs that include equipment and technology in order to assist with daily living. People with low vision from AMD may require a variety of aids, special equipment and home modifications to function adequately and to enhance their quality of life. Some of these are listed below:

- alternative format materials e.g., large print or Braille publications, labels and tags, locator dots;
- mobility aids – canes, guide dogs, torches;
- glasses, sunglasses (glare reducing);

- low vision devices – magnifiers (optical and electronic), telescopes and closed circuit TVs;
- computer aids – e.g., computer speech technology, large print or Braille display;
- daily living aids – clocks and watches, coin sorters, bathroom and kitchen accessories (e.g., liquid level indicators, needle-threaders), sport and recreation items (e.g., embossed dice or playing cards, ringing balls);
- recording and playback devices;
- talking appliances (e.g., talking calculators, scales, thermometers);
- educational aids for visual, audio or tactile learning; and
- enhanced lighting, grab rails.

Other direct costs from vision loss associated with AMD in 2010 were also estimated using the average other direct costs associated with all types of eye diseases Access Economics (2010a). Access Economics (2010a) estimated that in 2009 other direct costs totalled \$838.7 million.

Adjusting for inflation and the proportion of vision loss associated with AMD, it is estimated that in 2010, other indirect costs associated with people with AMD was \$158.6 million.

5.2.5 Summary of other financial costs

The total financial costs of vision loss from AMD, other than health costs, are presented in Table 5.2, together with the cost per person for each financial cost category.

Table 5.2: Summary of other financial costs associated with vision loss from AMD in 2010

	Total costs (\$m)	Cost per person (\$)
Productivity losses	18.7	175
Carer opportunity costs	47.5	443
Aids/home modifications/other carer/bring forward of funerals	158.6	1,480
DWL	164.4	1,533
Total	389.2	3,631

Source: Deloitte Access Economics calculations.

Financial costs, other than health expenditure, associated with AMD are estimated to be \$389.2 million in 2010 or around \$3,631 per person.

5.3 Loss of wellbeing from AMD

This chapter presents a quantitative analysis of the costs of pain and suffering from late stage AMD. These costs of disability, loss of wellbeing and premature death from vision loss are difficult to measure. The term ‘loss of well being’ is used here instead of the well-defined concept in health economics, ‘burden of disease’ as measured by disability adjusted life years (DALYs). ‘Burden of disease’ measures the disability and premature death from a disease or injury and does not imply that people experiencing disease or injury are a burden on society.

This section estimates the loss of wellbeing in 2010 resulting from vision disorders for people aged 40 or over associated with AMD. An imputed value of a statistical life year (VSLY) allows us to compare non-financial costs such as loss of wellbeing with the estimated financial costs of vision loss.

5.3.1 Methodology

In the last decade, a non-financial approach to valuing human life has been derived, where loss of wellbeing and premature mortality are measured in terms of DALYs. This approach was originally developed by the WHO, World Bank and Harvard University to provide a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990, projected to 2020 (Murray and Lopez 1996). Methods and data sources are detailed further in Murray et al (2001) and the WHO continues to revisit the estimates for later years.

A DALY of 0 represents a year of perfect health, while a DALY of 1 represents death. Other health states are attributed values between 0 and 1 as assessed by experts on the basis of literature and other evidence of the quality of life in relative health states. For example, the disability weight of 0.18 for a broken wrist can be interpreted as losing 18% of a person’s quality of life relative to perfect health, because of the inflicted injury. Total DALYs lost from a condition are the sum of the mortality and morbidity components – the year(s) of life lost due to premature death (YLLs) and the year(s) of healthy life lost due to disability (YLDs).

The DALY approach has been successful in avoiding the subjectivity of individual valuation and is capable of overcoming the problem of comparability between individuals and between nations, although some nations have subsequently adopted variations in weighting systems, for example age-weighting for older people. This report treats the value of a life year as equal throughout the lifespan.

As these approaches are not financial, they are not directly comparable with most other cost and benefit measures. In public policy making, it is often desirable to apply a monetary conversion to ascertain the cost of an injury, disease or fatality or the value of a preventive health intervention, for example, in cost benefit analysis. Such financial conversions tend to utilise ‘willingness to pay’ (WTP) or risk-based labour market studies as described in the next section.

5.3.2 Willingness to pay and the value of a statistical life year

The loss of wellbeing as measured in DALYs can be converted into a dollar figure using an estimate of the value of a statistical life (VSL). As the name suggests, the VSL is an estimate of the value society places on an anonymous life. Since Schelling's (1968) discussion of the economics of life saving, the economic literature has focused on WTP – or, conversely, willingness to accept – measures of mortality and morbidity, in order to develop estimates of the VSL.

VSL estimates may be derived from observing people's choices in situations where they rank or trade off various states of wellbeing (loss or gain) either against each other or for dollar amounts (e.g., stated choice models of people's WTP for interventions that enhance health or willingness to accept poorer health outcomes or the risk of such states). Alternatively, risk studies use evidence of market trade-offs between risk and money, including numerous labour market and other studies (such as installing smoke detectors, wearing seatbelts or bike helmets and so on).

The extensive literature in this field mostly uses econometric analysis to value mortality risk and the 'hedonic wage' by estimating compensating differentials for on-the-job risk exposure in labour markets; in other words, determining what dollar amount would be accepted by an individual to induce him/her to increase the probability of death or morbidity by a particular percentage. Viscusi and Aldy (2002), in a summary of mortality studies, found the VSL ranged between US\$4 million and US\$9 million with a median of US\$7 million (in year 2000 US dollars), similar but marginally higher than the VSL derived from studies of US product and housing markets. They also reviewed a parallel literature on the implicit value of the risk of non-fatal injuries.

Weaknesses in the WTP approach, as with human capital approaches to valuing life and wellbeing, are that there can be substantial variation between individuals. Extraneous influences in labour markets such as imperfect information, income/wealth or power asymmetries can cause difficulty in correctly perceiving the risk or in negotiating an acceptably higher wage in wage-risk trade off studies, for example.

As DALYs are enumerated in years of life rather than in whole lives it is necessary to calculate the **value of a statistical life year (VSLY)** based on the VSL. This is done using the formula:²³

$$VSLY = VSL / \sum_{i=0, \dots, n-1} (1+r)^i$$

Where: n = years of remaining life, and r = discount rate

Clearly there is a need to know n (the years of remaining life), and to determine an appropriate value for r (the discount rate). There is a substantial body of literature, which often provides conflicting advice, on the appropriate mechanism by which costs should be

²³ The formula is derived from the definition:

$$VSL = \sum VSLY_i / (1+r)^i \text{ where } i=0, 1, 2, \dots, n$$

where VSLY is assumed to be constant (ie. no variation with age).

discounted over time, properly taking into account risks, inflation, positive time preference and expected productivity gains.

Access Economics (2008) recommended an average VSL of \$6.0 million in 2006 Australian dollars (\$3.7 million to \$8.1 million). This equates to an average VSLY in 2006 of \$252,014 (\$155,409 to \$340,219), using a discount rate of 3% over an estimated 40 years remaining life expectancy. However, from this gross value, Access Economics deducts all costs borne by the individual, reflecting the source study VSL estimates, to avoid double counting. This provides a different net VSLY for different conditions (and for different age-gender groups).

The Office of Best Practice Regulation (OBPR) has provided an estimate of the VSLY in Australia, which appears to represent a fixed estimate of the net VSLY. The OBPR (2008) stated that the VSLY should be \$151,000 in 2007 dollars²⁴. The OBPR also advised that for use in 2009 this figure should be inflated to \$161,750 in 2009 dollars – which assumes that the annual consumer price index (CPI) was 4% for 2008 and 3% for 2009 ($\$151,000 \times 1.04 \times 1.03$).

The 2010 Value of a Statistical Life Year used in this report was assumed to be \$166,603, assuming a CPI of 2.9% for 2010 (ABS, 2010).

This triangulates well with the net VSLY estimated in Access Economics (2008).

5.3.3 Disability weights and YLDs

One of the main costs of vision loss is the loss of wellbeing and quality of life that it entails. This can be estimated by initially allocating disability weights to vision disorders that cause vision loss. Disability weights for AMD were taken from Access Economics (2005). YLDs in 2010 were estimated by multiplying the set of disability weights for AMD by the prevalence of vision loss from both neovascular AMD and geographic atrophy. Overall, there were approximately 23,370 YLDs in 2010 from AMD.

²⁴ Department of Finance and Deregulation Best Practice Regulation Guidance Note: *Value of statistical life PDF version* www.finance.gov.au/obpr/cost-benefit-analysis.html.

Table 5.3: Estimated YLDs from AMD in 2010

Age group	Disability weight	Prevalence in 2010	YLDs in 2010
60-69	0.22	1,366	298
70-79	0.22	17,860	3,893
80-89	0.22	52,444	11,433
90+	0.22	35,521	7,746
Total		107,191	23,370

Source: Deloitte Access Economics calculations.

5.3.4 YLLs due to AMD

In Section 3.3, it was estimated that there were an estimated 565 deaths in the above 40 age group, attributable to vision loss associated with AMD in 2010. YLLs were estimated from the age-gender distribution of deaths by the corresponding YLLs for the age of death in the Standard Life Expectancy Table (West Level 26), with a discount rate of 3% as used by the AIHW. In total, there were approximately 3,039 estimated YLLs in 2010, from vision loss due to AMD (Table 5.4).

Table 5.4: Estimated YLLs from AMD in 2010

Age group	Deaths in 2010	Average age at death	YLLs in 2010
60-69	7	65.5	103
70-79	89	75.5	849
80-89	331	85.5	1741
90+	138	95.5	345
Total	565		3,039

Source: Deloitte Access Economics calculations using Begg et al (2007)

5.3.5 DALYs due to AMD

Summing the YLD and YLL components results in an estimated 24,073 DALYS in 2010 from late AMD (Table 5.5).

Table 5.5: Estimated DALYs from AMD in 2010

Age group	YLDs	YLLs	DALYs in 2010
40-49	0	0	0
50-59	0	0	0
60-69	1,407	103	1,510
70-79	8,394	849	9,243
80-89	8,391	1741	10,133
90+	2,842	345	3,187
Total	21,034	3,039	24,073

Source: Deloitte Access Economics calculations.

Multiplying the total number of DALYs by the VSLY in 2010 (\$166,603) provides an estimate of the dollar value loss of wellbeing from vision loss.

The estimated monetary value of the lost wellbeing from late stage AMD was \$4.39 billion in 2010.

5.4 Cost summary

In 2010, the total cost of vision loss associated with AMD was estimated to be \$5.15 billion (\$48,028 per person), of which the financial cost was \$748.4 million (\$6,982 per person).

Of this total (summarised in Table 5.6, including cost per person with AMD):

- \$359.1 million was estimated health system costs;
- \$18.7 million was estimated productivity losses of those with vision loss associated with AMD;
- \$47.5 million was estimated carer (opportunity) costs.
- \$158.6 million was estimated other indirect costs (aids, modifications, other carer and bring forward of funeral expenses);
- \$164.4 million was estimated deadweight losses from transfers and lost taxation; and
- \$4.39 billion was the value of lost wellbeing.

Table 5.6: Total cost of vision loss associated with AMD in 2010 by cost type

Cost type	Total cost (\$m)	Per person with AMD (\$)
Health system costs (a)	359.1	3,350
Productivity losses	18.7	175
Carer opportunity costs	47.5	443
Other indirect (aids/modifications/other carer and bring forward of funeral)	158.6	1,480
DWL	164.4	1,533
Total other financial costs (b)	389.2	3,631
Total financial costs (a) + (b)	748.4	6,982
Loss of wellbeing (c)	4,399.8	41,047
Total economic cost (a) + (b) + (c)	5,148.2	48,028

Source: Deloitte Access Economics calculations.

6 Treatment of AMD

This chapter outlines the lack of treatment associated with dry AMD and the potential cost savings if a treatment for geographic atrophy could be found. It also outlines current treatment for wet AMD, focusing on the use and cost effectiveness of Lucentis.

6.1 Treatment of dry (atrophic) AMD

Geographic atrophy is usually associated with a significant decline in visual acuity over time where areas of atrophy continue to enlarge, even when already large at baseline (Sunness, 1999). The combination of reduced visual acuity with enlargement of atrophy, occurring in both eyes of most patients, can lead to significant associated health costs. Currently there is no effective treatment for geographic atrophy meaning that prevention is the first approach to reducing vision loss and the associated burden on society (Coleman et al, 2008).

Even though there is currently no effective treatment prescribed for geographic atrophy, controlling for modifiable risk factors such as diet and smoking (Section 4) could potentially prevent or delay the onset to the more advanced stages of AMD. Consequently, the costs of visual impairment associated with geographic atrophy could partially be eliminated. This suggests that there are substantial benefits for a successful intervention.

If cigarette smoking among early AMD cases was halved, reducing the number of cases of AMD by one sixth in time, the total savings would be in the order of \$247 million per annum, in 2010 dollars.

6.2 Potential cost savings from dry AMD treatment

The total financial cost of vision loss associated with visual impairment from geographic atrophy is provided in Table 6.1. The health system cost for people with geographic atrophy was adjusted to account for people with geographic atrophy not incurring the cost of Lucentis treatment. The table also presents the per person costs.

Table 6.1: Estimated total cost from visual impairment from geographic atrophy

Cost type	Total cost (\$m)	Per person with AMD (\$)
Health system costs (a)	29.4	832
Productivity losses	6.2	175
Carer opportunity costs	15.7	443
Other indirect (aids/modifications/other carer and bring forward of funeral)	52.3	1,480
DWL	54.2	1,533
Total other financial costs (b)	128.4	3,631
Total financial costs (a) + (b)	157.9	4,464
Loss of wellbeing (c)	1,323.5	37,415
Total economic cost (a) + (b) + (c)	1,481.4	41,879

Source: Deloitte Access Economics calculations.

(a) Health system costs excludes the cost of treatment with Lucentis.

The cost of visual impairment from dry AMD is estimated as \$1.48 billion (\$41,879 per person) in 2010, of which the financial costs were \$157.9 million (\$4,464 per person).

6.3 Treatment of neovascular AMD

The recent developments of new and effective treatments for neovascular AMD have meant that methods such as laser photocoagulation and sub-macular surgery are essentially no longer treatment options (Schmidt-Erfurt, 2007). PDT monotherapy was shown to reduce the rate of vision loss in patients with sub-foveal and relatively small lesion types, although visual acuity was uncommonly improved with PDT alone.

Understanding the pathogenesis of neovascular AMD has resulted in new efficacious pharmacological therapies that can now treat some components of angiogenesis (development of new blood vessels). For example, anti-vascular endothelial growth factor A (VEGF-A) agents have substantially advanced the therapeutic spectrum.

The treatment for wet MD has changed radically with the development of anti-VEGF injections such as ranibizumab (Lucentis), bevacizumab (Avastin) and aflibercept (Eylea; VEGF Trap-Eye).

6.3.1 Ranibizumab (Lucentis)

Ranibizumab (Lucentis) is currently the most effective registered treatment for neovascular AMD. In major randomised clinical trials (RCTs), Lucentis has been shown to be a safe and clinically effective treatment for wet AMD with around 95% of the participants who received monthly injections maintaining their vision (Bradley, 2007). Lucentis is a humanised recombinant antibody targeted against VEGF-A. VEGF-A has been shown to play a major role in the pathogenesis of choroidal neovascularisation (Adams, 2005).

Lucentis injections suppress the effects induced by VEGF-A and, as a result, inhibit the development of new blood vessels under the retina and the associated leakage that leads to the progression of macular degeneration. Although Lucentis is primarily indicated for subfoveal lesions with active disease, all three major CNV subtypes respond to Lucentis, indicating that treatment with Lucentis should be considered for all neovascular AMD lesions (Mitchell et al, 2010).

Lucentis is currently only PBS-listed for sub-foveal lesions associated with age-related macular degeneration. Neovascular lesions typically first develop in the extra-foveal area, very close to the fovea before quickly moving to the juxta-foveal and sub-foveal areas. Consideration should be given to allow the treatment of extra- and juxta-foveal lesions under the PBS as this could allow earlier intervention, potentially improving outcomes.

Most juxta-foveal lesions are not treatable with the alternative current treatment, laser photocoagulation, because of the need to overlap the new vessel with a margin of over 100 microns, which would lead to laser damage to the fovea in many cases. Laser treatment is also associated with a high (>50%) likelihood of recurrence and progressive associated macular damage.

6.3.1.1 Safety and efficacy of Lucentis

The clinical safety and efficacy of Lucentis has been assessed in three randomised, double-masked, sham or active-controlled studies in patients with neovascular AMD. These are the MARINA, ANCHOR and PIER studies. The MONTBLANC trial is a further masked study, while other unmasked studies (SUSTAIN and EXCITE) also provide additional evidence.

In the MARINA study, patients with minimally classic or occult with no classic CNV were randomised to receive monthly intravitreal injections of either Lucentis 0.3mg or 0.5mg or sham injections. A total of 716 patients were enrolled in this study.

In the ANCHOR study, patients with predominantly classic CNV lesions were randomised to receive either:

- monthly intravitreal injections of Lucentis 0.3mg and sham PDT;
- monthly intravitreal injections of Lucentis 0.5mg and sham PDT; or
- sham intravitreal injections and active verteporfin PDT.

Sham or active verteporfin PDT was given with the initial Lucentis injection and every three months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients were enrolled in this study.

In both the ANCHOR and MARINA studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing less than 15 letters of visual acuity at 12 months compared to baseline. Almost all Lucentis treated patients (approximately 95%) maintained their visual acuity. Around 34-40% of patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not affect the results. However, better presenting acuity was associated with greater visual acuity gain in both studies.

In the PIER study, patients with neovascular AMD (with or without a classic CNV component) received Lucentis 0.3mg or 0.5mg intravitreal injections or sham injections

once a month for three consecutive doses (loading phase), followed by a dose administered once every three months (maintenance phase). A total of 184 patients was enrolled in this study.

The primary efficacy endpoint was the mean change in visual acuity at 12 months compared with baseline. After an initial increase in visual acuity (following a loading phase of three months with three monthly injections, consistent with ANCHOR and MARINA, on average, patients dosed every three months lost the initial visual acuity gain at 12 months. However, around 90% of patients treated with Lucentis had maintained their visual acuity at 12 months.

Lucentis obtained marketing approval in Australia (registration) from the Therapeutics Goods Administration in February 2007, on the evidentiary basis outlined in the above trials.

6.3.1.2 Treatment guidelines for Lucentis

Several treatment guidelines have been developed based on the level of evidence. Clinical recommendation (level I evidence) indicated that 0.5 mg of Lucentis should be initiated with at least three consecutive monthly intravitreal injections, using an aseptic procedure (Mitchell et al, 2010). Treatment should also be commenced as early as possible with the ideal time period within a maximum of two weeks of diagnosis. Intra-treatment intervals of greater than one month duration are typically associated with an increased risk for vision loss. As an indication of this time interval, the screening periods permitted before treatment initiation in the clinical studies were 14 or 28 days.

Based on evidence derived from well-designed, randomised controlled trials, the clinical recommendation for treatment with Lucentis is a monthly regimen of Lucentis intravitreal injections for at least 2 years. This regimen demonstrated the best visual acuity outcomes in the clinical trials (Mitchell et al, 2010).

PRN and “inject and extend” regimens

In order to reduce the treatment burden and costs for patients and workload for doctors, many ophthalmologists have implemented treatment regimens involving reduced numbers of injections. Two approaches have been taken – “PRN” (as needed) and “inject & extend”.

PRN

Based on evidence derived from relatively weak studies (e.g., non-comparative studies without controls, descriptive studies, panel consensus or expert opinion) the clinical recommendation for PRN dosing was the following.

- When a monthly regimen is not possible, a flexible strategy with monthly monitoring is feasible. Benefits could be less than with monthly treatment. Frequent monitoring aims to detect active disease from: history, visual acuity assessments, slit-lamp examinations and OCT.
- Fluorescein angiography (FA) is generally not essential at this stage but could be considered, particularly if the retinal examination does not explain recent or progressive visual acuity deterioration (e.g., FA may identify recurrent leak or CNV enlargement).

- If the disease is present or reoccurs, additional treatment should be initiated quickly to improve functional outcomes.
- If the disease becomes inactive with dense subretinal fibrosis or subfoveal atrophy, retreatment may not be needed (Mitchell, 2010).
- This approach however, has not been able to reproduce the results seen in ANCHOR and MARINA.
- The largest PRN study is the CATT (Comparison of AMD Treatment Trial – CATT Research Group, 2011). In this trial, the outcomes from PRN treatment of neovascular AMD were much closer (over 12 months only, at time of publication), though still numerically inferior, to those from monthly treatment. In the CATT, patients on the PRN regimen were treated more aggressively than in earlier PRN studies such as PIER and EXCITE. More information on the CATT is given in section 6.3.2.

Inject & Extend

Once a patient has stabilised following a “loading phase” of at least three monthly injections, the treatment gap is extended by one week, to five weeks. If stable after five weeks, the patient should receive an injection and the next injection given after a six-week gap and so on. Should a patient experience a recurrence, the treatment gap should be returned to four weeks and then increased gradually to one week less than the duration which resulted in recurrence. Slight variations have been developed on this regimen. Two week extend intervals have also been recommended by some investigators.

This approach, if managed aggressively with careful monitoring and good patient understanding, could provide outcomes approaching those seen in ANCHOR and MARINA.

6.3.1.3 Reimbursement of Lucentis

Lucentis gained reimbursement for neovascular AMD on the PBS in August 2007. The submission to the Pharmaceutical Benefits Advisory Committee (PBAC) presented a series of preliminary (trial-based) economic evaluations based on the results from the ANCHOR, MARINA and PIER trials.

The PBAC recommended listing Lucentis for the treatment of subfoveal CNV due to AMD on a cost effectiveness basis against verteporfin with PDT in predominantly classic disease, and against placebo in minimally classic or occult disease. The listing was recommended at the price proposed in the submission on the basis of an average incremental cost per extra quality adjusted life-year (QALY) gained across all lesion types of between \$15,000 and \$45,000²⁵. The submission presented a series of modelled economic evaluations summarised in Table 6.2.

²⁵ For more information, see [http://www.health.gov.au/internet/main/publishing.nsf/Content/8273CE4F07D2021FCA2572F800047B3B/\\$File/Ranibizumab.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/8273CE4F07D2021FCA2572F800047B3B/$File/Ranibizumab.pdf), accessed 19 April 2010.

Table 6.2: Summary of economic evaluations from ANCHOR, MARINA and PIER

Lesions	Cost/QALY	Dosage	Period
Predominately classic CNV	\$15,000-\$45,000	0.5mg	Monthly
Predominately classic CNV	\$15,000-\$45,000	0.5mg	Monthly (3 months) then every two months
Minimally classic CNV	\$45,000-\$75,000	0.5mg	Monthly
Minimally classic CNV	\$105,000-200,000	0.5mg	Monthly (3 months) then every two months
Occult CNV	\$45,000-\$75,000	0.5mg	Monthly
Occult CNV	\$105,000-\$200,000	0.5mg	Monthly (3 months) then every two months
Weighted average CE ¹	\$15,000-\$45,000	0.5mg	Monthly
Weighted average CE	\$45,000-\$75,000	0.5mg	Monthly (3 months) then every two months

Source: PBS Public summary document for ranibizumab, 2007.

¹ CE=cost-effectiveness.

The economic evaluations conducted in the three key trials differed in the timing of dosage. ANCHOR and MARINA used a monthly dosing schedule whereas PIER used a 'monthly for three months then every three months after' regimen. A comparison across the results of the three trials suggests that injections given on a monthly basis may be associated with improved outcomes compared with injections given every three months, for everything except predominately classic CNV.

Since listing, expenditure on Lucentis PBS and the Repatriation Pharmaceutical Benefits Scheme (RPBS) was \$107.7 million in 2008, \$188.2 million in 2009 and \$269.9 million in 2010, although these figures do not include undisclosed rebates paid by Novartis to the federal government. A breakdown of PBS expenditure and the number of services is shown in Table 6.3 and Table 6.4, respectively.

Table 6.3: Government expenditure on Lucentis (\$million)

	2008	2009	2010
PBS			
General ordinary	13.8	23.0	33.1
General safety net	0.8	1.2	1.4
Concessional ordinary	67.4	120.9	175.8
Concessional safety net	5.3	9.4	12.7
Total – PBS	87.3	154.5	223.0
RPBS			
RPBS ordinary	19.3	31.9	44.6
RPBS safety net	1.1	1.8	2.3
Total – RPBS	20.4	33.7	46.9
Total – PBS + RPBS	107.7	188.2	269.9

Source: Medicare, 2011.

Table 6.4: Government funded services performed using Lucentis

	2008	2009	2010
PBS			
General ordinary	6,759	11,246	16,002
General safety net	378	564	643
Concessional ordinary	32,570	57,986	83,332
Concessional safety net	2,539	4,447	5,901
Total – PBS	42,246	74,243	105,878
RPBS			
RPBS ordinary	9,443	15,212	20,997
RPBS safety net	516	862	1,090
Total – RPBS	9,959	16,074	22,087
Total – PBS + RPBS	52,205	90,317	127,965

Source: Medicare, 2011.

6.3.1.4 Lucentis in other countries

Lucentis has been found to be cost-effective by central health assessment agencies in other countries. The National Institute for Health and Clinical Excellence (NICE) in the UK has recommended Lucentis as a cost-effective therapy for all eligible patients with wet AMD under the following conditions.

- The best possible visual acuity after correction with glasses or contact lenses is between 6/12 and 6/96.
- There is no permanent damage to the fovea.
- The area affected by AMD is no larger than 12 times the size of the area inside the eye where the optic nerve connects to the retina.
- There are signs that the condition has been getting worse.

NICE recommended that treatment should stop if a person's vision worsens and there are changes inside the eye which show that treatment is not working. The National Health Service covers the drug cost of Lucentis for the first 14 injections in each eye being treated. If people need more than 14 injections per eye, Novartis (the manufacturer of Lucentis) has agreed to take over the drug cost from the National Health Service.

Lucentis was approved for use in Canada in June 2007. In March 2008 the Common Drug Review, Canada's national drug review process, recommended that it be listed by Canada's publicly funded drug plans. Currently, Lucentis is reimbursed under public drug plans in Manitoba, Quebec, Ontario, British Columbia, Alberta, Saskatchewan, New Brunswick, Newfoundland and Labrador, and the Yukon, Nunavut and Northwest Territories. Nova Scotia and Prince Edward Island remain the only provinces where Lucentis is not reimbursed. The recommendation for Lucentis was for the treatment of neovascular AMD, limited to a maximum of 15 vials per patient, used to treat the better-seeing affected eye. Lucentis is not to be used in combination with verteporfin.

The Italian Pharmaceutical Agency has granted reimbursement status to Lucentis for the treatment of AMD after reaching a cost control agreement with Novartis as well as an agreement where the entire therapeutic process will be monitored to ensure the drug is

appropriately prescribed, and that its use is economically sustainable. Lucentis can only be used in hospitals. Patients are enrolled in a monitoring system which is part of the agreement between the medicines agency and Novartis. In its official recommendation on Lucentis, Italian Pharmaceutical Agency also announced the pricing of Lucentis. The ex-factory price of 10 mg/ml of injectable solution was set at €1,100 while the end user price was given as €1,815, both excluding value added tax.

The French Transparency Committee recommended including Lucentis on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services. The Transparency Committee announced “it will fund macular degeneration patients for the drug Lucentis. In making this announcement, France is providing their citizens with what is currently the best treatment available for this eye disease”.

6.3.1.5 Cost effectiveness models

Cost effectiveness analyses aim to compare the value derived from an intervention – in natural units rather than dollars – with the associated costs of the intervention. In cost utility analysis, a subset of cost effectiveness analysis, the outcome metric is QALYs gained or DALYs averted. There is a variety of opinion on where bounds for cost effective interventions lie. The WHO (2002)²⁶ defines cost effectiveness relative to gross domestic product (GDP) per capita as:

- cost effective: one to three times GDP per capita to avert one lost DALY (for Australia in 2010, around A\$50,000 to A\$150,000 per DALY averted);
- very cost effective: less than GDP per capita to avert one lost DALY (for Australia in 2010, less than A\$50,000/DALY averted).

A systematic review and economic evaluation of ranibizumab and pegaptanib for the treatment of AMD was conducted by the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton, UK. The Health Technology Assessment Programme, part of the National Institute for Health Research, was initiated in 1993. It produces research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the National Health Service in the UK.

The research findings from the Health Technology Assessment Programme directly influence NICE and the National Screening Committee, and also help to improve the quality of clinical practice in the National Health Service indirectly in that they form a key component of the ‘National Knowledge Service’. The findings of the systematic review and economic evaluation of the National Institute for Health Research are listed below.

- Patients with AMD of any lesion type benefit from treatment with Lucentis on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued treatment appeared to maintain benefits after two years of follow-up.
- In a sensitivity analysis for Lucentis (conducted separately for lesion types and alternative comparators) the majority of simulations were associated with increased QALYs (benefits) but also increased costs.

²⁶ http://www.who.int/choice/costs/CER_levels/en/index.html

- Lucentis for patients with predominantly classic lesions had a probability of being cost-effective (compared with PDT) of 72% at a WTP threshold of £20,000 per QALY and 97% at a WTP threshold of £30,000 per QALY.
- The equivalent values for the comparison with best supportive care were 95% at a WTP threshold of £20,000 per QALY and 97% at a threshold of £30,000 per QALY.
- For patients with minimally classic and occult no classic lesions, the probabilistic sensitivity analysis shows a 15% probability of Lucentis being cost-effective at a WTP threshold of £20,000 per QALY and 81% at a WTP threshold of £30,000 per QALY.

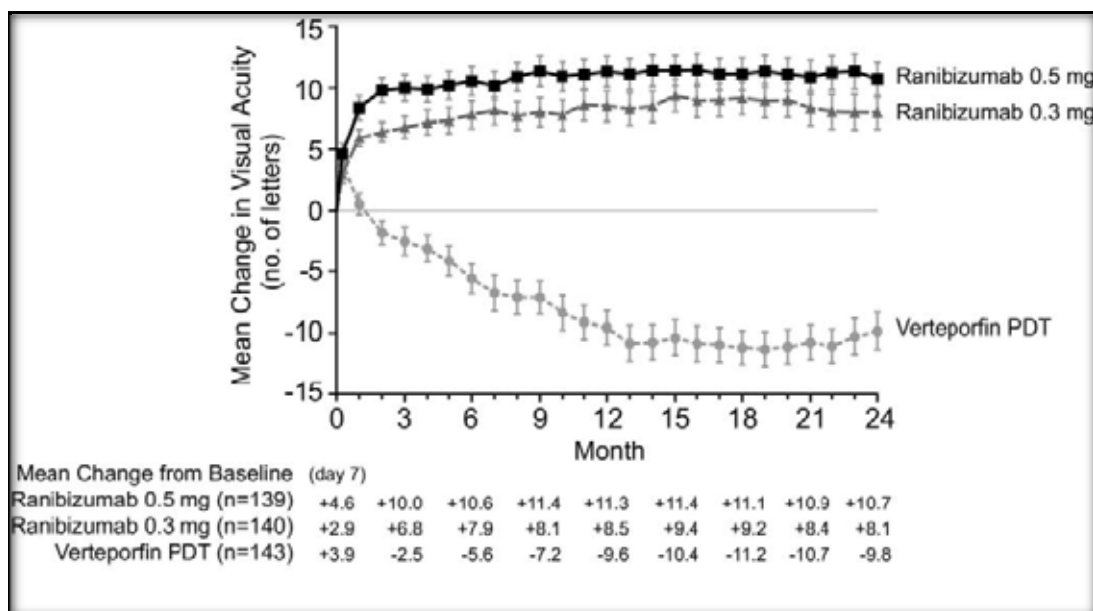
6.3.1.6 Number of people being treated with Lucentis

Genentech²⁷ estimated that the average number of Lucentis injections is expected to range between five and seven per year. In this report, the number of people being treated with Lucentis each year was estimated by assuming seven scripts. Using the total number of scripts in the 2010 year (127,965), it is estimated that 18,280 people with neovascular AMD acquired Lucentis in 2010.

6.3.1.7 Improvement in vision due to treatment

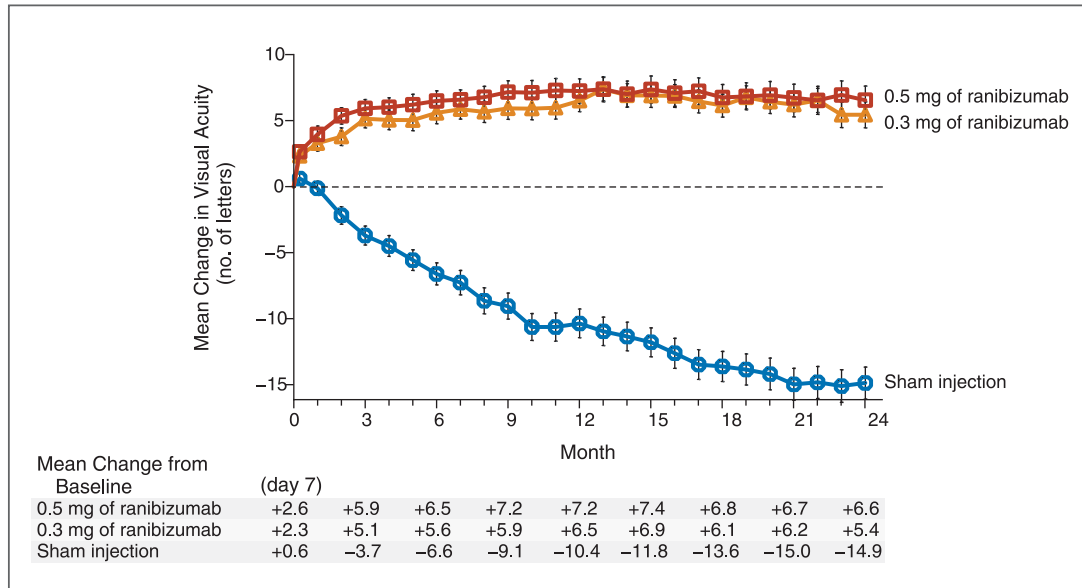
Improvements in visual acuity from Lucentis have been assessed in three key studies; the MARINA, ANCHOR and PIER study. Chart 6.1 and Chart 6.2 show the mean change in visual acuity in the ANCHOR and MARINA studies respectively.

Chart 6.1: Change in the visual acuity score using Lucentis in the ANCHOR study



Source: Brown et al (2009). © Elsevier. Used with permission.

²⁷ Lucentis was developed by Genentech and is being marketed by Genentech and Novartis for diseases or disorders of the eye. Genentech retains commercial rights in the United States and Novartis has exclusive commercial rights for the rest of the world (http://www.gene.com/gene/index.jsp?hl=en&q=Genentech+&btnG=Search&aq=f&aqi=g10&aql=&oq=&gs_rfai=)

Chart 6.2: Change in the visual acuity score using Lucentis in the MARINA study

Source: Rosenfeld et al (2006). © Massachusetts Medical Society. Used with permission.

In the ANCHOR study, Brown et al (2006) found that Lucentis was superior to PDT with verteporfin as an intravitreal treatment of predominantly classic neovascular AMD, on average at one year, and that Lucentis was associated with low rates of serious ocular adverse events.

Of the 423 participants enrolled in the ANCHOR study, 94.3% of those given 0.3 mg of Lucentis and 96.4% of those given 0.5 mg Lucentis maintained stable vision within 15 letters, compared with 64.3% of those in the PDT with verteporfin group. Visual acuity improved by 15 letters or more in 35.7% of the 0.3 mg group and 40.3% of the 0.5 mg group, compared with 5.6% of the PDT-V group. Mean visual acuity increased by 8.5 letters in the 0.3 mg group and 11.3 letters in the 0.5 mg group, as compared with a decrease of 9.5 letters in the verteporfin group (Brown et al, 2006) (Table 6.5)

Table 6.5: Visual change from ANCHOR study

	Lucentis (0.3 mg)	Lucentis (0.5 mg)	Sham
Lost fewer than 15 letters	94.3%	96.4%	64.3%
Improved by more than 15 letters	35.7%	40.3%	5.6%
Mean visual change (letters)	8.5	11.3	-9.5

Source: Brown et al (2006).

In the MARINA study, patients with AMD with either minimally classic or occult (with no classic lesions) CNV were randomly assigned to receive 24 monthly intravitreal injections of Lucentis (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months (Rosenfeld et al, 2006).

Of the 716 participants enrolled in the MARINA study, 94.5% of the group given 0.3 mg of Lucentis and 94.6% of those given 0.5 mg Lucentis lost fewer than 15 letters at 12 months,

as compared with 62.2% of patients receiving sham injections. Visual acuity improved by 15 or more letters in 24.8% of the 0.3 mg group and 33.8% of the 0.5 mg group, as compared with 5.0% of the sham-injection group. Mean increases in visual acuity were 6.5 letters in the 0.3 mg group and 7.2 letters in the 0.5 mg group, as compared with a decrease of 10.4 letters in the sham-injection group (Table 6.6).

Table 6.6: Visual change from MARINA study

	Lucentis (0.3 mg)	Lucentis (0.5 mg)	Verteporfin PDT
Lost fewer than 15 letters	94.5%	94.6%	62.2%
Improved by more than 15 letters	24.8%	33.8%	5.0%
Mean visual change (letters)	6.5	7.2	10.4

Source: Brown et al (2006)

The ANCHOR and MARINA studies showed that not only did Lucentis prevent vision loss, it was also associated with a mean improvement in vision at one year. Both studies found that the efficacy outcomes for patients receiving Lucentis at one year were maintained through the second year, whereas vision in patients in the sham-injection group continued to decline. That is, subjects treated with Lucentis in the MARINA study experienced a mean improvement from baseline of 6.6 letters at 2 years compared to a mean loss of 14.9 letters in the sham group.

6.3.1.8 Cost benefit analysis of Lucentis

As part of the process of the listing of Lucentis on the PBS, several cost utility analyses were conducted. This section assesses the economic cost of neovascular AMD as well as the indirect benefits and improvement in health from Lucentis treatment.

6.3.1.9 Economic cost of neovascular AMD

Based on the costing from Section 5, the total financial cost of vision loss associated with neovascular AMD is provided in Table 6.7. The health system costs include the costs associated with treatment using Lucentis and as such are greater than those incurred by people with geographic atrophy in Section 6.2.

The cost of visual impairment from neovascular AMD is estimated as \$3.67 billion (\$51,056 per person) in 2010, of which the financial costs were \$590.5 million (\$8,222 per person).

Table 6.7: Estimated total cost from visual impairment from neovascular AMD

Cost type	Total cost (\$m)	Per person with AMD (\$)
Health system costs (a)	329.7	4,591
Productivity losses	12.6	175
Carer opportunity costs	31.8	443
Other indirect (aids/modifications/other carer and bring forward of funeral)	106.3	1,480
DWL	110.1	1,533
Total other financial costs (b)	260.8	3,631
Total financial costs (a) + (b)	590.5	8,222
Loss of wellbeing (c)	3,076.3	42,835
Total economic cost (a) + (b) + (c)	3,666.8	51,056

Source: Deloitte Access Economics calculations.

6.3.1.10 A review of recent research on the cost of AMD

Ke et al (2006) reviewed two studies (Table 6.8). The Bonastre et al (2003) study sampled 105 patients over 60 years of age resident in the Paris region of France. All patients had a diagnosis of exudative AMD in at least one eye with a distant visual acuity in the better eye less than 20/40. Garattini et al (2004) had a sample size of 476 patients who were over 50 years of age and were classified into three clinical groups, namely, drusen, geographic atrophy and exudative AMD. In terms of the total annual mean cost per patient, Bonastre et al (2004) reported €3,660.29 (\$8,709 in 2010 Australian dollars) whilst Garattini et al (2004) reported €383.20 (\$911 in 2010 Australian dollars). Both groups of investigators reported that the cost-of-illness associated with AMD increases with the severity of the condition.

Table 6.8: Mean annual direct cost per patient: two study comparison

Category of cost	Bonastre et al (2003, 2004)		Garattini et al (2004)	
	original cost estimate in AUD	inflated to 2010 prices	original cost estimate in AUD	inflated to 2010 prices
	2000	2010	1996	2010
Ophthalmologist consultation	37.7	62.5	27.8	46.2
Fluorescein angiography	402.0	667.3	63.4	105.3
Photocoagulation therapy	100.5	166.9	66.6	110.6
Photodynamic therapy	209.5	347.9	81.4	135.1
Medications	1,739.0	2,887.0	-	-
Hospitalisation	87.1	144.5	40.1	66.6
Low-vision rehabilitation	41.5	69.0	236.9	393.3
Low-vision aids	59.5	98.8	-	-
Transport cost	764.7	1,269.6	-	-
Adjustment of home environment	590.4	980.2	-	-
Home help	27.7	46.0	-	-
Total annual mean cost per patient	821.4	1,363.6	-	-
	5,245.9	8,709.2	549.2	911.8

Source: Ke et al (2006)

Based on the assessment of the evidence, Bonastre et al (2003, 2004) argue that the scarcity of research studies on the direct cost of illness associated with AMD and wide variation in estimates produced from the few studies available make it difficult to assess with confidence the likely direct AMD average cost of illness.

Our cost estimate lies between the two studies. The differences appear to be explained, at least in part, by the fact that Bonastre includes a comprehensive list of costs and has relatively high severity (hence the higher average cost), while Garattini only includes a subset of these (and our) costs, and covers all severities (hence the lower average cost).

6.3.1.11 Benefits associated with Lucentis

In the MARINA study, Lucentis was compared with PDT with verteporfin in the treatment of predominantly classic neovascular AMD. The results showed that improvement in mean visual acuity was 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group. The average benefit associated with Lucentis was therefore 17.6²⁸ letters over the treatment period of one year.

According to the International Council of Ophthalmology (ICO) Visual Acuity Measurement Standard (1984), a line is considered read if “more than half” of the characters are identified correctly. For an Early Treatment Diabetic Retinopathy Study chart with five letters per line, an improvement of 17.6 letters means an improvement in three lines.

²⁸ 7.2+10.4

Equivalently each one line gain on the visual acuity chart represents a 0.1 unit decrease on the logMAR scale. By assuming a change of 0.3logMAR (3 units) over a -0.3logMAR to 1.3logMAR scale (17 units), the visual severity classification of some people with neovascular AMD can be reduced (see Table 2.2). For example, a person with 6/30 on the Snellen chart can be reclassified as having mild visual acuity after a change of 0.3logMAR.

The potential savings associated with Lucentis are estimated by multiplying the number of people who improve their visual severity classification by the cost difference between each classification.

The cost of neovascular AMD per person, by visual severity classification can be calculated by using the relationship between the average cost per person (Table 6.7) and the weighted prevalence in each severity group²⁹ (Section 3.1.5.1). That is:

Mild weight (x) + Moderate weight (y) + Severe weight (z) = weighted cost per person

$$0.079 (x) + 0.201 (y) + 0.720 (z) = \$51,056$$

Where:

x = the cost per person with mild visual impairment with neovascular AMD

y = the cost per person with moderate visual impairment with neovascular AMD

z = the cost per person with severe visual impairment with neovascular AMD

Visual severity cost relativities are proxied using the disability weights for AMD and associated depression and accidental falls (Table 6.9). For example, a person with severe visual acuity is assumed to experience a greater cost (29%) than someone with mild visual acuity associated with neovascular AMD.

Table 6.9: Disability Weightings

	EDS	Mild	Moderate	Severe
AMD, depression and accidental falls	0.333	0.346	0.446	0.620
Correlation between weights from Mild	0.96	1.00	1.29	1.79

Source: Access Economics (2006) using AIHW data.

EDS - Early disease stage of AMD. EDS is mapped to normal visual acuity.

The cost relativities between each visual severity group can be shown as:

$$1.29 (x) = y ; 1.79 (x) = z ; 1.79/1.29 (y) = z$$

The cost, per person, with mild (\$31,356), moderate (\$40,419) and severe visual impairment (\$56,188) is estimated by solving for x, y and z.

The number of people who improve their visual severity classification is estimated by assuming a uniform distribution in each classification. For example, since LogMAR is presented in a linear scale, it is assumed that a change of 0.3logMAR will transfer 50% of people from the moderate to mild group based on a 0.6LogMAR moderate severity range (Table 2.2).

²⁹ 7.9% would have mild visual impairment, 20.1% would b have moderate visual impairment and 72% would be likely to have severe visual impairment (Australian 'legal' blindness).

In summary, if all people with neovascular AMD in Australia were treated, the savings potentially associated with Lucentis are estimated to be \$887.5 million.

The largest savings is related to the reduction in the burden of AMD, but financial savings in 2010 would be worth some \$142.9 million, including fewer productivity losses from informal care, reduced need for low vision aids, and less downstream or alternative treatment for visual impairment (e.g., PDT).

Comparing the overall savings to the cost of Lucentis, the social benefit cost ratio was estimated to be over 2:1, and the \$/DALY averted is estimated as \$41,792.

6.3.1.12 Annual Lucentis treatment cost – Government and patient

The costs associated with standard neovascular AMD treatment using Lucentis were calculated based on the publicly funded components of AMD treatment.

The May 2010 Medicare Benefit Scheme (MBS) fee for Retinal Photography (multiple exposures of both eyes with intravenous dye injection) to diagnose subfoveal AMD (item 11218) was \$143.60. Also included in the standard treatment cost is an examination by an ophthalmologist, proxied by the MBS item number 104 (initial consultation, MBS Fee = \$80.85) or 105 (subsequent consultation, MBS Fee \$40.60) plus an intravitreal injection (item 42740, MBS Fee = \$284.25). It is assumed that individuals would require one 'initial consultation' (item 104) and six 'subsequent consultations' (item 105) in the first year of treatment (based on the assumption of seven injections (item 42740) per year from Section 6.3.1.6).

In relation to medication costs, the PBS standard treatment of Lucentis Solution (intravitreal injection 2.3 mg in 0.23 mL) was approved for \$1,976.60 (item 1382R). The out of pocket cost according to the PBS³⁰ was \$33.30 per non-concessional treatment and \$5.30 per concessional (2010 costs).

In a recent survey (Macular Degeneration Foundation, 2010), the average treatment cost per anti-VEGF injection was \$522, (for Items 105 and 42740), excluding an OCT scan. MBS reimbursements (at 85% of the 2010 MBS Fee) were \$276 per injection, leaving an average out-of-pocket cost of \$246 per injection, excluding the cost of any non-reimbursed OCT scans. Since a person with neovascular AMD has an estimated average of seven injections per year, the mean out-of-pocket treatment cost for someone being treated for one eye was \$1,722 or \$2,006 allowing for four unreimbursed OCT scans, (averaging \$71 each). If a pensioner being treated for one eye claims the additional reimbursement payable for Medicare items under the Extended Medicare Safety Net, he/she would typically have total out-of-pocket treatment and drug costs of about \$1,116 per year (including unreimbursable OCT scans). Similarly, the total annual out-of-pocket treatment and drug costs for non-pensioners would be about \$1,762. Patients being treated in both eyes would have

30

<http://www.pbs.gov.au/html/healthpro/search/results?term=lucentis&scope=PBS+STATIC+WEB+NEWS&form-type=simple>

significantly higher out-of-pocket costs. Given that the survey was conducted on a large sample, across all states of Australia, the out-of-pocket expenses reported in the survey were used in this analysis.

In addition to treatment costs, travel costs are also required for the treatment of neovascular AMD. The Macular Degeneration Foundation (2010) found that on average, AMD patients paid \$53 per treatment in travel costs (section 7.2.2) per consultation. Given that treatment in year 1 typically consists of one 'initial consultation' (item 104) and six 'subsequent consultations' (item 105), the total travel costs for the first year of Lucentis treatment is estimated to be \$371 per year.

Overall, the average total out-of-pocket costs (treatment, drug and travel) for a pensioner with neovascular AMD in one eye is therefore estimated to be \$2,377 per year, or \$1,487 after additional deductions via the Extended Medicare Safety Net.

Net benefit of treatment with Lucentis

From section 6.3.1.11, it can be estimated that the average savings associated with Lucentis treatment was \$12,357 per person per year. The reduction was largely due to the reduction in the burden of disease costs (72%). In section 6.3.1.12, the current out of pocket expenses for a pensioner was estimated to be \$1,487 per person per year, comprising largely treatment costs (73%).

Utilisation of Lucentis

In 2010-11, there were 140,489 doses of Lucentis reimbursed through the PBS and RPBS schemes (Table 6.10). As the overwhelming majority of cases of neovascular AMD occur in people aged 60+, the age-standardised utilisation of Lucentis, by state, in people aged 60 or over was calculated. On an age-standardised, per capita basis, NSW and Tasmania show the highest utilisation. Victoria and the Northern Territory have the lowest utilisation - less than half the rate of NSW. The reasons for this large difference are not clear and require further research.

Table 6.10: PBS/RPBS reimbursement of Lucentis, 2010-11

	Doses reimbursed	Age standardised rate per 1000 people over 60
NSW	63,862	44.4
VIC	23,346	21.7
QLD	26,491	34
SA	10,301	27.6
WA	10,113	26.5
TAS	4,390	40.1
NT	79	6.7
ACT	1,907	37.6
Total	140,489	33.2

6.3.2 Bevacizumab (Avastin)

Bevacizumab (Avastin) is an anti-VEGF drug that was primarily developed for treatment in cancer patients. Initial case series reports on the short term effectiveness of Avastin in ophthalmology showed the drug to be effective in patients with neovascular AMD. The use of Avastin for MD is not currently approved by the TGA and its use is considered “off-label”. Following the registration of Lucentis, its use has declined considerably, but it is still used for patients who do not qualify for PBS-reimbursed Lucentis, as it is much cheaper than non-reimbursed Lucentis.

Michels et al (2005) evaluated the short-term safety of systemic Avastin and its effects on visual acuity and CNV in patients with neovascular AMD. Significant increases in visual acuity were evident within one week of treatment, and by 12 weeks, the median and mean visual acuity letter scores increased by eight letters ($p = 0.011$) and 12 letters ($p = 0.008$), respectively. Following the pioneering work of Rosenfeld with the intravitreal use of Avastin (Rosenfeld et al, 2005), Bashshur et al (2007) conducted a study of 60 patients to investigate the efficacy of intravitreal Avastin for treatment of neovascular AMD. After 12 months, the authors found that the mean visual acuity improved from 45.7 letters at baseline to 53.1 letters ($p = .004$).

The National Eye Institute of the National Institutes of Health announced in October 2006 that it would fund a comparative study trial of ranibizumab (Lucentis) and bevacizumab (Avastin) to assess the relative safety and effectiveness in treating AMD. This study, called the Comparison of AMD Treatment Trials (CATT), (CATT Research Group, 2011), enrolled approximately 1,200 people with newly diagnosed neovascular AMD and randomly assigned the patients to one of four treatment groups:

- (Group 1) Lucentis with four-week dosing, and after one year, re-randomisation to Lucentis every four weeks or variable dosing as required based on diagnostic findings;
- (Group 2) Avastin with four-week dosing, and after one year, re-randomisation to Avastin every four weeks or variable dosing as required based on diagnostic findings;
- (Group 3) Lucentis on a variable dosing schedule for 2 years; after initial treatment, with monthly evaluation and re-treatment based on signs of lesion activity; and
- (Group 4) Avastin on a variable dosing schedule for 2 years; after initial treatment, with monthly evaluation and re-treatment based on signs of lesion activity.

Compared to ANCHOR and MARINA, CATT recruited patients with better VA (more patients with very good VA and fewer with very poor VA, slightly smaller overall lesion size, and many patients without subfoveal CNV). Key differences in patient characteristics between CATT and ANCHOR & MARINA are shown in Table 6.11.

Table 6.11: Key differences between CATT and ANCHOR & MARINA

Characteristic (%)	ANCHOR N = 140*	MARINA N = 240*	CATT N = 1185
Mean LogMAR VA	47	54	61
VA 6/12 or better	4%	15%	36%
VA 6/60 or worse	23%	13%	7%
Lesion size (DA)	1.8	4.5 (3.5)	2.7
Subfoveal choroidal NV	100%	100%	60%

* Only 0.5mg ranibizumab dose categories used for ANCHOR and MARINA data. Parentheses indicates average lesion size for ANCHOR and MARINA combined.

CATT is being conducted at 59 clinical sites throughout the US, and will follow the patients for two years. The randomised controlled clinical trial is expected to be completed by February 2012.

The 12 months results, (CATT Research Group, 2011) reported that when efficacy was assessed using visual acuity outcomes, monthly intravitreal Avastin demonstrated non-inferiority to monthly Lucentis. Aggressive PRN treatment with Avastin also demonstrated non-inferiority to PRN Lucentis although more injections were needed with Avastin (7.7 vs 6.9, $p=0.003$). While PRN Lucentis was shown to be non-inferior to monthly Lucentis, PRN Avastin could not demonstrate non-inferiority to monthly Lucentis. When measuring the effect on retinal thickness, subtle differences were also found, again favouring Lucentis treatment.

It should be noted that the 12-month PRN results seen in CATT are better than has been reported in other PRN studies such as SUSTAIN and PrONTO (Mitchell, 2010; Fung, 2007). This may be related to the more aggressive treatment recommendations and the generally smaller lesion size in the CATT study.

While this study was not designed or powered to assess safety, a small but statistically significant difference was noted in the rate of serious systemic adverse events, especially all-cause hospitalisations (Avastin 24.1% vs Lucentis 19.0%, favouring Lucentis, risk ratio 1.29, $p=0.04$). The significance of this finding requires further research.

These safety data were consistent with other studies (Matsuyama et al, 2010; Carneiro et al, 2011; Barras-Pereira et al 2011) and analysis of extensive Medicare data (Curtis et al, 2010; Gower et al 2011), which suggests the risk of all-cause mortality and stroke may be slightly higher with intravitreal Avastin compared to Lucentis.

Such differences could be explained by differences in the structure and metabolism of these agents (Matsuyama et al, 2010; Barras-Pereira et al 2011; Ferrara et al, 2006).

6.3.3 Aflibercept – VEGF Trap-Eye (Eylea™ - Regeneron/Bayer)

Eylea, also known as VEGF Trap-Eye is currently undergoing regulatory review in the USA, Europe and Australia, and is expected to be approved in late 2011 or 2012 in these jurisdictions. Eylea is a fully human fusion protein, consisting of portions of VEGF receptors 1 and 2, that binds all forms of VEGF-A and the related Placental Growth Factor (PlGF). Eylea is a specific and potent blocker of these growth factors.

The Eylea regulatory submissions for neovascular AMD are based on the positive results from two Phase 3 trials, the VIEW 1 and VIEW 2 studies (Regeneron, 2010). In these trials, all regimens of Eylea, including 2 mg of Eylea given as an intravitreal injection every two months (following three monthly loading doses) were shown to be non-inferior to Lucentis dosed every month. The adverse event profile of Eylea appeared to be similar to Lucentis.

7 Removing barriers to treatment

Although treatment for wet AMD is safe and effective, there are barriers that prevent Australians from achieving the full effects of treatment.

7.1 Research on barriers to treatment

Since 2007, the Macular Degeneration Foundation of Australia has carried out research through three projects (Project Vision I, II and III) to investigate risk factors for developing macular degeneration and barriers to accessing treatment and care services.

In the most recent study, the Macular Degeneration Foundation conducted a questionnaire mailed out in November 2009 (field cut-off 24 December 2009) to all people with wet macular degeneration for whom the Macular Degeneration Foundation had address details (1,801 in total). A total of 821 wet macular degeneration patients returned the survey either by mail or phone within the four weeks allowed for completion, providing a response rate of 46%. Of the returned surveys, 57 were incomplete leaving a total of 764 surveys. Within these responses a number of barriers to treatment were identified, including:

- awareness of AMD and early detection;
- out of pocket expenses – notably patient co-payments and travel costs;
- workforce supply and professional development constraints;
- demographic and socioeconomic disadvantage; and
- compliance and adherence issues.

Since awareness is a major barrier to the prevention and effective treatment of neovascular AMD, seven National Galaxy Polls have also been conducted since February 2007 to assess the awareness of AMD in Australians aged 16 years and older. The surveys typically included 1,100 individuals distributed throughout Australia. Sub-analyses have been conducted in the AMD ‘at-risk’ population aged 50+.

Since the fifth survey, the awareness of the associated symptoms of AMD among respondents aged 50 years and older has also been surveyed.

Awareness of AMD and early detection

Where possible, the best approach for the management of AMD is by early prevention (reducing risk factors through diet and lifestyle modification). When the disease has already progressed to the neovascular form, early detection and rapid initiation of anti-VEGF treatment is likely to produce the best outcomes. Indeed, in the MARINA and ANCHOR trials, the treatment of smaller (and therefore earlier) lesions produced the greatest improvement in visual acuity (Boyers, 2007; Kaiser, 2007).

A key reason that people with neovascular AMD do not start treatment (or stop treatment early) is the lack of awareness associated with AMD. Greater awareness of macular degeneration and its risk factors is essential to improving prevention, early diagnosis and treatment.

An early Galaxy Research survey, conducted in 2007 showed that of the Australians aged 16 years and over, only 47% were aware of the term 'macular degeneration'. Even more concerning was the fact that of those, one third were not even aware that it affects the eyes, confusing it with muscular dystrophy, which affects the muscles.

In response to the low awareness levels from polling results received in February 2007, the Macular Degeneration Foundation has conducted considerable public education campaigns and other awareness raising interventions, such as television, radio and newspaper advertising, the *Eye Health Care Partnership* Initiative, the *Eating for Eye Health* cookbook, the *Keep on Driving – Safely* campaign, and the *Vision Van* mobile macular degeneration screening unit³¹.

In the April 2011 Galaxy poll, 76% of Australian adults were aware of macular degeneration, considerably higher than the 47% in February 2007 (Table 7.1).

Table 7.1: Awareness of macular degeneration – results from Galaxy Omnibus survey

Aware macular degeneration	February 2007 N=1100	December 2007 N=1100	December 2008 N=1100	September 2009 N=1100	May 2010 N=1100	Oct 2010 N=1100	April 2011 N=1100
Yes	47%	46%	64%	72%	71%	77%	76%
No/Don't know	53%	54%	36%	28%	29%	23%	24%

Understanding that macular degeneration affects the eyes has also increased. As many as 68% of Australians aged over 16 now understand that macular degeneration is an eye disorder, up from 52% in December 2008, and more than double the figure obtained in the first poll undertaken in 2007.

The awareness of MD in the population at greatest risk (those aged 50+) is even higher. In April 2011, over eight out of ten (83%) Australians aged 50 years and over were aware of the term 'macular degeneration' compared to 58% in February 2007.

³¹ The *Vision Van* screened 3,607 people and signs of AMD were detected in one in eight people, closely reflecting the findings of the Blue Mountains Eye Study. Awareness of macular degeneration prior to diagnosis was very low among respondents, with only one in five patients with neovascular AMD previously aware of the condition and only 12% could definitely recall having their macula checked before their MD diagnosis (Macular Degeneration Foundation, 2010).

Table 7.2: Awareness of macular degeneration in adult Australians 50 years and over

	February 2007 N=447	December 2007 N=448	December 2008 N=455	September 2009 N=451	May 2010 N=448	Oct 2010 N=448	April 2011 N=450
Yes	58%	62%	79%	86%	85%	88%	83%
No	42%	38%	21%	14%	15%	12%	17%

The overall results showed that awareness of the term ‘macular degeneration’ has increased significantly in Australians aged 16 years over with awareness among 50 years and over respondents reaching a plateau. While awareness is now very high (arguably the highest in the world), symptom recognition remains low.

Regular surveys of optometrists since 2007 have also shown a significant increase in the number of people requesting an eye check, and in particular, a check of their macula, in response to the Macular Degeneration Foundation’s awareness campaign.

These encouraging results suggest that more people are aware of the term ‘macular degeneration’ and more are getting their eyes checked. Nonetheless, awareness of symptoms associated with AMD remains very low. Further efforts need to be made to encourage regular eye checks, and improved diet and lifestyle measures including cessation of smoking and weight reduction.

7.2 Out-of-pocket expenses

7.2.1 Patient co-payments

Of the respondents to the Macular Degeneration Foundation survey (2010), 3% had not received treatment because of affordability issues. Of the 453 respondents who had received anti-VEGF injections (excluding those on visual acuity pensions), two thirds (64%) were concerned about treatment costs and 21% had told their eye-care professional their concerns. Of these, a quarter experienced a positive outcome with reduced costs, there was no change for a further 26%, while 2% stopped treatment and 1% reduced treatment due to costs.

The survey asked patients about costs of treatment and those borne out-of-pocket. Of all respondents with wet AMD, 18% were on Department of Veteran Affairs pensions while 42% and 15% had full or partial private health cover, respectively. Of anti-VEGF patients, only 8% received injections at public hospitals, ranging from 5% in New South Wales/ACT to 33% in Western Australia (the WA figure is believed to be inflated due to a perception that the Lions Eye Institute is a public clinic). There was a substantial lack of awareness of the Extended Medicare Safety Net across respondents and only half had registered to access benefits.

The average out-of-pocket costs across Australia were \$38.45 for a consultation (item 105), \$207.35 for the injection fee (item 42740), \$108.90 for an angiogram (item 11218) (with an average of 1.6 angiograms per annum) and \$71 for an OCT scan (no Medicare rebate) with an average of 4 OCT scans per annum. For a typical visit comprising a consultation fee, injection plus OCT, the average out-of-pocket expenses after Medicare rebates (at 85%) were \$316.80 per visit. Even after the patient qualifies for the Extended Medicare Safety

Net, net out-of-pocket expenses averaged \$120 per injection if one eye is being treated and an OCT is given. Patients needing bilateral treatment will pay even more. The financial burden being placed on patients, most of whom are pensioners, to receive a safe and highly effective PBS listed treatment can be significant. In contrast to angiograms, the ongoing cost of OCT scans is borne fully by the patient. As OCT scans are now generally considered an essential component of the management of wet AMD patients, the lack of a Medicare item number needs to be addressed.

Significant variations in treatment costs were seen in different jurisdictions with the highest fees being charged in Queensland and the lowest in Victoria and Tasmania.

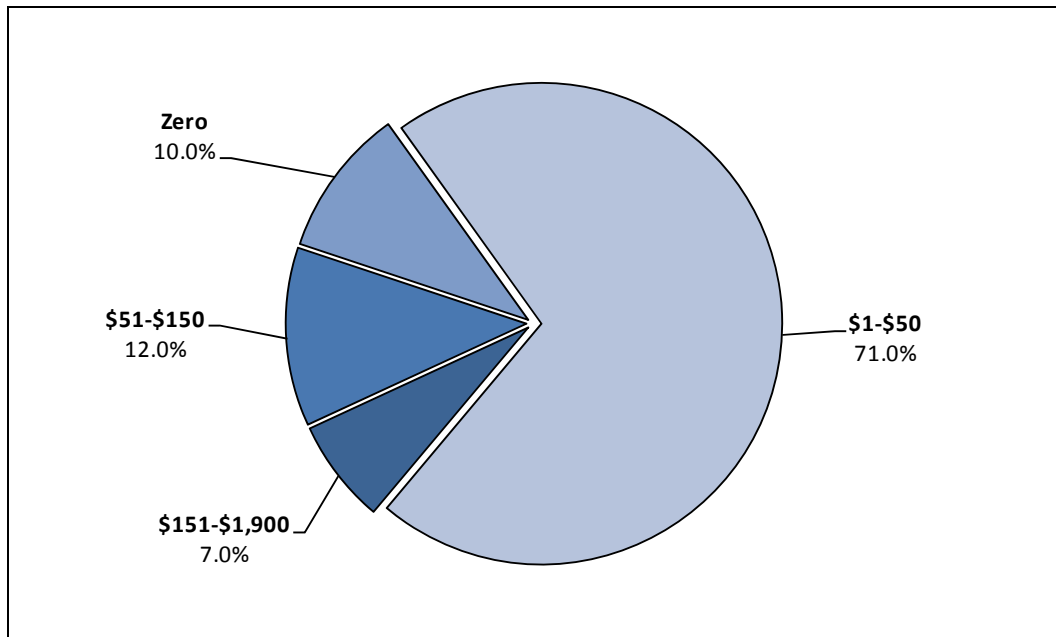
7.2.2 Travel costs

Of the respondents to the Macular Degeneration Foundation (2010) survey, 2% had not received treatment because of distance from treatment services. Of anti-VEGF patients, 11% had difficulties accessing treatment due to the distance required to travel. Unsurprisingly, for those in small rural or remote centres, this proportion doubled to 20%. One in five rural clients travelled over 100 kilometres for treatment.

For patients from large or small rural centres in the Macular Degeneration Foundation (2010) survey, 30% needed to stay overnight in order to receive treatment for wet AMD. Patients from such centres were significantly more likely to be concerned about the costs of travel than patients in capital cities or other metropolitan centres. Most commonly, a spouse or other relative (60%) was involved in travelling with the patient, although another 20% report attending their appointments independently. For nearly one in five of those who transported the patient, time off work (an average of two days or 14 hours) was required. Approximately 18% paid an average \$96 in patient transport costs.

On average, AMD patients pay \$53 per treatment in travel costs, but costs escalate considerably for patients in rural and remote locations.

For the majority (81%), their travel costs were less than \$50, but as Chart 7.1 shows, a small proportion (7%) needed to pay over \$150 (and up to \$1,900) to travel to a treatment centre. The survey results also showed that concern around travel costs was significantly higher among people living in rural Australia.

Chart 7.1: Distribution of average travel costs for wet AMD treatment

Source: Macular Degeneration Foundation (2010)

Some 15% of survey respondents had considered discontinuing treatment due to costs, despite the high priority they accorded to saving their sight. Low income patients were more likely to consider cessation. Some had re-mortgaged their home or approached wage-earning children to help them to afford treatment.

7.3 Workforce supply and professional development constraints

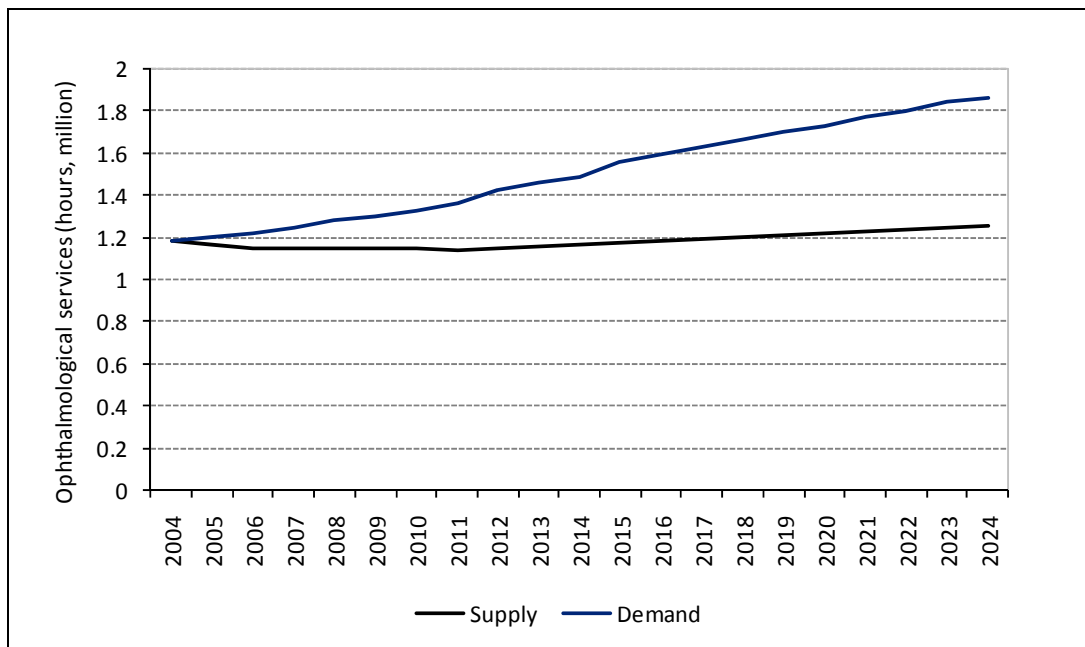
Demand for ophthalmology and optometry services is profoundly affected by the changing age demographic within the Australian population over the next twenty years, due to the epidemiology of eye diseases, where prevalence is strongly age correlated.

Access Economics has modelled the demand and supply for ophthalmology and optometry services in Australia (Access Economics, 2006c).

In ophthalmology, the workforce demand model was based on a detailed analysis of Medicare data for the 'top 20' items (comprising consultations, investigations and procedures) which accounted for some 90% of services rendered. Demand projections were based on population growth, population ageing, service substitution, rising real incomes, rising expectations, and new technologies. Overall, these factors contributed to an estimated net 60% rise in demand for ophthalmologists' time (in hours) over the period 2005-2015. On the supply side, the projections were based on training places available, productivity improvements, workforce feminisation, and average hours worked by age and gender of the ophthalmologist. The total supply of ophthalmologists was projected to

change little over the forecast period, resulting in growing workforce shortages due to the gap between supply and demand (Chart 7.2).

Chart 7.2: Supply and demand for ophthalmological services, 2004-2024



Source: Access Economics (2006c).

The optometry model also revealed emerging and growing workforce shortages, with substantial workforce maldistribution. The greatest workforce problems were evident in rural Queensland (Access Economics, 2006c).

Health workforce measures in recent years have alleviated some of these supply constraints. The AIHW Health Labour Force Survey (AIHW, 2009) shows the number of full-time equivalent (FTE) ophthalmologists and optometrists increased by 15% and 11%, respectively, between 2001 and 2006, and the number of FTE orthoptists increased by 20%. There was a slight increase in the number of trainee ophthalmologists and course completions in ophthalmology, as a proportion of employed ophthalmologists between 2001 and 2006. The same was true of optometrists. AIHW (2009) estimates the eye health labour force at 735 FTE ophthalmologists (2006 estimate) and 421 FTE ophthalmic nurses (2004 estimate). Based on the 2006 ABS Census of Population and Housing there were also:

- 3,329 FTE optometrists;
- 471 FTE orthoptists;
- 3,177 FTE optical dispensers; and
- 1,081 FTE optical mechanics.

On average, ophthalmologists are older than other eye health workers. In 2006, the average age of ophthalmologists was 52 years. The average age of other eye health occupations ranged from 36 years (orthoptists) to 46 years (ophthalmic nurses). In 2006, about 80% of eye health workers lived in major cities, compared to 70% of the Australian population and 67% of Australians with eye disorders (ABS, 2006c). The ABS data

corroborate the regional workforce constraints identified in the Access Economics modelling. There is a clear need to increase the number of retina-trained ophthalmologists to address the imbalance between supply and demand for treatment.

For AMD specifically, additional workforce constraints exist due to a relative lack of opportunities for Fellowship places for ophthalmologists to further their education. The rapidly changing landscape in ophthalmology means there is a need for regular professional updating for eye-care professionals and for GPs.

The Macular Degeneration Foundation's *Eye Health Care Partnership* project recognised the importance of the GP in early detection of eye disease and referral for diagnosis, treatment and rehabilitation. After successful application for Federal Government funding, the MD Foundation undertook a pilot project to provide GPs with a professional development program through a comprehensive Eye Health Workshop. The program was accredited by the Royal Australian College of General Practice at the highest level.

Key objectives of the GP Education Program (Phase 1) were to:

- deliver a comprehensive, accredited Continued Professional Development program for GPs;
- improve the skills of GPs in relation to eye health;
- improve GPs' knowledge of MD, especially prevention, early detection and disease management;
- outline and encourage clear and seamless referral pathways between GPs and eye health professionals;
- understand the physical, social, emotional and economic impacts of low vision;
- create awareness of the services the Macular Degeneration Foundation provides for GPs, their patients, family and carers; and
- link and familiarise GPs with their local services for the vision impaired;

The program was attended by over 168 GPs across six Divisions of General Practice in NSW – Sutherland, Northern Rivers, Tweed Valley, Northside (Ryde), Illawarra and the Hunter. The program evaluation showed:

- over 87% of GPs who attended the Eye Health Workshops believed it was entirely relevant to their practice;
- all GPs felt that their learning needs were met with over 77% reporting their needs were fully met; and
- there was a high need for the program, since an average of over 40% of GPs had no knowledge of four key areas of macular degeneration before attending the workshop.

The lack of knowledge of GPs of AMD, as per the evaluation findings, results in low referral rates which is a major barrier to treatment. Even among some eye-professionals, there is a lack of understanding of the clinical sequelae of AMD.

7.4 Demographic and socioeconomic disadvantage

As shown in Section 3.1.3 the majority of Australians with AMD are aged 65 or older. The age of the patient population can result in specific barriers to treatment, some of which are outlined below.

- **Health literacy:** Older people are less likely to have access to or use the internet to acquire information about disease, and may be less aware of the latest treatments as a consequence.
- **Dementia:** Dementia is also highly age correlated. Loss of cognitive skills associated with Alzheimer's disease and other forms of dementia mean that people with AMD may be less able to recognise or respond quickly to early disease symptoms.
- **Other co-morbidities:** Older age is characterised by multiple co-morbidities including a high prevalence of cardiovascular disease, diabetes, arthritis, osteoporosis, and other sensory impairments (e.g., hearing loss). These conditions may inhibit a person's ability to access services e.g., transport for treatment if driving is no longer an option due to sight deterioration - or it becomes difficult to walk to public transport due to musculoskeletal or heart/lung problems.
- **Loss of partner:** ABS data show that an increasing number of older Australians live alone, partly due to higher longevity for females, changed social structures and higher divorce rates in recent decades. For example, it can be more difficult to access treatment services if there was a reliance on support from a partner to transport or assistance.

7.5 Adherence to therapy

A person is described as 'adherent' to a therapy regimen if they follow the recommended dosage and protocol (compliance) for the recommended treatment period (persistence).

The current accepted 'gold standard' treatment for wet AMD involves monthly injections of Lucentis for at least 2 years. As this regimen places considerable burden on both patient and clinician, many ophthalmologists have attempted to implement a treatment regimen requiring fewer injections, using either the "PRN" or "inject & extend" approach (see section 6.3.1.2).

It has been hoped that these approaches would not compromise outcomes. However, recent studies (e.g., SAILOR, SUSTAIN) indicate that the PRN approach is clearly inferior to monthly injections while the 'inject and extend' approach requires further study. Regardless, the patient must be alert to any sudden changes in vision and be actively monitored to ensure results are not compromised. Patient awareness, co-operation and responsiveness are vital to ensure that the first signs of any changes in vision are acted upon urgently.

However, as shown in the Macular Degeneration Foundation (2010) survey data outlined above in this chapter, a substantial proportion of people receiving treatment for wet AMD discontinue treatment or have treatment interruptions. The most common reason for discontinuation reported was that the treatment was no longer considered effective or for

other clinical reasons, such as serious side effects. The proportion of survey respondents subjectively believing Lucentis treatment stabilised or improved vision (60% for current Lucentis users, and 45% for past Lucentis users) was significantly less than that reported in MARINA and ANCHOR (90 to 95%). While the MDF survey reported subjective patient opinions, as opposed to objective clinical measures in MARINA and ANCHOR, it is possible that the lower (perceived) effectiveness may be related to under treatment. It is crucial that treating ophthalmologists reinforce the importance of regular followup, and teach the correct daily use of an Amsler grid to monitor any early signs of vision loss. Patients must be encouraged to contact the doctor immediately any changes in vision are noticed.

While some side effects require reduction or discontinuation of treatment, others do not. Serious but rare side effects related to the injection procedure include serious eye infections, detached retina, cataract, inflammation inside the eye and increased eye pressure. The most common but less serious side effects include red eyes, eye pain, small specks in vision, increased tears, or the feeling that 'something is in your eye'. The most common non-eye-related side effects include: nose and throat infections, headache, respiratory infection and urinary tract infection. It is important that patients are prepared for the potential side effects so they do not walk away from treatment unnecessarily.

In the Macular Degeneration (2010) survey, more than one in five wet AMD patients changed doctors because of a lack of communication. The three areas which were most likely not communicated by their eye care professional were cost breakdowns; written information on treatment; and potential side effects. Analysis showed no significant differences between reasons for optometrists and ophthalmologists. Core areas raised by survey respondents in relation to desired improvements in communication and treatment comprised improving logistical or procedural aspects, providing more information, or improving affordability of treatment. Particularly common was a desire to improve the long wait times between seeing their professional and receiving an injection. Nearly half (46%) of respondents had changed their eye care professional in the course of their ongoing treatment.

It is also of concern that 33% of surveyed patients had to wait longer than 3 weeks to receive their first injection following diagnosis of wet AMD. Indeed, nearly 10% waited at least 7 weeks for their first injection. Given that early initiation of anti-VEGF treatment for neovascular lesions improves outcomes, the reasons for such lengthy delays requires further research.

Education of patients is important to help improve adherence with therapy, as well as measures to improve communication between patients and their eye and health care professionals.

8 Low vision rehabilitation

Rehabilitation is an important part of the continuum of care for AMD patients with vision loss. This chapter outlines the types of rehabilitation services offered, the benefits of rehabilitation, barriers to rehabilitation services, and outlines suggestions to improve rehabilitation uptake in Australia.

8.1 Rehabilitation services

Without treatment, most people with late stage AMD will have moderate to severe visual impairment. Except for the effectiveness of managing risk and protective factors, there is no cure. While most people with neovascular AMD can now obtain highly effective treatment with anti-VEGF agents, some still experience a significant loss of vision. Many others have lost vision before effective treatments became available. For people with dry AMD (geographic atrophy), there are currently no treatments that can restore lost sight. Dry AMD accounts for one-third of all late stage AMD.

Loss of vision affects quality of life and levels of independence and requires adjustment and adaptation to new circumstances. The emotional, social and economic impact on quality of life from visual impairment can be severe. Emotional impact can include pain and suffering from such feelings as depression, anxiety, confusion and fear.

Vision loss impacts upon the ability to read, drive, see faces and colours clearly. The loss of reading ability can severely impact upon quality of life and independence.

Vision loss can also limit mobility, through a reduced capacity to navigate when walking to the removal or restriction of a driving licence. This can lead to social isolation and further psychological impacts. People with AMD related visual impairment can also be financially impacted due to the cost of health care services and other indirect costs, such as aids and technologies.

Vision loss prevents healthy and independent ageing and it is associated with the following:

Risk of falls increased two times

Risk of depression increased three times

Risk of hip fractures increased four to eight times

Admission to nursing homes three years early

Twice as likely to use health services (Access Economics, 2010a)

Low vision rehabilitation is considered the best option for reducing the impact of AMD related vision loss when medical treatments have been unsuccessful in restoring an appropriate level of vision (Hooper et al 2008).

Rehabilitation services aim to help people minimise the health and social impacts of visual impairment so they can maintain quality of life and independence with their remaining vision. In Australia, comprehensive rehabilitation comprises a variety of interventions related to managing impacts of vision loss and includes:

- low vision clinical assessment and prescribing of suitable devices;
- equipment and training for daily living activities;
- one-on-one counselling, peer support groups and a helpline;
- orientation and mobility training/aids;
- community and social services;
- assistance with education and employment;
- print alternatives, such as talking books;
- transportation;
- home modification; and
- case management.

Interventions are ideally offered by a multidisciplinary team that may include ophthalmologists, occupational therapists, orientation and mobility specialists, optometrists, orthoptists, counsellors, psychologists, employment services, recreational support and others that provide information services.

It should be noted however, that the range and quality of services varies greatly across the country, with few agencies able to offer a full range of services. People with vision impairment do not always receive all the help required from one low vision rehabilitation provider and may hence seek help from multiple providers (Riazi, 2010), adding to the complexity of management. This highlights the importance of seamless and timely interagency referrals.

The provision of services for those with low vision or who are legally blind has historically been state based in origin and provided by NGOs, typically not-for-profits. In the last ten years there have been changes in the number of providers and the services offered. There is also very little provision of low vision rehabilitation within the public health sector or in private practice (O'Connor, 2008) despite the proven benefits that rehabilitation offers.

The delivery of low vision and hearing services in Australia is an example of the inconsistencies in accessibility.

The Australian Hearing Program began in 1947 in response to the high rate of hearing loss in returning World War II veterans. In March 1997, the Office of Hearing Services was formally established as a unit within the then Department of Health and Family Services. Presently, the Hearing Services Voucher System, established under the Hearing Services Administration Act 1997, allows eligible clients to obtain services and hearing devices from contracted service providers.

The Office of Hearing Services (Department of Health and Ageing) has a providers' section on their website which lists 2,298 permanent, visiting and remote sites for hearing services and devices throughout Australia. These sites are serviced by providers contracted under the Australian Government Hearing Services Program with many having a large number of accessible shop-front services across Australia.

The Office of Hearing Services is also working with various organisations around Australia to develop hearing aid banks around the country. People can donate unused aids to the Office. These aids are then cleaned, refurbished and re-tuned and given to people for a low administrative charge.

In comparison, it is estimated that there are approximately 100 low vision offices and clinics in Australia. Further research is required on the exact number of low vision services available, where they are located, what services are provided and the standard of care.

It is also difficult to ascertain exactly how many optometrists and private practitioners are providing low vision services.

In May 2005, Medicare added a new optometrist item number for low vision assessment (Item 10942, for which the fee in 2011 is \$34.20). Utilisation of this item is low and has been dropping in recent years (Table 8.1). Reasons for this low utilisation require more research as this option could significantly increase and improve the access and choice for people with low vision. The low utilisation may be related to the fee paid relative to the time taken to provide a low vision assessment, or to the lack of training and accreditation of optometrists in the area of low vision or to other factors.

Table 8.1: Low Vision services provided using Medicare optometrist

	2005-6	2006-7	2007-8	2008-9	2009-10	2010-11
Item 10942	5,033	5,043	4,536	4,069	4,221	4,010

Source: Medicare

Services provided using Medicare optometrist item number 10942 (Low vision assessment)

8.2 Benefits of rehabilitation

Several studies have investigated the impacts of rehabilitation on quality of life. However, it is problematic to draw conclusions regarding the effectiveness of specific interventions due to considerable variation in service delivery. Furthermore, varying study design quality and outcome measures have confounded specific conclusions. Meta-analyses that have investigated low vision service studies allow more general conclusions to be drawn (Hooper et al 2008; Binns et al 2009). In particular:

- rehabilitation has a positive effect on the ability to read, in terms of speed and accuracy;
- low vision aids are valued by users, although there is no device that is most effective for everyone;
- education and supervised practice with a low vision aid can significantly improve their value through enhanced performance;
- rehabilitation using self-management groups can improve mood, decrease symptoms of depression and improve confidence in performing tasks;
- independent living programs and adaptive skills training can improve the activities of daily living and adjust to vision loss; and
- both inpatient and outpatient rehabilitation programs can have a large positive effect on self reported functional ability.

The effectiveness of low-vision rehabilitation on reducing the impact of vision loss has been specifically measured in Victoria. Lamoureux et al (2007) surveyed adults attending rehabilitation by using the Impact of Visual Impairment (IVI) questionnaire, and concluded that low-vision rehabilitation services increased participation in daily living activities and improved quality of life.

There are benefits from retraining and education courses which include the utilisation of low vision aids and technologies as these can help those with a vision loss to stay in, return to, or enter the workplace in either paid or unpaid work. In the absence of retraining, even simple education in the use of technologies would be helpful, especially for volunteer work.

8.3 Barriers to access

It has been estimated that 90% of people with vision impairment have useful residual vision that could benefit from rehabilitation services (Hinds, 2003). Although rehabilitation services can reduce the impact of vision loss, it is estimated that only 20% of Australians that could benefit from these types of services actually use them (O'Connor and Keeffe, 2007).

Several reasons have been identified for the low uptake of rehabilitation services. Pollard et al (2003) surveyed people with mild, moderate and severe visual impairment attending clinics in Victoria, and followed up with in-depth focus groups. They found that barriers to accessing low vision rehabilitation were:

- a lack of awareness of services offered among those with visual impairment and referring professionals;
- some people did not recognise (or accept) that they had vision loss that would warrant specialised services;
- misconceptions that rehabilitation services are only for those with severe vision loss, which is heightened by rehabilitation service organisations directing publicity to people who are blind;
- confusion with the referral process; and
- problems using transport to access rehabilitation services.

Other barriers to low vision service uptake have been noted (O'Connor and Keeffe, 2007). These include a poor understanding of the benefits that can be derived from rehabilitation, accepting poor vision as a consequence of old age, cognitive impairment (e.g., dementia), or an unrecognised impact of vision loss on quality of life. Personal factors can also act as a barrier to access, such as culture, gender, co-morbidities and family. Similar results were found in a survey in Melbourne, in which people either accepted low vision rehabilitation service referrals but failed to attend or else refused a referral. It was concluded that many services are not reaching those who could benefit (O'Connor et al, 2008).

Matti et al (2011) concluded that one of the main barriers to low vision service uptake is patient perception that either the service was not required or would not help. They further noted that referral and triage processes appeared to be major enablers of low vision service uptake.

Once a referral to a low vision agency is received, patients need a seamless, efficient and timely entrée to obtaining an initial low vision assessment. As those with vision impairment are at risk in such areas of falls, depression and social isolation, it is vital that low vision services are provided in a timely and convenient way.

There are no national guidelines, standards or formal accreditation processes for the provision of low vision services. Further research is required to provide guidance on the status of existing service standards and to clearly articulate future directions for service standards, necessary for professional referral and client information.

Given the significance of depression in people with impaired vision, it imperative that clients are aware of the possibility of depression, and know where to obtain help and support. It is also important that psychologists have appropriate training and experience in low vision. This again requires further research and discussion with key stakeholders in the referral pathway.

Health professionals

There are also barriers to rehabilitation imposed by health professionals. Pollard et al (2003) found that focus group participants believed that communication between the patient and health care professional was not effective when discussing the referral. Often a referral to rehabilitation occurred at the end of the treatment process. Even though visual acuity of less than 6/12 has been shown to impede functional ability and that rehabilitation may therefore be beneficial (Lamoureux, 2007), in practice, referral is frequently delayed until acuity is less than 6/21 (Keeffe, 1996; Lovie-Kitchin, 1996), thereby contributing to the mismatch between need and uptake.

Furthermore, information on coping with low vision was found lacking, and this was made worse by patients not knowing what type of questions to ask. Focus group members also thought health care professionals tend to be too medical in nature, forgetting to discuss the non-medical issues associated with visual impairment. O'Connor et al (2008) found that lack of awareness regarding low-vision services, and poor communication between patients and health professionals, were reasons for clients refusing a referral or not attending rehabilitation even though a referral was accepted.

There is currently little or no formal training of general practitioners in the area of low vision. It is vital that general practitioners are aware of the challenges faced by people with low vision and are aware of all aspects related to the detection, referral, monitoring, counselling and managing of patients with low vision.

In 2009, the Macular Degeneration Foundation, with funding under the Federal Eye Health Demonstration Grants Program, undertook a two year pilot project in NSW (Eye Health Care Partnerships Initiative) to provide professional education for general practitioners.

Over 168 general practitioners across six Divisions of General Practice in NSW participated and received the maximum Continuing Professional Development (CPD) points from the program accredited by the Royal Australian College of General Practice (RACGP). The program covered two three hour sessions, one being the physiology of AMD and the other session, the social and emotional aspects of low vision. Over 87% of general practitioners who attended the eye health workshops believed it was entirely relevant to their practice.

The evaluation, through a standardised questionnaire administered prior to the education session showed that only 37% of general practitioners had ever referred patients with AMD to a low vision organisation, 44% percent reported that they did not know that risk of depression increases three fold for people with AMD and 66% did not know which agencies provided low vision assessments.

Comments from general practitioners included “I now understand my role in detection, treatment, talking to patients and how to slow down the rate of progression” and “I had very little awareness, especially regarding the association of factors such as depression, suicide, falls and fractures with low vision”.

Low vision aids and technologies

Using aids and technologies can help to maintain independence and quality of life. This can range from simple hand-held optical magnifiers to more technology based options such as electronic magnifiers, reading machines and computer software.

Advances in technology, specifically the internet, as well as mobile phones and computers have changed the way people communicate in both the spoken and written word. Among the advantages of new technologies for those who are blind or are vision impaired is that information becomes more accessible.

Aids to assist people with low vision vary in their complexity and cost, but despite their clear ability to help people with low vision maintain independence and quality of life, only limited and sporadic subsidies are available from some state governments. The majority of private health funds only provide minimal reimbursement, if any, for low vision aids.

The 2011 reviews of the aged care and disability systems through the Productivity Commission provides the opportunity to ensure better access to low vision services as well as aids and technologies. The report, ‘Caring for Older Australians’, recommends a range of changes that may affect older people with vision impairment. It is critical that final recommendations adopted by government incorporate the specific needs of people with vision loss related to low vision aids and technology and includes access to disability services, assessment, counselling and the education and training of workers in aged care and disability sectors.

8.4 Improving uptake of rehabilitation services

An improved uptake of rehabilitation has the potential to improve quality of life outcomes for many people with AMD related visual impairment. Removing barriers to access is essential, and may offer a relatively inexpensive way of improving quality of life compared to improving service outputs.

Several solutions to improve uptake of rehabilitation in Australia have been offered by O'Connor and Keeffe (2007). For example, rehabilitation services must be tailored to client needs and preferences, including an evaluation of the scale and nature of the vision loss, offering a choice in services, and monitoring and evaluating outcomes. Preferences for alternative types of services will vary depending on age, gender, cultural and linguistic background, family support structure, living arrangements, and co-morbidities.

Adequate information and practical training must be provided to people requiring low vision devices in order to promote greater performance, increased value and sustained use. Furthermore, programs must encourage greater capacity for people to manage their visual loss in order to promote self confidence, reduce stress and improve overall quality of life (O'Connor and Keeffe, 2007). Emotional support services should be delivered from an early stage of treatment as they are more likely to be effective. Further research is required to ascertain the waiting periods for low vision assessments across Australia and benchmarking for the delivery of such services.

O'Connor et al (2008) noted that close proximity to services facilitated access to services, while Matti et al (2011) concluded that distance to travel or transport difficulties were not significant barriers. This requires further research. Additional means of delivery of rehabilitation services, including provision through public hospitals and private providers such as optometrists should also be considered in future planning.

Referral pathways could be strengthened by improving knowledge of AMD and low-vision rehabilitation services among health professionals, and encouraging health professionals to promote rehabilitation as an effective tool for reducing the impact of vision loss. The future introduction of e-health in Australia (where records can be shared across health professionals) has the potential to assist inter-agency referral and information exchange.

As rehabilitation has the capacity to substantially improve outcomes for people with AMD related vision loss, medical referrals for rehabilitation should be offered immediately a problem has been recognised. Late referral can lead to lower participation in rehabilitation services and subsequent deterioration in emotional wellbeing. Consequently, access to information and services should be provided without delay, with regular assessment of rehabilitation services to ensure they change with the needs and preferences of the client. The referral process is more likely to succeed if clinicians make clear recommendations and follow up the outcome of referral.

There is a significant need for increased training of others involved in patient care including general practitioners, pharmacists, optometrists, orthoptists, ophthalmologists, psychologists, occupational therapists and nursing home staff regarding the importance of rehabilitation and the value of early referral.

In conclusion, it is paramount that:

- there is equity in access to rehabilitation services, including the provision of quality, affordable low vision aids and technologies;
- such services are offered early to all with low vision; and
- standards are established to ensure the quality of services and facilitate comparison and choice.

The United Nations Declaration on the Rights of Disabled Persons

This report acknowledges that Australia ratified the United Nations “Declaration on the Rights of Disabled Persons” in July 2008. This declaration includes statements that persons with disabilities have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability. In particular, persons with a disability should:

- Receive free or affordable healthcare and programmes of the same quality, range and standard as provided to others
- Receive early identification and interventions as appropriate
- Be provided with health services as close as possible to their own community
- Be enabled to attain and maintain maximum independence, ability and social inclusion
- Be encouraged to use and be trained in the use of assistive devices and technologies
- Receive access to information about treatments and rehabilitation in a manner which is tailored to their needs.

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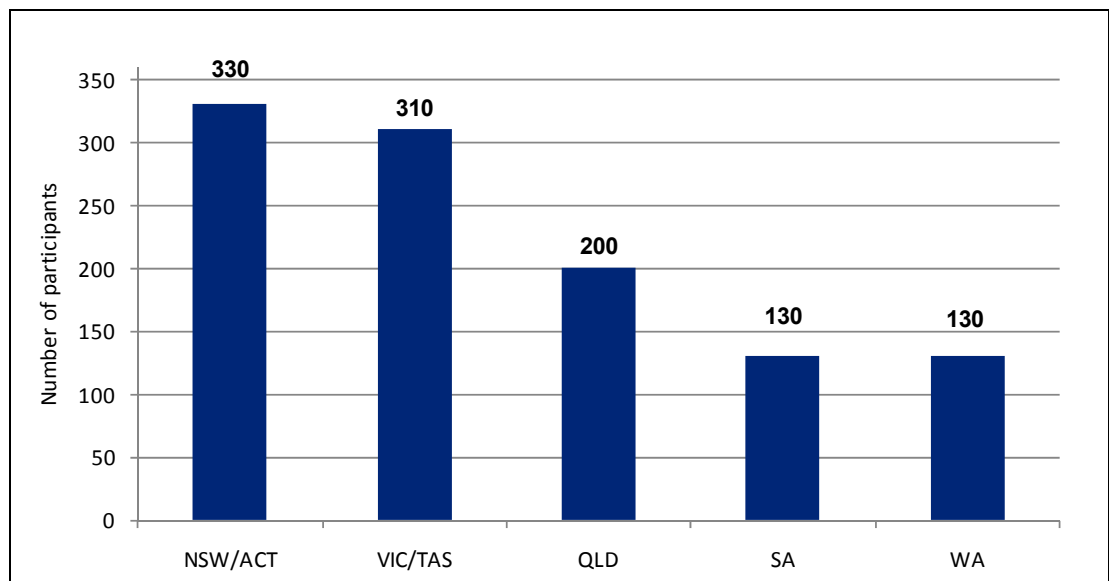
Appendix A – Summary of Galaxy polls

This appendix summarises key data derived from two recently completed Galaxy polls on macular degeneration awareness.

The Macular Degeneration Awareness Report

The Macular Degeneration Awareness Report is the seventh in a series of telephone studies conducted by the Galaxy Omnibus. This study was conducted in April 2011 and assessed the awareness of macular degeneration among respondents aged 16 years and older. The respondents included 1,100 individuals distributed throughout Australia, as shown in Chart 8.1.

Chart 8.1: Number of respondents by jurisdictions



Source: Macular Degeneration Awareness Report.

The results showed that since the commencement of the Macular Degeneration Foundation's campaign in 2007 in newspapers, and on radio and television, awareness of the term 'macular degeneration' has increased dramatically. In the latest study, 76% of Australians over 16 were aware of macular degeneration, an impressive increase from the 47% in February 2007 (Table 8.2).

Table 8.2: Awareness of macular degeneration in Australians aged 16+

Aware macular degeneration	February 2007 N=1100	December 2007 N=1100	December 2008 N=1100	September 2009 N=1100	May 2010 N=1100	Oct 2010 N=1100	April 2011 N=1100
Yes	47%	46%	64%	72%	71%	77%	76%
No/Don't know	53%	54%	36%	28%	29%	23%	24%

Awareness of macular degeneration in Australians aged 16+ – results from Galaxy Omnibus survey

Understanding that macular degeneration affects the eyes has also increased. As many as 68% of Australian adults now understand that macular degeneration is an eye disorder, up from 52% in December 2008, and 32% in February 2007. In the main target audience for the Macular Degeneration Foundation's campaigns (those aged 50+), awareness is even higher, consistently rating well over 80% for several surveys (Table 8.3).

Table 8.3: Awareness of macular degeneration in Australians aged 50 years and over

	February 2007 N=447	December 2007 N=448	December 2008 N=455	September 2009 N=451	May 2010 N=448	Oct 2010 N=448	April 2011 N=450
Yes	58%	62%	79%	86%	85%	88%	83%
No	42%	38%	21%	14%	15%	12%	17%

The proportion of Australians aged 16 years and over believing that their macula had been checked continues to grow. More than one in three (35%) believed that their macula was checked in the past two years, and 43% thought that it had macula checked at some time (Table 8.4).

Table 8.4: Eye check-ups in Australians aged 16+

Last time had macula checked by optometrist or ophthalmologist	February 2007 N=1100	December 2007 N=1100	December 2008 N=1100	September 2009 N=1100	May 2010 N=1100	October 2010 N=1100	April 2011 N=1100
In past 12 months	12%	15%	23%	24%	27%	26%	28%
1-2 years ago	6%	6%	9%	11%	9%	10%	11%
Total in past 2 years	19%	21%	32%	35%	36%	36%	39%
2-5 years ago	2%	2%	4%	6%	4%	4%	6%
Over 5 years ago	1%	1%	1%	2%	1%	2%	2%
Total ever had macula checked	22%	24%	38%	43%	42%	43%	47%
Never/Don't know	78%	76%	62%	57%	58%	57%	53%

More than half (59%) of respondents aged 50 years and over believed their macula had been checked in the past two years, an increase from 33% in February 2007 (Table 8.5).

Table 8.5: Eye check-ups in adult Australians 50 years and over

Last time had macula checked by optometrist or ophthalmologist	February 2007 N=447	December 2007 N=448	December 2008 N=455	September 2009 N=451	May 2010 N=448	October 2010 N=448	April 2011 N=450
In past 12 months	24%	26%	37%	43%	42%	41%	45%
1-2 years ago	9%	9%	13%	15%	14%	15%	14%
Total in past 2 years	33%	35%	49%	58%	58%	56%	59%
2-5 years ago	3%	1%	6%	7%	4%	6%	7%
Over 5 years ago	2%	1%	1%	1%	2%	3%	1%
Total ever had macula checked	38%	38%	56%	43%	64%	65%	67%
Never/Don't know	62%	62%	44%	33%	36%	35%	33%

In the latest survey, 83% of those aged over 50 are aware of the term macular degeneration, and 75% are aware that it is an eye disease. Unfortunately, awareness of the typical symptoms of macular degeneration remains very low with only 12% able to spontaneously name any symptom. This figure has remained low since this measure was first taken in early 2010. As the awareness campaign has not focused on symptoms, such a result is not surprising.

Limitation of our work

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Contact us

Deloitte Access Economics
ACN: 49 633 116

Level 1
9 Sydney Avenue
Barton ACT 2600
PO Box 6334
Kingston ACT 2604 Australia

Tel: +61 2 6175 2000
Fax: +61 2 6175 2001

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To reduce the incidence and impact
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Our focus is your vision

Macular Degeneration Foundation

Level 9, 447 Kent Street
Sydney NSW 2000

Helpline: 1800 111 709
www.mdfoundation.com.au

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