Deloitte Access Economics

The economic impact of diabetic macular oedema in Australia

Bayer Australia Ltd

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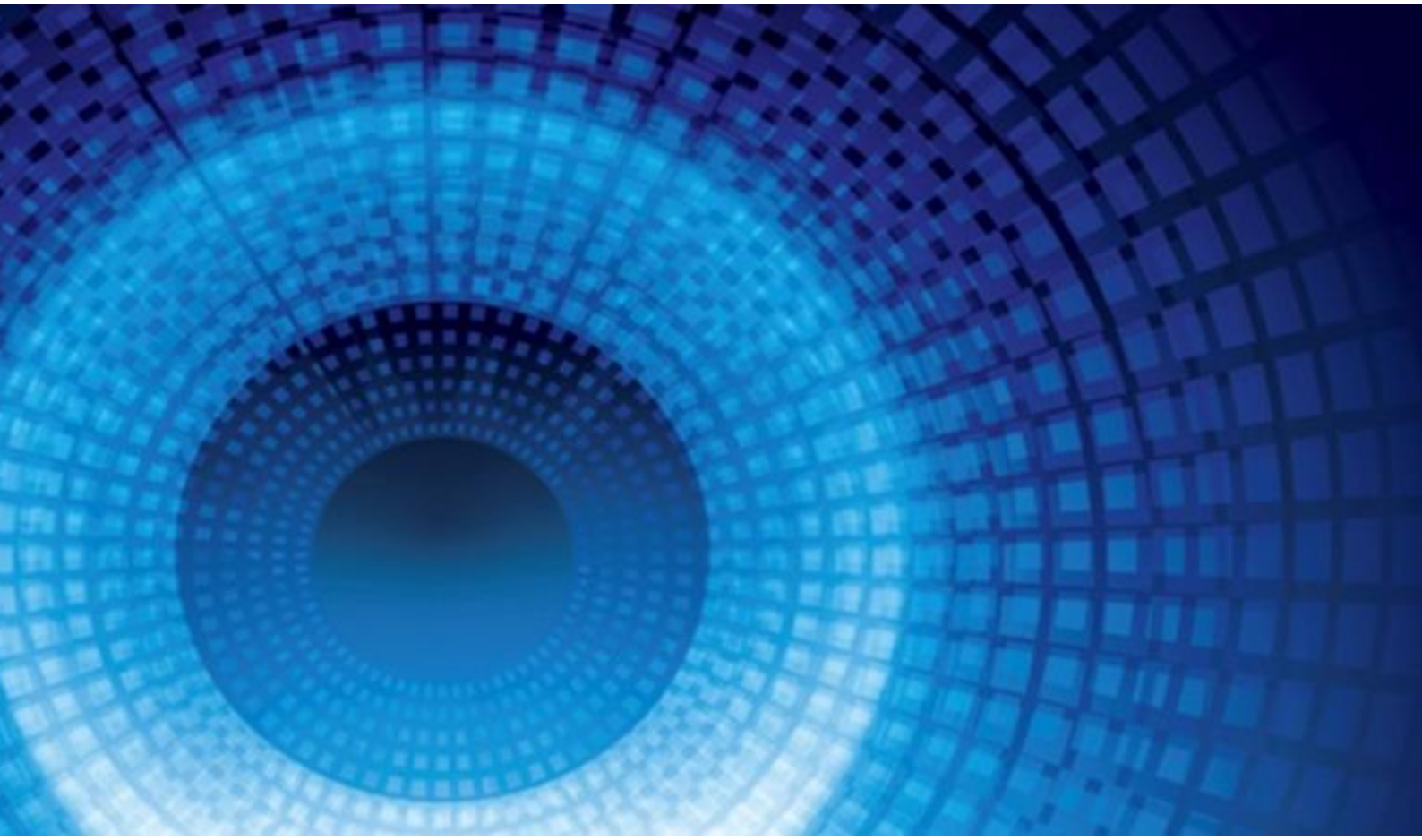

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Glossary

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
AUSDIAB	Australian Diabetes, Obesity and Lifestyle study
BCVA	best corrected visual acuity
BDES	Beaver Dam Eye Study
BMES	Blue Mountains Eye Study
BMI	body mass index
BTOS	Broad Type of Service
CI	confidence interval
CMT	central macular thickness
CSME	clinically significant macular oedema
CVD	cardiovascular disease
CWS	soft exudates or cotton-wool spots
DA	disc area
DALY	disability adjusted life year
DRCRnet	Diabetic Retinopathy Clinical Research Network
DME	diabetic macular oedema [abbreviated as per convention]
DR	diabetic retinopathy
DSP	Disability Support Pension
DWL	deadweight loss
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FTE	full time equivalent
GDP	gross domestic product
GP	general practitioner
H/MA	haemorrhages/microaneurysm
HEx	hard exudates
HbA1C	glycosylated haemoglobin
HDL	high-density lipoprotein
HEX	hard exudates
ILM	internal limiting membrane
IRMA	intra-retinal microvascular abnormalities

MA	Microaneurysm
MBS	Medicare Benefits Schedule
MVIP	Melbourne Visual Impairment Project
NDIS	National Disability Insurance Scheme
NHMRC	National Health and Medical Research Council
NHS	National Health Survey
NPDR	non-proliferative DR
NVD	neovascularisation involving the optic disc
NVE	neovascularisation elsewhere in the retina
OAA	Optometrists Association of Australia
OBPR	Office of Best Practice Regulation
OCT	optical coherence tomography
PBS	Pharmaceutical Benefits Scheme
PDR	proliferative DR
QALY	quality adjusted life year
RPBS	Repatriation Pharmaceutical Benefits Scheme
RR	relative risk
SDAC	Survey of Disability, Ageing and Carers
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
VA	visual acuity
VB	venous beading
VEGF	vascular endothelial growth factor
VI	visual impairment
VSL(Y)	value of a statistical life (year)
VTDR	vision threatening diabetic retinopathy
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
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

Definitions

Diabetes	A condition where the hormone insulin is no longer produced in sufficient amounts or at all by the body meaning that glucose cannot be converted into energy, resulting in issues pertaining to blood sugar levels.
Diabetic Macular Oedema	This is a specific type of diabetic retinopathy, which is characterised by swelling or thickening of the retina in patients with diabetes mellitus due to leaking of fluid from blood vessels within the macula.
Diabetic Retinopathy	A condition of the eye where there is abnormal growth in blood vessels over the surface of the retina, which affects sight. Retinopathy also involves a swelling and leakage of blood vessels, resulting in deformation and alteration of the general structure of the eye.
Fovea	A pinpoint, depressed area of the central retina. This is the retinal area with the greatest visual acuity. It normally lacks retinal blood vessels.
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 (defined 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
QALY and DALY	The Quality Adjusted Life Year (QALY) is a measure of health gain that expresses the number of healthy life years that would be added due to a particular intervention. In contrast, DALYs measure disease burden in terms of both morbidity (healthy life years lost) and years lost from premature death due to a condition, or the DALYs averted due to an 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
Relative risk or hazard ratio	The ratio of risk in the affected group and the risk in the non-affected group. For example, a relative risk of 7.0 means that the affected group has seven times the risk of a non-affected group
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 metres could be seen by a healthy eye at 60 metres.

Scope

- All figures presented in this report are estimates only.
- The information contained in this report is accurate as at April 2015.
- All estimates of the total economic impact of DME are limited to indirect costs only. Please see section 4 for further detail.

Foreword[1]

Diabetes is a complex, chronic condition which can cause serious damage and complications in many parts of the body, including the eyes. Diabetes has now reached epidemic proportions in Australia with 280 people developing diabetes every day, and over 1.7 million Australians currently living with the disease.

Everyone with diabetes is at risk of developing diabetic eye disease. People with diabetes who are most at risk include those whose diabetes is poorly controlled, those with related problems including high blood pressure, and those who have had diabetes for many years. Diabetic retinopathy (DR) remains the leading cause of blindness in working age Australians. The good news is that with optimal management of diabetes, and with regular eye tests and timely treatment when indicated, almost all vision loss due to diabetes may be prevented.

Diabetic macular oedema (DME), a frequent manifestation of DR, is a common cause of vision loss from diabetes which is both preventable and, if diagnosed early, treatable. Presently, an estimated 72,000 people with diabetes have DME and approximately 3 in 5 of these people experience poor sight. It is estimated that at least 50% of people with diabetes do not access regular eye tests according to national guidelines. If nothing is done to address this growing problem it is estimated that in the next 15 years, the number of people with DME will increase by 42%. Regular eye examinations are vital to enable timely intervention as this unquestionably results in the best outcomes.

Vision loss from DME not only impacts the person with disease but also has a ripple effect in its impact upon others, especially the family. Since many Australians with DME are of working age, the impacts of vision loss are broad-reaching and long-lasting. It can prevent people from working at full capacity or, in the worst case, from working at all. In fact, 91% of the indirect costs of DME in 2015 is caused by lower work force participation and absenteeism. Research into blindness in Australia has found that it is second only to cancer among the medical conditions that people fear most.

The emotional and social burden of DME carries with it enormous cost to government and the taxpayer and importantly the quality of life of those living with diabetes and DME and their families and carers. It is for these reasons Australia needs a national diabetes blindness prevention program with clear targets and measures to ensure that every person with diabetes has their eyes checked as recommended to help prevent retinopathy, macular damage and blindness. Many countries now have national eye screening programs for people with diabetes and have documented significant reductions in the incidence rate of vision loss and blindness.

There is clearly a significant need for Australians to be more aware of diabetes related eye disease, the importance of careful diabetes control to prevent eye damage and blindness, and the importance of regular eye checks to ensure early detection and optimal treatment.

[1] This foreword represents the views of its two authors, not necessarily those of Deloitte Access Economics.

In almost all cases, this will help prevent vision loss. If vision loss has already occurred, we need timely referral to rehabilitation, as this can dramatically improve independence and quality of life.

Julie Heraghty
CEO, Macular Disease Foundation Australia

Greg Johnson
CEO, Diabetes Australia

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Key facts at a glance

ALL FIGURES PRESENTED IN THIS REPORT ARE ESTIMATES ONLY. ALL INFORMATION IS ACCURATE AS AT APRIL 2015.

DIABETIC MACULAR OEDEMA (DME) IS A POTENTIALLY DISABLING EYE DISEASE

- The macula is the central portion of the retina in the eyes. Proper functioning of this small area is essential for detailed central vision, for the eye to detect colours, and for daytime vision.
- DME occurs when damaged blood vessels inside the retina leak fluid into the central macular area, leading to tissue swelling and potentially to loss of sight.
- People with DME may experience significant difficulties in reading, seeing faces, and fully participating in other activities that require acute central vision.

DME IS A MAJOR AND GROWING CAUSE OF VISION IMPAIRMENT IN AUSTRALIA

- In 2015, over 1.7 million Australians are estimated to be living with diabetes and related health issues.
- In 2015, an estimated 72,000 people with diabetes have DME, and approximately 3 in 5 of these people experience poor sight.
- By 2030, 2.45 million Australians are estimated to be living with diabetes. In the next 15 years, the number of people with DME is projected to increase by 42% to 102,000 people.

IN 2015, THE BURDEN OF DME ON PATIENTS, THEIR FAMILY AND OUR SOCIETY IS SIGNIFICANT

- The total indirect cost of vision loss associated with DME is estimated to be $2.07 billion.
- A significant part of this cost is because of a loss of wellbeing and as people of working age could not work ($553.42 million lost to lower employment), or could not work at full capacity (an additional $4.38 million lost to absenteeism) due to poor vision caused by DME.
- An estimated 218 deaths among individuals with DME may be avoided in the absence of visual impairment, assuming a causal relationship between visual impairment and higher mortality.
- On average, DME patients with poor vision suffer a disability equivalent to losing approximately one and a half months out of every year because they are not in perfect health (i.e. a 'disability weight' of 0.1275). This loss of wellbeing is valued at $1,445.5 million in 2015.

UNDERTAKING SCREENING AND PROVIDING TREATMENT WILL BE LIKELY TO LESSEN THE DISEASE BURDEN AND ECONOMIC COSTS OF DME

- Anti-vascular endothelial growth factor (anti-VEGF) therapy prevents vision loss more effectively than laser surgery for people living with DME.
- Approximately 1 in 2 people with diabetes do not have their eyes examined within the recommended timeframe, which highlights the importance of raising awareness of eye testing for early detection and treatment.

- With current methods of screening, an additional estimated 9,200 cases of DME could potentially be detected per year if retinal examinations were provided to all people with diabetes currently not being screened in that year.
- If two thirds of all people living with DME who had visual impairment were treated with anti-VEGF therapy, the benefits potentially associated with improvement in vision and wellbeing would amount to $353.13 million in 2015.

Executive summary

ALL FIGURES PRESENTED IN THIS REPORT ARE ESTIMATES ONLY. ALL INFORMATION IS ACCURATE AT APRIL 2015.

Diabetic retinopathy (DR) is one of a myriad of neurological and cardiovascular complications of diabetes mellitus. People with DR have damage to the blood vessels inside the retina. The disease starts with micro-aneurysms or balloon-like swellings in the retinal blood vessels. As the disease progresses, the swellings cause blockages to the blood vessels and damage to the retina, and may cause swelling or thickening of the central retina (i.e. the macula) due to leaking of fluid from blood vessels. This swelling is known as diabetic macular oedema (DME).

If left untreated, diabetic macular oedema can result in visual impairment and even blindness. This can have significant impact on patients, their families and society.

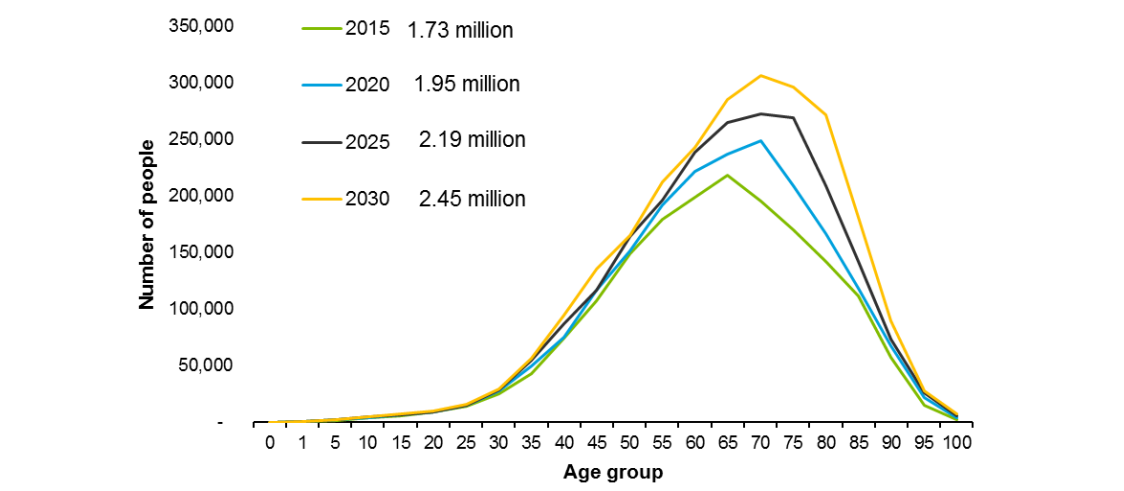
The evidence presented in this report demonstrates that DME has a significant impact on the wellbeing of patients and their families, which can translate into considerable personal and economic cost for them, and societal burden for Australia.

PREVALENCE

Over 1.7 million Australians are living with diabetes and its consequences in 2015.

The study presented in this report estimated that there are approximately 1.73 million people currently living with diabetes mellitus in Australia (Chart i). This corresponds to an overall national prevalence rate of 7.22%. Cases of type 2 diabetes account for approximately 93.4% of diagnosed and undiagnosed diabetes cases. Due to demographic ageing, type 2 diabetes prevalence is increasing and shifting towards older age groups. The number of Australians with diabetes is projected to increase by 42% to 2.45 million in 2030.

Chart i: Prevalence of diabetes mellitus

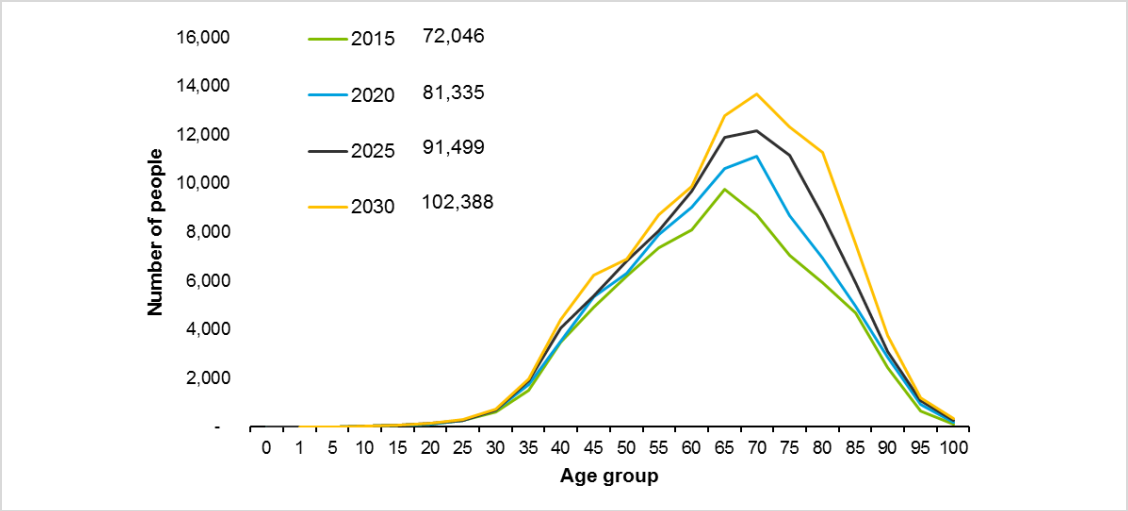


Source: Deloitte Access Economics calculations

With the increasing prevalence of diabetes in Australia, DR and DME are major and growing causes of vision impairment. In 2015, an estimated 72,000 people with diabetes have DME and about 3 in 5 of these people experience vision impairment.

The study presented in this report estimated that 736,300 people in Australia have DR, which is equivalent to 1 in 30 Australians of all ages. Of these people, 72,000 people have DME. This corresponds to a prevalence of 4.2% among **all** people with diabetes. This estimate is comparable to the prevalence figures reported in various epidemiological studies based on different study populations and methodologies in Australia (range = 1.9% to 8.9%) and internationally (range = 1.2% to 8.7%) (see Section 3.1 for further discussion). This study predicted that the prevalence of DR and DME would increase in the 15 years to 2030 by over 40% to 1.05 million (not shown) and 42% to 102,400 people, respectively (Chart ii).

Chart ii: Prevalence of DME



Source: Deloitte Access Economics calculations

INDIRECT ECONOMIC COSTS OF DME

In 2015, the total indirect cost of vision loss associated with DME is estimated to be $2.07 billion, which corresponds to $28,729 per person with DME. A significant part of this cost is associated with a loss of wellbeing and because people of working age could not work ($553.42 million), or could not work at full capacity ($4.38 million lost to absenteeism) due of poor vision caused by DME.

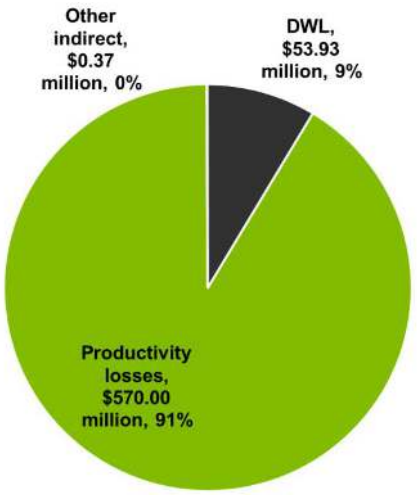
The study presented in this report quantified a range of costs, including productivity losses, aids and modifications, transfer costs and the associated deadweight loss (DWL, refer to glossary and definitions) related to DME, and the costs of lost wellbeing. This study did not include health system expenditure (direct costs) because of a lack of publicly available data specific to DR or DME and an inability to accurately estimate DR/DME-attributable healthcare costs from available MBS statistics, and other data on outpatient services and hospital admissions, detailed later in the report. This study found that the total indirect cost of vision loss associated with DME amounts to $2.07 billion. As presented in Table ii, a large part of this estimated cost was due to the loss of wellbeing associated with DME, and

productivity losses associated with visual impairment resulting from DME in individuals of working age. Due to a lack of robust data, this study did not include the costs of informal care, lower productivity while at work (i.e. presenteeism), and welfare payments. Thus, the estimate may understate the true economic impact of DME.

Table ii: Summary of estimated indirect economic costs of DME in Australia

Cost type	Total cost
Total indirect costs (a)	**$624.30 million**
Productivity losses	$570.0 million
Other indirect	$0.37 million
DWL	$53.93 million
Loss of wellbeing (b)	**$1,445.5 million**
Total indirect economic cost (a) + (b)	**$2,069.80 million**

Distribution of indirect financial costs only



NOTE: Productivity losses: lower workforce participation, absenteeism from paid and unpaid work, and premature deaths associated with visual impairment among people with DME. **DWLs:** deadweight losses associated with the inefficiency of transfer payments (e.g. raising taxes to pay for public services).

PREVENTION AND TREATMENT OF DME

Early detection through screening and treatment of DME with anti-vascular endothelial growth factor (anti-VEGF) therapy or laser photocoagulation can improve visual acuity or at least prevent the deterioration of vision.

In Australia, ophthalmologists and optometrists provide most publicly funded DR screening. Patients with diabetes may also receive DR screening integrated into the Diabetes Annual Cycle of Care of the Commonwealth Government Practice Incentive Programs for diabetes management. In 2012-13, one in four Australians with diabetes had Medicare claims for a completed annual cycle of care (Productivity Commission, 2014). In addition to medical services provided via the Medicare Benefits Scheme, there are a number of retinal photography screening programs for DR in Australia implemented in a range of settings, such as mobile units and pathology collection centres.

There is a range of surgical and drug treatments available for DME in Australia.

Depending on the severity and location of the disease, patients with DME may receive ocular treatment in the form of intra-vitreal therapy or laser photocoagulation of the retina (focal /panretinal with or without surgical vitrectomy), in addition to receiving ongoing medical management of systemic risk factors such as hypertension, hyperglycaemia and dyslipidaemia. A number of randomised controlled trials have now demonstrated the efficacy and safety profile of anti-VEGF medicines. Overall, these studies reported

statistically significant improvement from baseline for the anti-VEGF treated patients, compared to laser photocoagulation, in:

- the average best-corrected visual acuity;
- the proportion of eyes gaining at least 15 letters on the EDTRS scale[2]; and
- the average reduction in central retinal thickness.

These studies also found that patients tolerated anti-VEGF treatments well and the overall incidence of eye-related, non-eye-related and serious adverse events was similar across comparison groups.

CHALLENGES OF SCREENING AND TREATMENT OF DME

Current screening for DR and treatment of DME have various challenges, including low rates of screening and DR awareness and suboptimal service coordination.

Addressing the following issues would enhance the efforts to achieve the aims of the *National Framework for Action to Promote Eye Health and Prevent Avoidable Blindness and Vision Loss*, as endorsed by the Australian Health Ministers' Conference (November 2005):

- **Low rate of screening and awareness**

  Approximately 1 in 2 people with diabetes had not undergone a retinal examination within the National Health and Medical Research Council guidelines' recommended timeframe; 74% of general practitioners (GP) surveyed indicated that they did not routinely examine the eyes of their patients with diabetes, instead referring them to an optometrist or ophthalmologist for assessment. While it may be appropriate, a high demand for GP services means that they have limited time to undertake screening themselves. Furthermore, many GPs do not have the equipment required for undertaking screening and some do not have the required skills and confidence. Low rates of screening are also related to the low level of awareness of the link between diabetes and blindness, and the need for eye tests, among the population with diabetes and the general population.

- **Service coordination**

  Some researchers have suggested promoting a closer relationship between GPs and optometrists in recognition of the central role of optometrists in the delivery of primary eye health care, to encourage more referrals to optometrists rather than solely to ophthalmologists (Jamous et al 2014). Robust communication is required between screening services, optometrists, GPs and ophthalmologists, especially when there is no centralised system in Australia to monitor screening compliance and outcomes.

- **Lack of reimbursement for optical coherence tomography (OCT)**

  OCT allows mapping and measuring of macular thickness to help with early detection, diagnosis and treatment guidance for retinal diseases and condition, including DME. Currently, patients need to pay for the test when their ophthalmologists or optometrists require information from OCT to inform diagnosis and treatment decisions, and to monitor treatment response.

[2] A type of specialised eye chart that consists of uppercase letters arranged in rows, with the largest letters at the top of the chart and progressively smaller letters towards the bottom of the chart.

BENEFITS OF SCREENING AND TREATMENT

Increasing screening coverage in patients with diabetes, and providing access to anti-VEGF treatment, laser or vitrectomy procedures for those confirmed to have vision-impairing DME, will confer significant health and potential economic benefits.

A modelling study presented in this report found that screening 10% of the people with diabetes not currently undertaking retinal examination would identify 918 new cases of DME in 2015. An additional 9,179 cases of DME could potentially be detected earlier in 2015 if retinal examination were provided to all people with diabetes not being screened (Table iii). The model found that screening 10% to 100% of people currently not being screened and providing subsequent anti-VEGF treatment to people with confirmed vision-impairing DME eligible for treatment (65%), would improve vision in 139 to 1,393 people while preventing worsening visual acuity (VA) in 53 to 529 people. Accordingly, there would be a significant reduction in Disability Adjusted Life Years (DALYs) of 32-317 years, and savings in non-health care costs of $1.67-$16.65 million in 2015. The total social benefit was estimated to be $76.03 million. The benefits would be even greater if non-DME eye disease (e.g. earlier stage DR, PDR, macular degeneration, glaucoma) detected through screening were taken into account.

Table iii: Summary of findings, by coverage of people not currently being screened

Output parameter \ Screening rate	+10%	+25%	+50%	100%
Number of individuals detected with DME (true positives)	+918	+2,295	+4,589	+9,179
Number of people with visual acuity (VA) improvement ≥3 lines at 1 year	+139	+348	+696	+1,393
Number of people with worsened VA	-53	-132	-265	-529
Reduction in disability adjusted life years	32	79	159	317
Savings in non-health care costs	$1.67 million	$4.16 million	$8.33 million	$16.65 million
Savings in economic costs (non-health care) + value of statistical life year	$7.60 million	$19.01 million	$38.02 million	$76.03 million

If approximately two thirds of people with vision-impairing DME were eligible for anti-VEGF therapy, the savings potentially associated with improvement in vision and wellbeing would amount to $353.13 million in 2015.

The model found that providing anti-VEGF treatment to 10% of people with known vision-impairing DME would improve vision (3 lines or more) in 1,218 people, and prevent vision loss in up to 3,009 people if people with vision-impairing DME were eligible for treatment with anti-VEGF. These benefits would translate into a significant reduction in the costs associated with productivity losses and other non-healthcare costs of up to $15.62 million. The benefits would also reduce lost wellbeing, avoiding up to 1,803 DALYs. In monetary terms, this corresponds to a total saving of between $54.33 million to $353.13 million (Table iv).

Table iv: Summary of findings, by treatment coverage of people with known DME

Output parameter \ Treatment rate	10%	25%	50%	65%
Number of people treated	4,539	11,347	22,695	29,503
Number of people with visual acuity (VA) improvement ≥3 lines at 1 year	+1,218	+3,044	+6,089	+7,916
Number of people with worsened VA	-463	-1,157	-2,315	-3,009
Reduction in DALYs	277	693	1,387	1,803
Savings in non-health care costs	$2.40 million	$6.01 million	$12.02 million	$15.62 million
Savings in economic costs (non-health care) + value of statistical life year	$54.33 million	$135.82 million	$271.64 million	$353.13 million

In summary, investment in preventing vision impairment associated with DME through undertaking effective screening and providing treatment with established safety profile and efficacy now, will lessen the associated disease burden and economic costs in the future, including people's reliance on government funded disability services.

1 Background

Since 1997, the Australian Government has identified diabetes mellitus as one of the National Health Priority Areas, in recognition of the high social and financial costs it imposes on Australian society. Since this time, Australian State and Federal Governments have provided considerable investment in diabetes care, from prevention to treatment, with a view to lessening the burden of diabetes.

Diabetes will remain a major public health issue in Australia now and in years to come. In 2011-12, 4.0% of the Australian population, or 875,400 people reported having diabetes (ABS 2012).[3] The rate of diabetes increases with age, with people aged 65-74 years currently having the highest rate of diabetes (16.0%) in Australia. A growing number of children and adolescents are also now affected by type 2 diabetes, in large part due to the increasing prevalence of obesity[4] (Baker IDI Heart & Diabetes Institute 2012). Australia has the seventh highest prevalence of type 1 diabetes[5] in children aged 0-14 years and the sixth highest incidence of new cases globally. These statistics, together with an ageing population, suggest that diabetes will continue to be a major health priority in Australia.

Diabetic retinopathy (DR) is one of a myriad of neurological and cardiovascular complications of diabetes. People with DR have damage to the blood vessels inside the retina. The disease starts with micro-aneurysms or balloon-like swellings in the retinal blood vessels. As the disease progresses, the swellings cause blockages to the blood vessels and damage to the retina. DR occurs in an estimated one in seven Australians with diabetes (Dirani et al, 2013). If left untreated, it results in visual impairment and even blindness. In fact, with the increasing prevalence of diabetes, DR is set to become the main cause of vision impairment.

Diabetic macular oedema (DME) is a specific type of DR. The estimated prevalence of DME varies according to the study design and methodology, and the populations under study. Kaidonis et al (2014) undertook a review of studies performed after 1990 in Australia and found that an estimated 4.9% of non-Indigenous Australians with diabetes had DME. The prevalence in Indigenous Australians estimated in this study was significantly higher at 7.6% (p=0.01). The estimate is comparable to the overall global prevalence of DME of 6.81% (95% confidence interval: 6.74-6.89) in people with diabetes (Yau et al, 2012). Three other Australian studies with different study designs and covering different time-periods also provide useful information about the extent of DME in Australia:

- The AusDiab study, conducted in 2000 and in 2004, found that 3.3% of those people with type 2 diabetes had DME.
- The Melbourne Vision Impairment Project (MVIP) conducted between 1992 and 1996 found that 5.6% of people with diabetes had clinically significant DME.

[3] The figure excludes pregnant women with gestational diabetes.
[4] There are no recent trend data for Body Mass Index using measured height and weight. However, self-reported data from the National Health Survey show that there was an 8.7% increase in overweight and obese Australian adults, from 56.3% in 1995 and 61.2% in 2007-08.
[5] Please refer to Appendix A for a comparison of type 1 and type 2 diabetes.

- The Blue Mountains Eye Study (BMES), carried out from 1992 to 1994, among people aged 49 and over, found that 4.3% of people with diabetes had clinically significant DME.

Chapter 3 provides more in-depth discussion on the epidemiology of DME.

DME is the leading cause of visual loss resulting from diabetes and has a broad range of personal and economic impacts. A study in the United States by Gardner et al (2009) investigated the relationship between visual acuity and DME using data from 584 eyes in 340 placebo-treated patients in the 3-year Protein Kinase C Diabetic Retinopathy Study. The authors found that **73% of eyes evaluated had sustained moderate visual loss that was attributable to DME**. Vision impairment due to DME imposes burden for individuals and the health care system, and may have economy-wide impacts. From the patient perspective, DME has a significant impact on health related quality of life and may limit the person's capacity to work. A Canada-based study found that composite scores for vision-related quality of life declined with increasing visual acuity loss (Gonder et al, 2014). Family, carers and friends may also be involved in the provision of day-to-day care and support for blind or visually impaired people due to untreated DME (i.e. informal care).

DME has impacts on economic productivity. People with lower levels of vision reported lower job satisfaction, less freedom to decide their employment situation, fewer opportunities to develop new skills, less support and recognition, and fears that their health may limit their ability to work until regular retirement age (Mojon-Azzi et al, 2010). People who are blind experience lower than average employment rates compared to the general population. Productivity losses amongst this population are composed of loss of earnings associated with low employment rates and subsequent taxation losses.

Early detection and management of DME can prevent vision loss and minimise the impact of DME. While laser photocoagulation therapy has been the mainstay of medical management of DME, **the recent advent of anti-vascular endothelial growth factor (anti-VEGF) agents has advanced the treatment of patients with DME**. A systematic literature review concluded that anti-VEGF drugs were effective compared to both laser and placebo without major unwanted side effects and seemed to be more effective than steroids in improving best corrected visual acuity (BCVA) (Ford et al 2013). Effective treatment of DME is highly dependent on the identification of patients with DME. For this reason, screening for DR by medical practitioners and optometrists is an important part of a holistic program to prevent vision loss. However, despite the clinical practice guidelines for screening for DR by the National Health and Medical Research Council (NHMRC), there is evidence that people with diabetes do not regularly utilise eye services for early prevention of vision loss (Livingston et al, 1998; Tapp, 2004).

1.1 Purpose of this report

Since it is well-established that screening and treatments confer benefits to patients and society, it is important to quantify their economic and quality of life impacts and communicate these benefits to key stakeholders.

To this end, Bayer Australia has appointed Deloitte Access Economics to undertake a study to assess the epidemiology of DME in Australia and the links with the epidemiology of diabetes; the direct and indirect costs of DME annually; and the economic impact of screening and drug treatments registered for DME in Australia.

1.2 Report structure

The following chapters provide an exposition on various topic areas:

- **Chapter 2** describes the aetiology, disease characteristics, and risk factors associated with DME. It includes the identification of DME according to its progression from DR.
- **Chapter 3** explores the epidemiology of DME and presents estimates on the prevalence of DME in Australia using data from the literature.
- **Chapter 4** considers and estimates the economic costs associated with DME, including health system expenditures, other financial costs, and the value of the loss of healthy life.
- **Chapter 5** discusses the benefits of screening for DR and the treatments for DME, particularly with anti-VEGF agents.

2 About DR and DME

2.1 Pathophysiology and definitions

DR and DME are common complications in patients with diabetes mellitus. DR occurs when high blood sugar levels, as well as high blood pressure and lipids, damage the small blood vessels (i.e. capillaries) inside the retina. While there are several pathophysiological pathways that initiate vascular dysfunctions, DR typically starts with micro-aneurysms, or abnormal bulges in the wall of the capillaries. As the disease progresses, some of these impaired capillaries are blocked, causing deprivation of nutrients and oxygen supply to the retinal tissues (i.e. hypoxia).

In response to local hypoxia in order to maintain nutrient and oxygen supply, affected tissues in the retina and elsewhere increase the production of growth factors, such as VEGF. VEGF is a potent stimulus for generating new blood vessels, but it also induces vascular permeability that causes leakage of fluid into the retinal tissue (Ciulla et al, 2003; Callanan et al, 2013). DR therefore encapsulates two stages: non-proliferative DR (NPDR), which includes haemorrhages in the retina, and significant leakage of fluid due to this higher permeability of the retinal vessels; and proliferative DR (PDR) involving the growth of abnormal, fragile new blood vessels on the surface of the retina which bleed, thus impairing sight and vision.

Patients with DR may develop DME at any time during the progression of DR. DME is swelling or thickening of the central retina (i.e. the macula) in patients with diabetes mellitus due to leaking of fluid from blood vessels within the macula (US National Eye Institute, 2015). The macula is the central specialised portion of the retina in the eyes. This small area is dense in specialised nerve endings, known as the cone cells, which enable the eye to see fine detail, detect colours and are essential for detailed daytime vision. As the swelling or oedema develops in the macula, thickening of the retinal tissue may develop around the foveal centre – the part of the macula that enables very fine detailed visual acuity.

2.2 Classifications of DR and DME

Accurate diagnosis and classifications of DR and DME would help to ensure proper management of the conditions. The first standardised classification of DR was developed during the 1968 Airlie House symposium. This classification scheme was modified for use in various studies, including the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS). The ETDRS staging system introduced the term clinically significant macular oedema (CSME) with the following definition:

- thickening of the retina at or within 500µm of the centre of the macula; or
- hard exudate at or within 500µm of the centre of the macula associated with thickening of adjacent retina; or
- a zone of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula.

Investigators in clinical trials and epidemiologic studies generally consider the ETDRS the gold standard for grading. Table 2.1 shows the simplified ETDRS classification based on the Wisconsin grading system[6] and the predictive value of retinal lesions based on the findings of ETDRS Report 18 (Mitchell et al, 2008). However, the usefulness of this grading system is limited in daily clinical practice because of complicated rules, multiple severity levels and the need to correlate with standard photographs.

Table 2.1: Classification of DR (Wisconsin level) and predictive value of retinal lesions

Retinopathy stage	Definition	Rate of progression (%)			
		to PDR		to high-risk stage	
		1 year	3 years	1 year	5 years
Minimal NPDR (level 20)	MA only	not documented			
Mild NPDR (level 35)	MA and one or more of: retinal haemorrhage, HEx, CWS, but not meeting Moderate NPDR definition	5	14	1	15
Moderate NPDR (levels 43, 47)	HMA ≥ standard photo 2A in at least one quadrant and one or more of: CWS, VB, IRMA, but not meeting Severe NPDR definition	12-26	30-48	8-18	25 - 39
Severe NPDR pre-proliferative (level 50+)	Any of : H/MA > standard photo 2A in all four quadrants, IRMA > standard photo 8A in one or more quadrants, VB in two or more quadrants	52	71	15	56
PDR (level 60+)	Any of: NVE or NVD < standard photo 10A, vitreous/ pre-retinal haemorrhage and NVE <1/2 DA without NVD	n/a	n/a	46	75
High-risk PDR (level 70+)	Any of: NVD> 1/4 to 1/3 disc area, or with vitreous/ pre-retinal haemorrhage, or NVE > 1/2 DA with vitreous/ pre-retinal haemorrhage	Severe visual loss (VA ≤ 5/200) develops in 25-40% within 2 years.			
Advanced PDR	High-risk PDR with fractional detachment involving macula or vitreous haemorrhage obscuring ability to grade NVD and NVE				
ME	Retinal thickening within 2 disc diameters of macular centre	Can occur at any stage of DR			
Clinically significant macular oedema (CSME)	Retinal thickening within 500µm of macular centre or hard exudates within 500µm of macular centre with adjacent thickening	Can occur at any stage of DR			

NOTE: **MA** = microaneurysm; **H/MA** = haemorrhages/microaneurysm; **HEx** = hard exudates; **CWS**= soft exudates or cotton-wool spots; **NVD** = neovascularisation involving the optic disc; **NVE** = neovascularisation elsewhere in the retina; **DA** = Disc area; **IRMA** = Intra-retinal microvascular abnormalities; **VA** = Visual acuity; **NPDR** = non-proliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy.

Source: Mitchell et al, 2008

[6] haemorrhages/microaneurysms (H/MA), hard exudates (HEx), venous beading (VB), intraretinal microvascular abnormalities (IRMA), soft exudates or cotton-wool spots (CWS), neovascularisation involving the optic disc (NVD) or elsewhere in the retina (NVE), as well as preretinal or vitreous haemorrhage.

To simplify the classification of DR, the Global Diabetic Retinopathy Project Group developed the International Clinical Disease Severity Scale for DR (Wilkinson et al, 2003). This scale proposed five levels of DR severity as none, mild, moderate, severe and proliferative, in the presence or absence of DME (Table 2.2).

Table 2.2: Diabetic Retinopathy Disease Severity Scale

Disease severity levels	Findings upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: • More than 20 intra-retinal haemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants **and** no signs of proliferative retinopathy
PDR	One or both of the following: • Neovascularization • Vitreous/pre-retinal haemorrhage
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME present	**Mild:** Some retinal thickening or hard exudates in posterior pole but distant from the centre of the macula **Moderate:** Retinal thickening or hard exudates approaching the centre of the macula but not involving the centre **Severe:** Retinal thickening or hard exudates involving the macular centre

Note: **NPDR** = non-proliferative diabetic retinopathy; **PDR**= proliferative diabetic retinopathy; **IRMA** = intra-retinal microvascular abnormalities; **DME** = diabetic macular oedema
Source: Wilkinson et al, 2003

More recently, there have also been attempts to implement classification using information gathered from Optical Coherence Tomography (OCT) – a non-invasive, non-contact trans-pupillary imaging technique (Panozzo et al, 2004; Maalej et al, 2012). This is because the OCT provides information that demonstrates the complex morphological microscopic intra-retinal changes in DME, and a simple "clinical" definition may not sufficiently indicate the improvement in visual outcomes. For example, Panozzo et al (2004) described a classification based on information on retinal thickness, diffusion, volume, morphology and presence of vitreous traction gathered from OCT.

A Cochrane review by Virgili et al (2015) concluded that the central retinal thickness measured with OCT was not sufficiently accurate to diagnose the central type of CSME. However, the authors concluded that “the increasing availability of OCT devices, together with their precision and the ability to inform on retinal layer structure, now make OCT widely recognised as the new reference standard for assessment of DME, even in some screening settings”.

2.3 Visual impairment in DR and DME

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. Visual acuity is measured using specialised eye charts. These charts usually consist of uppercase letters arranged in rows, with the largest letters at the top of the chart and progressively smaller letters towards the bottom of the chart.

The Snellen chart is the current standard for measurement of visual acuity in clinical practice because of its simplicity. According to the Snellen scale, normal vision is recorded as 6/6, or 20/20 in Imperial/US measures, which means that the person in question can see at 6 metres (or 20 feet) what a person with normal vision can see at 6 metres (or 20 feet). Degrees of visual impairment are measured similarly, where the first number is the furthest 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 see clearly at six metres (but not further), an object that a person with unimpaired vision could see clearly at up to 12 metres (Taylor et al, 2005).

LogMAR is an improved visual acuity scale, which expresses visual impairment as the logarithm of the minimum angle of resolution. It measures visual acuity loss, 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) because it provides a more scientific equivalent for the traditional clinical statement of 'lines lost' or 'lines gained', which is valid only 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. Table 2.3 (p.7) presents the conversion between Snellen units and LogMAR.

Table 2.3: Conversion of Snellen Acuity into LogMAR

LogMAR	Snellen (imperial)	Snellen (metric)	Decimal	LogMAR	Snellen (imperial)	Snellen (metric)	Decimal
1.5	**20/640**	6/192	0.03	0.5	**20/63**	6/20	0.32
1.4	**20/500**	6/152	0.04	0.4	**20/50**	6/15	0.4
1.3	**20/400**	6/120	0.05	0.3	**20/40**	6/12	0.5
1.2	**20/320**	6/96	0.063	0.2	**20/32**	6/10	0.63
1.1	**20/250**	6/76	0.08	0.1	**20/25**	6/7.5	0.8
1.0	**20/200**	6/60	0.1	0.0	**20/20**	6/6	1.0
0.9	**20/160**	6/48	0.125	-0.1	**20/16**	6/5	1.25
0.8	**20/125**	6/38	0.16	-0.2	**20/12.5**	6/3.75	1.6
0.7	**20/100**	6/30	0.20	-0.3	**20/10**	6/3	2
0.6	**20/80**	6/24	0.25				

Source: Kaiser 2009

A number of studies have investigated the effectiveness of different measures of visual acuity in predicting macular and visual function in patients with DR and DME (e.g. Hatef et al, 2014; Kaiser, 2009; Vujosevic et al, 2006). However, mapping between visual acuity and disease classification of DME, as outlined in Table 2.1 and Table 2.2, is difficult because individuals with the same disease severity, for example as defined by ETDRS, may have different levels of visual impairment or no impairment. Table 2.4 shows an attempt to map DR stages to visual acuity reported by Kawasaki et al (2015).

Table 2.4: DR stages and corresponding visual acuity (and utility value)

Disease severity levels	Visual acuity	Utility value
No apparent retinopathy	≥1.0	1.00
NPDR	≥1.0	0.98
Severe NPDR	<0.8	0.85
PDR	<0.4	0.553
High risk PDR	<0.2	0.419
CSME (high visual acuity)	<0.4	0.553
CSME (low visual acuity)	<0.2	0.419
Stabilised retinopathy (low visual acuity)	≥0.5	0.94
Stabilised retinopathy (high visual acuity)	<0.4	0.553
Blindness	<0.1	0.350

Note: **NPDR** = non-proliferative diabetic retinopathy; **PDR**= proliferative diabetic retinopathy; **CSME** = clinically significant macular oedema
Source: Kawasaki et al, 2015

More recently, the advent of OCT has led to better characterisation of DME. A number of studies reported a correlation of visual acuity in eyes with DME and a number of factors, including central macular thickness, macular volume, inner segment/outer segment junction integrity and retinal inner layer tissue (e.g. Sun et al, 2014). In general, people with the early stages of DR would continue to maintain normal vision and therefore the cost of DR to the person and society would be relatively low. However, DME and PDR would have greater negative effects on an individual's vision; the cost to the person and society would likely be much higher for these conditions.

2.4 Risk factors for DME

Risk factors can be both modifiable and non-modifiable. Modifiable risk factors mostly relate to lifestyle choices or factors that can be partially or fully controlled, such as tobacco smoking and glycaemic control. In contrast, non-modifiable risk factors are immutable, including genetic factors, age, sex, and ethnicity. Although people may have one or more risk factors, this does not mean they will develop a condition such as DME. Conversely, DME can arise even in the absence of known risk factors. In general, however, the more risk factors a person has, and the greater the severity of each risk factor, the greater the likelihood of developing DME.

Epidemiological studies have identified a number of factors that can increase the risk of developing DME and increase the speed at which the disease progresses. The following section provides a detailed discussion of these factors, which include:

- **Modifiable risk factors:** glycaemic control, hypertension, dyslipidaemia, tobacco smoking; and
- **Non-modifiable risk factors:** duration of diabetes and age of onset, gender, genetic variation, advancing age, ethnicity.

2.4.1 Modifiable risk factors

2.4.1.1 Glycaemic control

It is well accepted that long-term elevation of blood glucose levels (i.e. hyperglycaemia) is one of the main risk factors for developing DR and DME (the Diabetes Control and Complications Trial Research Group, 1995). A recent meta-analysis presented by the Disease (META-EYE) Study Group found increased prevalence of DR and DME in populations with high levels (>7.0%) of glycosylated haemoglobin level (HbA1c) – an indicator of poorly controlled diabetes (Table 2.5)

Table 2.5: Increased prevalence of DR and DME in individuals with higher glycosylated haemoglobin level (HbA_{1c})

HbA_{1c}	Any DR	PDR	DME	Vision threatening DR
≤7.0%	17.99 (17.64-18.33)	3.1 (2.93-3.26)	3.59 (3.42-3.76)	5.40 (5.19-5.60)
7.1-8.0%	33.13 (32.64-33.62)	6.87 (6.63-7.10)	6.30 (6.06-6.54)	10.82 (10.53-11.10)
8.1-9.0%	43.1 (42.53 - 43.66)	9.64 (9.37-9.90)	7.69 (7.46-7.93)	13.64 (13.33-13.95)
>9.0%	51.2 (50.80 - 51.60)	10.93 (10.76-11.11)	12.49 (12.31-12.67)	18.35 (18.13-18.58)

Note: Figures are in percentages (95% confidence interval) for individuals with diabetes aged 20-79 years.
Source: Yau et al (2012)

There is also evidence to suggest that the variability of glycaemic control is an independent risk factor for DR in patients with diabetes, although this association remains controversial. The systematic review by Hsu et al (2014) found evidence that long-term glycaemic fluctuation, as measured by variation of levels of HbA1c, appeared to show a stronger association with DR in patients with type 1 and type 2 diabetes than their counterparts with stable glycaemic control. The findings suggest the need to minimise glycaemic variability to reduce the development and progression of DR.

2.4.1.2 Hypertension

The National Heart Foundation of Australia (2008) guidelines define high blood pressure as systolic pressure at or above 140mmHg or diastolic pressure at or above 90mmHg. A number of studies have found a statistically significant association between the presence of hypertension and DME (e.g. Klein et al, 1984; Diep et al, 2013; Romero 2007). The meta-analysis by Yau et al (2012) also reached similar findings: DME was present in approximately twice as many people with hypertension and diabetes than their counterparts who were normotensive (Table 2.6). Hypertension was also a risk factor for all DR at other levels of severity, including vision threatening diabetic retinopathy (VTDR).

Table 2.6: Increased prevalence of DR and DME in individuals with hypertension

Status	Any DR	PDR	DME	VTDR
Normal	30.84 (30.59-31.09)	4.16 (4.07-4.25)	5.45 (5.35-5.55)	7.60 (7.48-7.72)
Hypertensive	39.55 (39.19-39.91)	12.32 (12.08-2.57)	10.59 (10.37-10.81)	17.63 (17.36-17.9)

Note: Figures are in percentages (95% confidence interval) for individuals with diabetes aged 20-79 years
Source: Yau et al (2012)

2.4.1.3 Dyslipidaemia

Yau et al (2012) found that total cholesterol of ≥4.0mmol/L was associated with higher prevalence of DME and VTDR, and to a lesser extent, PDR (Table 2.7).

Table 2.7: Age-standardised prevalence of DR by type in diabetic subjects

Status	Any DR	PDR	DME	VTDR
<4mmol/L	31.64 (31.11- 32.17)	5.12 (4.87-5.36)	4.60 (4.37-4.83)	8.09 (7.78-8.40)
≥4.0 mmol/L	31.06 (30.82-31.29)	5.67 (5.56-5.78)	6.78 (6.67-6.9)	9.55 (9.42-9.69)

Note: Figures are in percentages (95% confidence interval) for individuals with diabetes aged 20-79 years
Source: Yau et al (2012)

In contrast, a recent analysis of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[7] – one of the best sources of evidence in relation to the epidemiology of DR and DME – found no associations of serum total or high-density lipoprotein cholesterol and incident PDR or DME after adjustment for covariates (Klein et al, 2014). It also did not identify evidence to suggest that the use of statins decreased incidence of PDR or DME.

2.4.1.4 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. While the literature has extensively considered the relationship between smoking and aged-related macular degeneration (Klein et al, 2002; Smith et al, 1996; Thornton et al, 2005; Seddon et al, 2006; Coleman et al, 2008), research on the link between smoking and DME is less conclusive.

For example, Romero et al (2007) conducted a 15-year follow-up study of 112 people with type 1 diabetes without DR or nephropathy, with a view to ascertaining the incidence of DME and associated risk factors. This research found that cigarette smoking was not a significant factor in developing DME. In contrast, Kamoi et al (2013) found that smoking was a predictor for CSME among diabetic patients in Japan, although the sample size of this study is small. This inconsistency is also evident in broader research on the potential

[7] The WESDR is a large epidemiologic study conducted in the United States that involved all persons with younger-onset type 1 diabetes (996 people) and older-onset persons mostly with type 2 diabetes (1,370 people) who were first examined from 1980 to 1982. Since its inception in 1979, there have been six follow-up examinations of the cohort completed in 1984-86, 1990-92, and 1995-96, 2000-01, 2006-07, and 2012-14.

correlation between smoking and the prevalence and incidence of macular oedema (Klein et al, 1984; Moss et al, 1996).

Nevertheless, smoking does increase the likelihood of developing diabetes, and smoking with diabetes increases the likelihood of hyperglycaemia. The literature indicates that smokers are more likely to develop diabetes than non-smokers (Eliasson 2003). This relationship exists because smoking increases insulin resistance and central fat accumulation (Chiolero et al, 2008). As a result, smoking increases the risk of metabolic syndrome and diabetes. Smoking has also been shown to worsen glucose metabolism, which may lead to the onset of type 2 diabetes (Fagard et al, 2009). As discussed in Section 2.4.1.1, hyperglycaemia is a major medical factor associated with development and progression of DR and DME.

The evidence linking smoking and the risk of developing diabetes is extensive. For example, the *US 2014 Surgeon General's Report: The Health Consequences of Smoking* reported that smokers are 30–40% more likely to develop type 2 diabetes than non-smokers. The Health Professionals' follow-up study showed that the relative risk of diabetes (adjusted for alcohol consumption, BMI, physical exercise, and family history of diabetes) in men who smoked 1–14, 15–24, and ≥25 cigarettes was 1.37 (95% CI: 0.77, 2.43), 2.38 (1.57, 3.59), and 1.94[8] (1.25, 3.03), respectively, compared with non-smokers (Rimm et al, 1995). Similar results were observed in cohorts of women (Rimm et al, 1993; Hu et al, 2001).

Furthermore, research indicated that diabetes patients who smoked had higher blood sugar levels than non-smoking diabetics (Solberg et al, 2004; Sherman et al, 2005). This may increase their risk of hyperglycaemia, a major risk factor for DME. The literature also indicates that smoking in individuals with abnormal blood lipid levels can worsen DME more than abnormal blood lipid levels alone (Miljanovic et al, 2004).

Smoking has many other effects on the eye, including increasing the risk of macular degeneration, increasing the likelihood of developing cataracts, and lowering the age at which they develop (Tan et al, 2008), as well as exacerbating thyroid eye disease, and ocular inflammatory conditions.

2.4.2 Non-modifiable factors

2.4.2.1 Gender

The literature surrounding the impact of gender on DME arrives at a range of different conclusions. The WESDR found that men were more likely to experience DME (Klein et al, 1984). Kamoi et al (2013) considered risk factors for CSME and found that gender was statistically insignificant among diabetic patients in Japan.

2.4.2.2 Genetic variations

The development of DR and DME is associated with complex genetic and environmental factors, varying between individuals. A number of studies have identified a range of genetic

[8] This means that men who smoked 25 cigarettes or more had 1.94 times the risk of developing diabetes compared to men who did not smoke.

factors that may be associated with the development of DR and DME, independently or via the development of diabetes. These include genes associated with aldose reductase, VEGF, and pancreatic function and control of insulin secretion (Liew et al, 2009).

For example, Deissler et al (2013) found that elevated expression of VEGF-A correlates with increased vascular permeability and simultaneously decreased tight junction protein (i.e. ZO-1) content in the vitreous of patients with DR. Another example is the significant correlation between the progression of DR in patients with type 2 diabetes and the presence of genetic variations of the MTHFR gene (Maeda et al, 2008).

2.4.2.3 Ethnicity

Diabetic retinopathy is more common among some ethnic groups than others. For example, African Americans with type 2 diabetes have a greater prevalence and severity of the disease than Caucasians and Asians (see Table 2.8). This may be explicable by higher prevalence of risk factors for diabetes among these populations, which predisposes the development of DR as a complication of the disease. Racial differences may not be fully explainable by the prevalence of risk factors alone and there may be other (e.g. genetic) predispositions involved.

Table 2.8: Age-standardised prevalence of DR by type in diabetic subjects of different race

Race	Any DR	PDR	DME	VTDR
Caucasian	45.76 (45.44-46.07)	12.04 (11.87-12.21)	8.42 (8.28-8.57)	15.45 (15.25-15.64)
Chinese	25.08 (24.25-25.91)	2.67 (2.26-3.07)	8.12 (6.88-9.36)	5.14 (5.55-6.73)
South Asian	19.12 (18.88-19.35)	1.29 (1.22-1.36)	4.93 (4.82-5.04)	5.2 (5.05-5.34)
African Americans	49.56 (48.59-50.52)	8.99 (8.58-9.40)	10.35 (9.90-0.79)	16.89 (16.32-17.46)
Hispanic	34.56 (33.24-35.87)	5.10 (4.91-5.29)	7.15 (7.0-7.3)	10.85 (10.44-11.25)
Asian (combined)	19.92 (19.7-20.14)	1.54 (1.48-1.61)	5.0 (4.89-5.12)	5.25 (5.12-5.39)

Note: Figures are in percentages (95% confidence interval) for individuals with diabetes aged 20-79 years.
Source: Yau et al, 2012

Three epidemiological studies investigated the prevalence of DME in Indigenous populations in Australia (Durkin et al, 2006; Landers et al, 2010; Xie et al, 2011). Depending on the population and the methods of investigation, the reported prevalence of DR ranged between 22% and 29.7%, and the reported prevalence of DME was as high as 8.9% (see Table 3.2). A review of Australian studies by Kaidonis et al (2014) also found that prevalence of DME in Indigenous Australians was 1.5 times higher than that reported for non-Indigenous Australians.

This higher prevalence of DR and DME in Indigenous populations is in line with the evidence that risk factors for developing DR and DME are much higher in Indigenous populations. For example, the AIHW analysis of the 2004-05 National Aboriginal and Torres Strait

Islander Health Survey found that diabetes among Indigenous Australians was 3 times as common as in non-Indigenous Australians, after taking into account differences in age structure between the two populations (AIHW 2015). Furthermore, Indigenous people have poorer access to healthcare services (e.g. Scrimgeour and Scrimgeour, 2007). This may result in poorer management of diabetes and other risk factors (see section 2.4.1), and detection of ophthalmic complications at later stages of disease.

No formal epidemiological studies investigated the prevalence of DME in other high-risk populations. However, it is known that Australians living in areas of most disadvantage were more than twice as likely to have diabetes (5%) as those living in the least disadvantaged areas (2%), after adjusting for age structure (ABS 2011). Furthermore, due to a range of genetic, biological, behavioural and environmental risk factors, some culturally and linguistically diverse groups in Australia have a high prevalence of diabetes compared with the Australian-born population (Thow et al, 2005). These populations include people who were born in the South Pacific, Southern and Eastern Europe, Middle East and North Africa. These communities may also have higher prevalence of DR and DME. Preventative activities and the provision of health services would need to be tailored to the needs of these communities.

> Indigenous Australians and other ethnic groups in Australia have higher prevalence of diabetes. There are studies reporting much higher prevalence of DR and DME in Indigenous populations.

2.4.2.4 Duration of diabetes and the age of diagnosis

> Duration of diabetes is one of the strongest risk factors for DME.

As a longitudinal study lasting several decades, the WESDR is one of best sources of evidence to indicate the relationship between the duration of diabetes and the age of diagnosis, and the development of DME. The WESDR found that for individuals who are <30 years old at diagnosis, and have had type 1 diabetes for more than 20 years, 29% have DME, whereas of those who have had diabetes for less than five years, 0% have DME (Klein et al, 1984). Similarly, for those who are >30 years old at diagnosis, and have had diabetes for more than 20 years, 28% have DME, and for those with diabetes for less than 5 years, 3% have DME. The WESDR found that cumulative risk of developing DME increases with the duration of diabetes.

The WESDR also indicated that DR was rare among children aged 10 years and younger. About 10% of teens with diabetes, aged 15 to 19 years, have DR. The proportion rose from 10% to 40% between ages 20 and 29 years. By age 30 years, about 60% of people with diabetes had DR, and by age 45 years the figure rose to 70%. The overall prevalence of DME was 11.1% for younger onset diabetic patients (aged less than 30 years) (Klein et al, 1984). The prevalence was 0% in younger onset patients with a diagnosis of diabetes for fewer than five years, and 29% in younger onset patients with diabetes for 20 years or more (Klein et al, 1984).

The overall prevalence of DME was 8.4% for older (aged more than 30 years) onset patients (Klein et al, 1984). Among older onset patients, the prevalence was 3% for patients with a

diagnosis of diabetes for fewer than five years, and 28% in older onset patients with diabetes for 20 years or more (Klein et al, 1984). In this group, DME was also more prevalent among insulin users than non-insulin users. Fifteen years after the diagnosis of diabetes, DME was present in 20% of those using insulin and 12% of those not using insulin (Klein et al, 1984).

Other cross-sectional studies also provide evidence to demonstrate the association between the duration of diabetes and the prevalence of DME. For example, Varma et al (2014) undertook cross-sectional analysis of 1,038 participants aged 40 years or older with diabetes and valid fundus photographs in the 2005 to 2008 National Health and Nutrition Examination Survey. They found that people with 10 years or more of diabetes had 8.5 (95% CI: 3.70-19.54) times the odds of DME compared to people with less than 10 years of diabetes.

2.4.3 Summary of risk factors

Table 2.9 presents a summary of the evidence relating to the risk factors for DR and DME.

Table 2.9: Summary of key risk factors for developing DR and DME

Risk factor	Findings
Glycaemic control	Hyperglycaemia is one of the main risk factors for developing DR and DME Minimising glycaemic variability may reduce the risk for development and progression of DR
Hypertension	There is a positive correlation between hypertension and DME and severity of DR
Total cholesterol	Mixed findings: Yau et al (2012) found that total cholesterol was associated with higher prevalence of DME; Klein et al (2014) did not find an association
Tobacco smoking	Smokers more likely to develop diabetes; diabetics who smoke tobacco may be at higher risk of DR and DME
Gender	Mixed findings: Klein et al (1984) found that men were more likely to experience DME; Kamoi et al (2013) did not find that gender was statistically significant
Genetic variations	A range of genetic factors (genes associated with aldose reductase, VEGF, pancreatic function and control of insulin secretion) may be associated with DR and DME
Ethnicity	African Americans have a higher prevalence of DR than Caucasians and Asians. Indigenous Australians and other ethnic groups have higher prevalence of diabetes. There are studies reported much higher prevalence of DR and DME in Indigenous population than non-Indigenous population
Duration of diabetes and the age of diagnosis	Literature demonstrates that the cumulative risk of DME increases with the duration of diabetes. Those with younger onset diabetes are more likely to have DR and DME (due to longer duration of diabetes)

With the advancement in medical care and treatment, a number of modifiable risk factors for developing DR and DME, such as high blood sugar levels and high blood pressure, can now be addressed with better results.

3 Epidemiology of DR and DME

This chapter provides information on estimates for both the prevalence and incidence of DME reported in studies conducted in Australia and internationally. It includes findings from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the Blue Mountains Eye Study (BMES) and the Melbourne Visual Impairment Project (MVIP).

3.1 Prevalence of DR and DME

3.1.1 Systematic reviews

Prevalence refers to the total number of cases of a disease in a population at a given time. There are numerous epidemiological studies of DR and DME conducted internationally over the past 30 years. Two recent large systematic reviews by Ruta et al (2013) and Yau et al (2012) provide summation of the extant evidence on the prevalence of DR and DME.

Ruta et al (2013) conducted a systematic literature review of the prevalence of DR, including studies reporting diabetic maculopathy, in patients with type 2 diabetes[9] in developing and developed countries. The review included findings reported for 33 countries, of which 13 were developing countries. The 72 studies reviewed collected data from registries (6 studies), primary care clinics (23 studies) and directly from recruited subjects drawn from the population (43 studies). The authors noted that there were major differences in study characteristics and methodologies, including the methods for diagnosing DR: fundus photography; medical records; or clinical fundoscopy via direct or indirect ophthalmoscopy, or slit-lamp biomicroscopy. These differences made comparisons "very difficult". Across all studies, the authors found the following median (interquartile range) prevalence estimates for study participants with known diabetes aged 47-76 years:

- any DR = 27.9% (22-37%);
- PDR = 2.3% (1-4%); and
- CSMO = 5.7% (2-7%).

Yau et al (2012) undertook a systematic review of 35 population-based studies that had ascertained DR from fundus (retinal) photographs. The authors undertook meta-analysis for the prevalence of DR, DME and VTDR and risk factors. To this end, the authors sought individual participant data from the studies' investigators regarding presence and severity of DR, DME status, age, sex, ethnicity, diabetes type and duration, HbA1c, systolic and diastolic blood pressure, lipid profile, cigarette smoking status, BMI, and current use of diabetes, antihypertensive, and lipid-lowering medications. Overall, the study found that the overall age-standardised prevalence for any DR was 34.6% (95% CI 34.5–34.8), for PDR was 6.96% (6.87–7.04), for DME was 6.81% (6.74–6.89), and for VTDR was 10.2% (10.1–10.3). The prevalence estimates were higher when the authors restricted the analysis to studies with similar methodologies and ophthalmologic definitions (Table 3.1). The prevalence findings were similar to those reported by Ruta et al (2013) except for the findings for PDR.

[9] Some studies comprised a mixed population that included type 1 diabetes patients

Table 3.1: Age-standardised prevalence of DR in diabetic subjects aged 20-79 years, using studies with similar methodology

	Studies included	Number of cases	Number of study participants	Age standardised prevalence (%, 95% confidence interval)
ALL				
Any DR	18	4,487	12,650	35.36 (35.17-35.56)
PDR	21	957	13,436	7.24 (7.15-7.33)
DME	20	1,039	14,554	7.48 (7.39-7.57)
VTDR	18	1,481	12,710	11.72 (11.61-11.83)
Men				
Any DR	18	2,263	6,252	36.27 (35.99-36.55)
PDR	21	469	6,376	7.53 (7.39-7.66)
DME	20	486	7,010	7.44 (7.30-7.57)
VTDR	18	704	6,051	11.74 (11.57-11.00)
Women				
Any DR	18	2,224	6,368	34.46 (34.19-34.73)
PDR	21	488	7,060	6.98 (6.86-7.10)
DME	20	553	7,544	7.54 (7.42-7.66)
VTDR	18	777	6,659	11.70 (11.55-11.86)

Source: Yau et al (2012) Table 2

Yau et al (20112) also found that all prevalence increased with diabetes duration, HbA1c level, and blood pressure levels (see data presented in section 2.4). The prevalence was also higher in people with type 1 diabetes compared with type 2 diabetes.

3.1.2 Australian studies

This report identified six studies of different design and time-period that reported information regarding the extent of DR and DME in Australia (Table 3.2).

Table 3.2: Studies reporting the prevalence of DR and DME in Australia

Study, first author (year)	Sample size, population type mean age (range), diabetes type	Any DR	PDR	DME or CSME
BMES Mitchell 1998	256 participants, general 68 years (51-96 years), mixed	32.4%	1.6%	4.3%
MVIP McKay 2000	234 participants, general 64 years (45-91 years), mixed	29.1%	4.3%	5.6%
AusDIAB Tapp 2003	703 participants, general 65 years (>25 years), mixed	21.9%	2.1%	3.3%
Durkin 2006	771participants, Indigenous (Not reported), Type 2	22%	Not reported	1.9%
Landers 2010	1,033 participants, Indigenous 49 years (≥40), Type 2	22.2%	2.8%	5.3%
Xie 2011	394 participants, Indigenous (≥40 years), Type 2	29.7%	3.1%	8.9%

Note: **BMES** = Blue Mountains Eye Study; **MVIP** = Melbourne Visual Impairment Project; **AusDIAB** = Australian Diabetes, Obesity and Lifestyle study

Overall, studies with samples drawn from the general population reported a prevalence range of 21.9% to 32.4% for any DR, 1.3% to 4.3% for PDR, and 3.3% to 5.6% for DME or CSME. It is important to note that the results relate to older people with type 2 diabetes; the study findings were less applicable to persons with type 1 diabetes who may have onset of diabetes at very young ages.

The studies undertaken in Indigenous populations reported prevalence of DR comparable to those reported for the general population. However, a review of Australian studies performed after 1990 by Kaidonis et al (2014) looked at the prevalence of DME in Indigenous and non-Indigenous Australians and found that an estimated 4.9% of non-Indigenous Australians with diabetes had DME, compared to 7.6% amongst Indigenous Australians (p=0.01). As noted in Section 2.4.2.3, Indigenous Australians (and other minority ethnic groups in Australia) have higher prevalence of diabetes. This explains their higher prevalence of DR and DME.

3.1.3 International studies

Table 3.3 presents the findings of a selected set of international studies on the prevalence of DR and DME. The reported prevalence rates from these studies were comparable, but generally higher than those reported in the studies undertaken in Australia (Table 3.2). It is likely that the variations in the reporting prevalence estimates were related to the study populations, which may have variations in the prevalence of risk factors influencing the development of DR and DME (see section 2.4).

Table 3.3: International studies reporting the prevalence of DR and DME

Study name, first author (year), location	Sample size, population, mean age (range), diabetes type	Any DR	PDR	DME or CSME
WESDR Wisconsin, US	1,313 participants, general, types 1 and 2	50.3%†	6.9% (includes severe NPDR)	5.1%
BDES Wisconsin, US	410 participants, general, types 1 and 2	35.1%†	2.2% (includes severe NPDR)	1.2%
NHANES Zhang (2010) US	1,006, general (≥ 40 years), types 1 and 2	40-64 years = 28.0% (23.0-33.6) ≥65 years = 29.5% (25.4-33.9)	1.5% (1.1-2.2)	2.7% (1.8-4.0)
Hove (2004) Denmark	378participants, general 65 years, type 2	31.2%	2.9%	5.3%
Ellis (2011) UK	295 participants, general 65 years, type 2	37.3%	2.7%	3.5%
Simmons (2007) New Zealand	150 participants, general 64 years, type 2	37.4%	2.7%	8.7%

NOTE: **BDES** = Beaver Dam Eye Study; **WESDR** = Wisconsin Epidemiology Study of Diabetic Retinopathy; **NHANES** = National Health and Nutrition Examination Survey

†Figures were obtained from The Eye diseases Prevalence Research Group (Kempen et al, 2004) who obtained data from study investigators.

3.1.4 Prevalence by type of diabetes

This report did not identify studies reporting the prevalence of DME in Australia by the type of diabetes. Three UK-based studies reported the prevalence of DME according to the patient's type of diabetes (Table 3.4). Both studies that reported the prevalence rates of any DR found higher prevalence among people with type 1 diabetes than those with type 2 diabetes. This is consistent with the literature, which suggests that patients with type 1 diabetes had lower age of onset and therefore longer duration of diabetes, which would increase the risk of developing DR and DME. In fact, the systematic review by Yau et al (2012) found that more than three in four persons with type 1 diabetes would develop DR (Table 3.5).

However, the reported prevalence figures for DME were less consistent. For example, Thomas et al (2013) found higher prevalence of DME among individuals with type 1 diabetes (4.2%) compared to those with type 2 diabetes (1.4%), but these figures were much lower than the age standardised prevalence reported by Yau et al (Table 3.5). In contrast, Broadbent et al (1999) and Prescott et al (2014) found lower prevalence of DME among patients with type 1 diabetes than those with type 2 diabetes (Table 3.4). These discrepancies are likely to be due to the differences in the study methodology, and the distribution of underlying risk or protective factors (e.g. glycaemic control, age distribution of participants and so on).

Table 3.4: Literature that considered DME prevalence by diabetes type

First author (year)	Study population	Any DR	DME
Thomas (2013)	91,393 persons: T1DM =5,003 T2DM= 86,390 Age = 36.5 (T1DM); 65.3 years (T2DM)	T1DM = 56% T2DM = 30.3%	T1DM = 4.2% (3.7 - 4.8)† T2DM = 1.4% (1.3 to 1.5) †
Broadbent (1999)	357 persons: T1DM =49 T2DM = 308 Age =60.3 years (13-92)	All = 33.6% T1DM = 36.7% T2DM = 31.3% (non-insulin) or 45.0% (insulin)	All = 6.4% T1DM = 2.3% T2DM = 5.7% (non-insulin) 16.2% (insulin)
Prescott (2014)	3,170 patients with T1DM or T2DM Age = 60 years (49-69)	Not reported	T1DM = 3.95% T2DM = 8.69%

Note: **T1DM** = Type 1 Diabetes Mellitus; **T2DM** = Type 2 Diabetes Mellitus; †Maculopathy with background DR

Table 3.5: Age-standardised prevalence of DR by type in diabetic subjects

Status	Any DR	PDR	DME	VTDR
Type 1	77.31 (76.34-78.28)	32.39 (31.76-33.01)	14.25 (13.86-14.64)	38.48 (37.80-39.16)
Type 2	25.16 (24.96-25.36)	2.97 (2.91-3.02)	5.57 (5.48-5.66)	6.92 (6.83-7.02)

Note: Figures are in percentages (95% confidence interval) for individuals with diabetes aged 20-79 years
Source: Yau et al (2012)

3.2 Incidence and progression of DME

3.2.1 Incidence of DME

Incidence is the number of new cases occurring within a given period. The incidence of DME is typically reported as a percentage per year, or a cumulative percentage during a specific period. In line with the disease prevalence, incidence of DME was strongly associated with time since diabetes diagnosis. Few studies reported detailed information on the incidence. The WESDR reported the incidence of DME by age and duration of diabetes (Klein et al, 1998 & 1989). The study found that cumulative risk in general increases with the duration of diabetes (Table 3.6). However, the relationship is not linear due to the increased risk of death associated with increased age and duration of diabetes.

Table 3.6: Cumulative incidence of DME by age and duration of diabetes (WESDR)

Age	14 years	25 years	Diabetes duration	14 years	25 years
0-9 years	10.4%	23.2%	0-2 years	12.9%	17.7%
10-14	18.7%	28.8%	3-4	19.3%	29.2%
15-19	22.6%	26.1%	5-9	29.2%	34.0%
20-24	26.4%	29.7%	10-14	33.1%	37.7%
25-29	29.3%	39.9%	15-19	24.1%	26.1%
30-34	30.4%	29.9%	20-24	33.7%	36.0%
35+	31.1%	23.4v	25-29	27.0%	19.1%
All groups	26.0%	28.6%	30+	16.7%	9.6%

Source: Klein et al (1998; 1989)

This report did not identify studies undertaken in Australia that reported incidence estimates specific to DME. However, a number of Australian studies reported the incidence of DR. For example, the BMES estimated an annual incidence rate of 4.5% for DR, compared to 8.0% in the Newcastle Diabetic Retinopathy Study (Mitchell et al, 1985). Jaross et al (2005) reported 5.6% (95% CI 3.0-10.0) of Indigenous Australian with diabetes would develop DR in a year.

It is worth noting that while the prevalence of diabetes has increased over time, management of diabetes has improved considerably, thereby reducing the incidence rate of complications, possibly including DME.

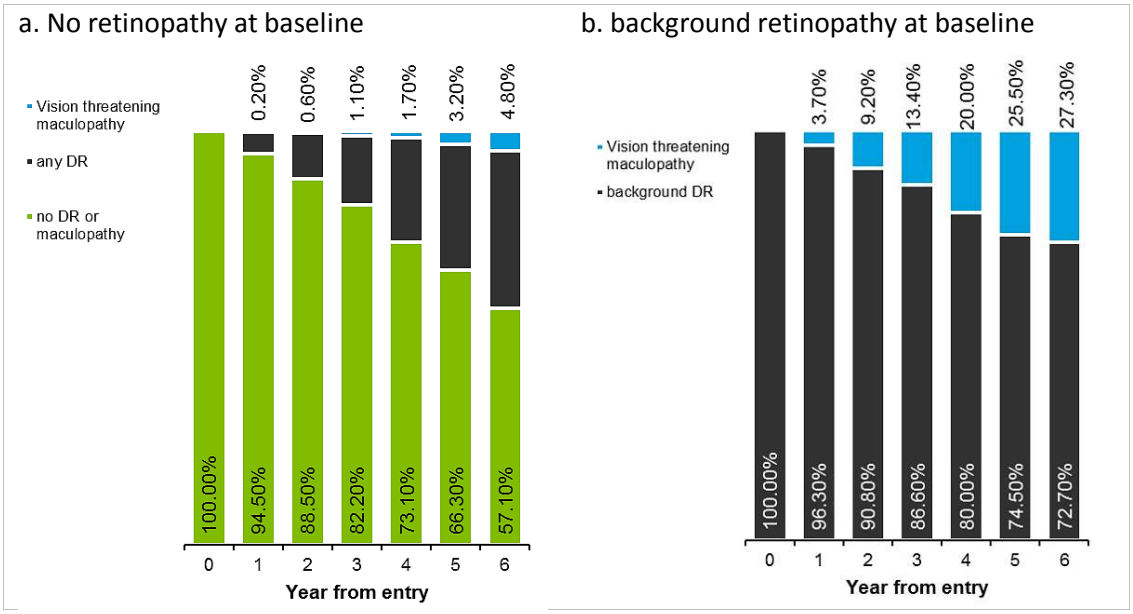
Amongst European countries, the following incidence rates were observed:

- In the UK, the 2-year incidence of CSME was 4.79% (Ling et al, 2002);
- In Sweden, the 1-year incidence of CSME was 2.3% per year for the overall diabetic population (Henricsson et al, 1999);
- In Spain, the 15-year incidence of DME in type 1 diabetic patients was 20.5% (Romero-Aroca et al, 2007); and
- A clinic-based study in Denmark also showed a decline in the incidence of DME in patients over time. The incidence after 15 years of diabetes duration was 11% and 12% for patients diagnosed in 1965–1969 and 1970–1974, respectively, while only 5% for patients diagnosed in 1975–1979 (Rossing et al, 1998).

3.2.2 Natural history and progression of DR and DME

Younis et al (2003) reported the yearly cumulative incidence rates of ophthalmologic complications in patients with type 2 diabetes who participated in the Liverpool Diabetic Eye Study. This study found that 4.8% of patients with type 2 diabetes who did not have DR would develop vision-threatening maculopathy (VTM) at 6 years; this translates into an annual probability of 0.82%. For those people with background DR at baseline, about 1 in 5 individuals would develop VTM at 6 years, corresponding to 5.18% annual probability.

Chart 3.1: Cumulative incidence rates of vision threatening maculopathy in people with type 2 diabetes who had (a) no retinopathy or (b) background retinopathy at baseline



Source: Younis et al (2003) Tables 2 and 3

Clinical trials for assessing treatment efficacy also provided information on the progression of DR and DME. Table 3.7 presents the onsets of visual impairment at different time points during the follow up period for participants of the Diabetic Retinopathy Study (DRS) and ETDRS. In general, approximately 25% of untreated CSME would develop moderate visual loss after 3 years (defined as at least doubling of the visual angle e.g. 20/40 to 20/80) (Aiello et al (1998).

Table 3.7: Onset of visual loss with or without treatment

Retinopathy level	Follow-up	Untreated	Treated
NPDR†	2 years	3%	3%
	4 years	13%	4%
PDR†	2 years	7%	3%
	4 years	21%	7%
High risk PDR†	2 years	28%	6%
	4 years	42%	12%

Retinopathy level	Follow-up	Untreated	Treated
CSME with visual centre involvement‡	1 year	7.5%	1.0%
	3 years	22.1%	13.2%
CSME without visual centre involvement‡	1 year	13.3%	7.5%
	3 years	33.0%	13.8%

NOTE: †DRS - onset of severe visual loss (VA=5/200); ‡ETDRS - onset of moderate visual loss (≥doubling of angle)
Source: Aiello et al (1998)

3.2.3 Visual impairment

Visual impairment (VI) and blindness are the health outcomes of clinical and policy relevance. These outcomes affect younger and older-onset DME patients at different rates, as demonstrated by the WESDR (Table 3.8).

In the baseline analysis of the WESDR data, 1.4% of the **younger-onset diabetic patients** (aged <30 years at diagnosis) had moderate VI (best corrected visual acuity in the better eye of 20/80 to 20/160) and 3.6% were legally blind (visual acuity in the better eye of 20/200 or worse) (Klein et al, 1984). The prevalence of VI among younger-onset diabetic patients with a 15- to 19-year duration of diabetes ranged from 2% to 13% (13% among those diagnosed from 1960 through 1969, 2% from 1970 to 1974 and 4% from 1975 to 1979) (Klein et al, 1984). For those with a 30- to 34-year duration of diabetes, prevalence of VI ranged from 9% to 16% (Klein et al, 1984).

In the **older-onset group** (aged ≥30 years at diagnosis), 3.0% had moderate VI and 1.6% were legally blind. The 10-year incidence rates of blindness were 4.0% for the older-onset taking insulin group, and 4.8% for the older-onset not taking insulin group (Sjolie et al, 1987). The 10-year incidence rates of VI were 37.2% for the older-onset taking insulin group, and 23.9% for the older-onset group not taking insulin (Sjolie et al, 1987).

Table 3.8: Summary of incidence rates of health outcomes amongst younger and older onset patients, based on WESDR data

	Younger-onset (%)	Older-onset (%)
Visual Impairment	1.4	3.0
Blindness	3.6	1.6
10 year incidence rates		
Blindness	1.8%	
Taking insulin		4.0
Not taking insulin		4.8
Visual Impairment	9.4%	
Taking insulin		37.2
Not taking insulin		23.9

Source: Klein et al (1998; 1989)

This data indicated that patients diagnosed more recently had a lower prevalence of VI. Moss et al (1994) interpreted this to be due to the diminishing incidence of PDR or CSME, possibly due to better glycaemic control and more timely interventions.

3.3 Mortality associated with visual impairment

Past studies have shown that the presence of visual impairment is a predictor of mortality. Based on the data collected in the BMES, Wang et al (2001) found persons with any visual impairment had an age- and sex-standardised mortality rate of 26% over 7 years compared to 16% in people without visual impairment. The difference in mortality rates persisted after adjustments for potential confounding factors, including health risk behaviour and medical conditions (relative risk = 1.7, 95% CI: 1.2-2.3). A 13-year follow-up study by Karpa et al (2009) also found that higher mortality was associated with non-correctable visual impairment (HR=1.35; 95% CI, 1.04-1.75) and was stronger for ages <75 years (HR, 2.58; 95% CI, 1.42-4.69). The authors found that only disability in walking demonstrated a significant indirect pathway for the link between visual impairment and mortality.

In the WESDR data set, CSME in older-onset diabetic patients was associated with increased all-cause mortality (HR=1.55; 95% CI: 1.25-1.92) and ischaemic heart disease mortality (HR=1.56; 95% CI: 1.15–2.13), when adjusting for age and gender (Klein et al, 1989; 1998). After controlling for other risk factors, the association remained significant for ischaemic heart disease mortality (HR, 1.58; 95% CI, 1.07–2.35; p=0.02) among those taking insulin (Hirai et al, 2008).

A Finnish study by Kulmala et al (2008) found that the risk for mortality among the 75-year-olds with lowered vision (VA of ≥0.3 but ≤0.5) and with visual impairment was almost double the risk in those with normal VA (RR=1.98, 95 % CI 1.25-3.13 and RR=1.90, 95% CI 1.12-3.20, respectively). However, the authors found that controlling for lower walking speed, physical inactivity, cardiovascular diseases, injurious accidents, diabetes and depressed mood each attenuated the risk markedly, suggesting that there may be other unobserved confounding factors.

A case control study by Wearn et al (2002) investigated the relationship between illness (including visual impairment) and suicide among 100 consecutive cases of suicide in Scandinavian born people aged ≥65 years who underwent autopsy at the Gothenburg Institute of Forensic Medicine from January 1994 to May 1996. This study found that people with visual impairment had 7 times the risk of committing suicide (95% CI: 2.3 – 21.4) compared to control subjects living in the same area as the deceased who were matched by age and gender.

4 Health and economic burden of DME

This chapter estimates the health burden and economic costs of vision loss associated with DME in Australia for the year 2015.

The costs considered comprise health system costs, and indirect economic costs such as productivity costs for people with DME, low vision aids, the cost of care, and the deadweight efficiency losses from welfare and taxation transfers. In addition, the cost of loss of healthy life was estimated. The methodology adopted in this report is consistent with that used in Access Economics (2010).

4.1 Prevalence of diabetes, DR and DME in Australia

4.1.1 Prevalence of diabetes

The prevalence of diabetes mellitus was estimated using the following sources of information:

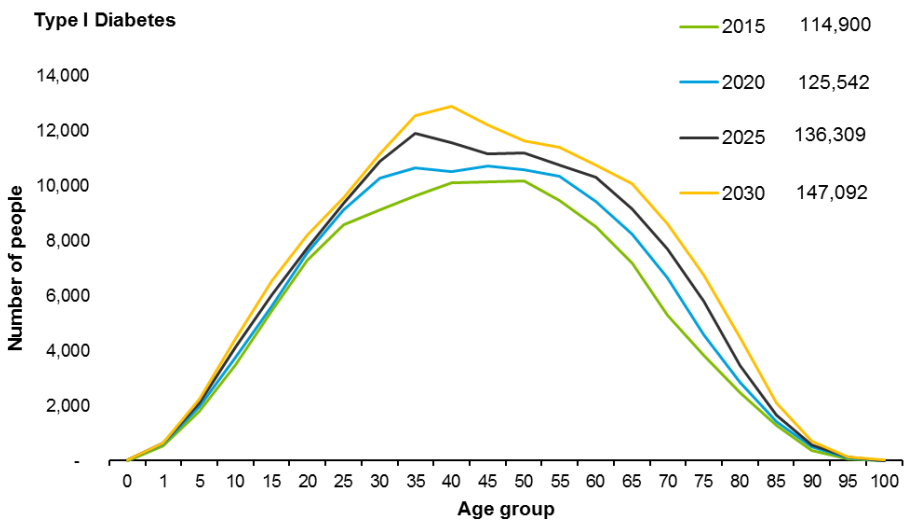
- Population projections for Australia, developed by the ABS (ABS, 2014): the ABS publishes different population projections by making various assumptions about future levels of fertility, mortality, overseas migration and internal migration. This study applied projection "series B" because it largely reflects current trends in fertility, life expectancy at birth and net overseas migration.
- The AusDiab study conducted in 1999-2000 (Dunstan et al, 2000) and the North West Adelaide Health Survey (Grant et al, 2005): these studies found different estimates for the rate of undiagnosed diabetes cases in Australia (50% and 18.3%, respectively).
- Of the studies reported in Beagley et al (2013), there were 16 studies conducted in high-income countries since the year 2000. Two of these were excluded as the reported result could not be verified; one other study was excluded since it calculated the undiagnosed rate specifically related to type 2 diabetes. Taking the average of the remaining 13 studies and two Australian studies, gave the rate of undiagnosed diabetes as 36%.

By combining the rate of undiagnosed diabetes with the self-reported rate of diabetes from the 2011-12 AHS (4.6%) (ABS, 2013d), the total prevalence rate for Australia is estimated at 7.2%. This estimate implies that the prevalence of diabetes in Australia is approximately 1.73 million people in 2015.

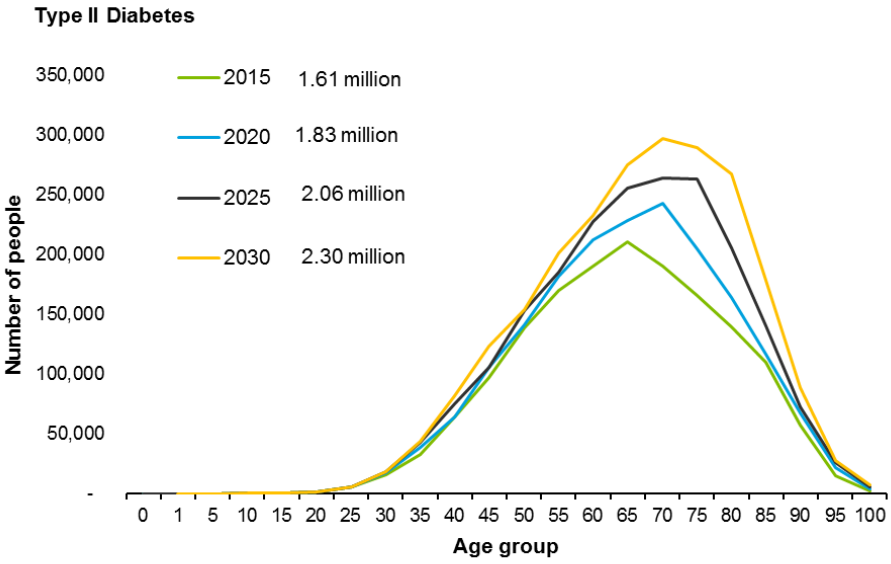
Chart 4.1 shows the estimated prevalence of type 1 and type 2 diabetes in Australia from 2015 to 2030. In younger age categories (0-34 years), the prevalence of type 1 diabetes is higher than the prevalence of type 2 diabetes, reflecting the underlying risk factors and pathophysiology for the two types of diabetes.

Chart 4.1: Estimated prevalence of (a) Type 1 and (b) Type 2 diabetes, 2015-2030

a.



b.



Source: Deloitte Access Economics 2015

Demographic ageing over the coming decades will result in an increase in the proportion of people in older age groups, thereby increasing the number of people with type 2 diabetes (Chart 4.1).

> The number of Australians with diabetes is projected to increase by 42% from 1.73 million in 2015 to 2.45 million in 2030.

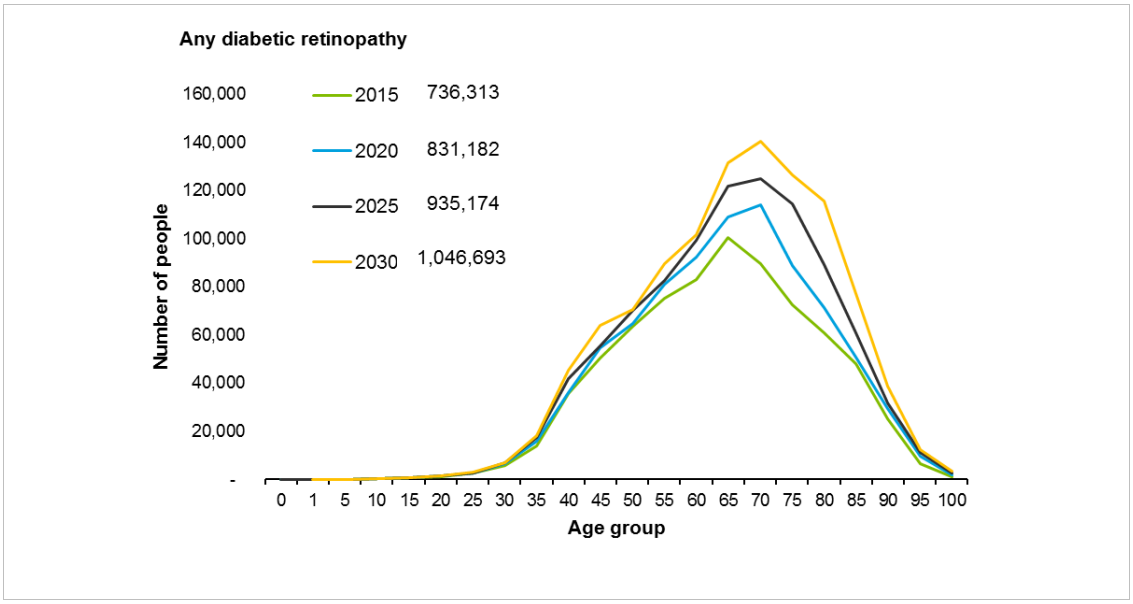
4.1.2 Prevalence of DR and DME

Based on the projected prevalence of type 1 and type 2 diabetes, this study estimated the prevalence of DR and DME by age groups based on a number of studies presented in section 3.1.

Most of these studies presented the prevalence of DR and DME in older populations with type 2 diabetes. This study applied the prevalence rate of DR reported by Downie et al (2011), who found that prevalence rates of DR in 1,604 patients with type 1 diabetes aged 12-20 years seen at a hospital for children in NSW between 1990 and 2009 declined from 53% to 12%. The authors found that the trend was in parallel with a decline in HbA1c and intensification of management. Similarly, the finding of Eppens et al (2006) was used to estimate the prevalence of DR in adolescents with type 2 diabetes, reported to be 4.0%. The significant difference in the rate of DR in type 1 and 2 diabetes observed in this study may have been solely related to the duration of diabetes. The prevalence of DME was estimated based on the average ratio between DR and DME prevalence rates reported across studies, and the overall estimate was validated against the reported prevalence for DME.

Chart 4.2 presents the estimated prevalence of DR in Australia between 2015 and 2030. This report estimated that in 2015 there are around 736,300 people in Australia with DR. The prevalence will increase over the next two decades by 45.7% to 1.05 million people, with a shift in the prevalence towards the older age groups due to demographic ageing. The overall prevalence rate of DR among the diabetic population is 42.6%.

Chart 4.2: Prevalence of DR in Australia, 2015-2030



Source: Deloitte Access Economics 2015

Table 4.1 presents the estimates for DME in Australia. It is estimated that approximately 72,000 people in Australia in 2015 have DME, with a projected growth in cases of 42.1% to 103,000 in 2030. Overall, the estimated prevalence of DME represents approximately 4.2% of the projected population with diabetes of all ages. This finding is comparable to the estimates presented in Table 3.2 (p.17).

Table 4.1: Prevalence estimates for DME in Australia, 2015-2030

Start age in group	2015	2020	2025	2030
10	41	44	49	52
15	64	66	71	77
20	131	135	138	147
25	267	283	290	297
30	614	683	715	730
35	1,503	1,738	1,908	1,984
40	3,477	3,518	4,067	4,436
45	4,928	5,342	5,389	6,235
50	6,190	6,313	6,839	6,889
55	7,354	7,897	8,055	8,730
60	8,083	9,016	9,691	9,895
65	9,779	10,625	11,894	12,811
70	8,724	11,122	12,164	13,678
75	7,058	8,675	11,168	12,314
80	5,929	6,945	8,680	11,285
85	4,687	4,948	5,926	7,537
90	2,444	2,862	3,083	3,765
95	651	937	1,104	1,197
100	123	185	269	329
TOTAL	**72,046**	**81,335**	**91,499**	**102,388**

Source: Deloitte Access Economics 2015

As presented in Sections 2.4.2.3 and 3.1.2, Indigenous populations and some groups of culturally and linguistically diverse Australians have higher prevalence of diabetes and DME. A detailed analysis of the prevalence in these communities is beyond the scope of this report.

> In 2015, an estimated 736,300 people in Australia have DR, equivalent to 1 in 30 Australians of all ages. Of these people, 72,000 people have DME. By 2030, due to demographic ageing, the numbers with DR and DME would increase by over 40% to 1.05 million and 102,000 respectively.

4.1.3 Prevalence of visual impairment associated with DME

While there are data on the incidence of visual impairment among trial participants, there is limited literature that provides information on the distribution of the level of VI among individuals with DME. A retrospective study used records from the South-western Ontario database to observe the demographics, prevalence, and treatment characteristics of VI due to DME and found that 63% of patients with DME had VI, defined as VA <20/40 (Petrella et al, 2012).

> Accordingly, this study estimates that approximately 45,389 individuals with DME in Australia have visual impairment in 2015.

4.2 Healthcare expenditure

This study attempted to estimate the direct healthcare expenditure[10] related to DME. However, as explained in the following paragraphs, publicly available data are non-specific to DR or DME, making accurate estimation impossible. Therefore, this report only presents the indirect costs associated with DME.

The aggregated data on health system expenditure for various eye conditions are available from the AIHW by special request. This dataset includes the costs of hospital admitted services, out-of-hospital medical services, pharmaceuticals requiring a prescription and research for eye diseases. However, such data are not specific to DME and the estimation method would require multiple assumptions to ascertain the costs attributable to DME.

Specific issues with estimations from aggregated health system expenditure included

- The AIHW data did not include costs for outpatient services provided by hospitals, over-the-counter pharmaceuticals, services provided by other health professionals and aged care homes.
- The data for hospital admitted services of eye diseases did not include DR, because admissions for DR were coded in ICD-10 as ophthalmic complications of diabetes mellitus rather than as eye disease.
- Medicare Services Schedule (MBS) items related to the management of DME were identified based on literature and stakeholders' comments. Many of these services are not specific to DR or DME, making attribution challenging. Some of these items are for general health services not specific to ophthalmology. For example ophthalmologists may have sought reimbursement for the services they provided to people with DME using the following MBS items:
  - Item 104: Specialist, referred consultation – surgery or hospital; and
  - Item 105: Each attendance subsequent to the first in a single course of treatment.

  However, specialists in other medical fields also used these MBS items. Publicly available statistics for these items did not present by specialty, making the attribution of costs to DME impossible. For this reason, this report did not estimate MBS related costs associated with DME.
- In terms of the accurate estimation of costs associated with pharmaceuticals, there are also other items used to treat DME which may not be registered by the TGA or reimbursed for use in DME. These treatments may not be approved by the TGA for ophthalmic use. This off-label use is difficult to quantify thus making it likely that an estimation of pharmaceutical costs attributed to DME would be an underestimate.

> Direct healthcare expenditure related to DME is not estimated in this report due to a lack of specific data.

[10] Healthcare 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).

4.3 Indirect costs

There is a range of indirect costs such as productivity losses for people of working age who have DME, and the cost of providing care for people living with DME. Productivity losses occur when a person does not work due to poor health. The productivity loss is the value of the lost production including any premium that has to be paid to a replacement worker (eg, overtime), as well as staff turnover costs and retraining in the event that the worker is unable to work for an extended period. Different elements of these costs are borne by:

- **employer**: sick leave, the overtime premium for the replacement worker, staff turnover costs and employer 'excess' contributions to compensation payouts if the DME was work-related;
- **worker**: reduced income after tax, which may be partially offset by disability or compensation payments;
- **government**: reduced taxation receipts and higher welfare payments (e.g. Disability Support Pension); and
- **society**: compensation payments.

Other financial costs include items such as:

- **carer costs**: people who are unwell may require others to care for their needs and this care often does not enter into health system expenditure – for example, an informal (unpaid) family carer assisting with personal care or taking someone to appointments, or a formal sector (paid) carer coming in to perform household tasks;
- **aids and home modifications** not included in health system expenditure that the person may need to purchase as a result of the DME; and
- **Deadweight loss (DWL)**: the redistribution of public sector resources to care for the sick person incurs deadweight costs on society, such as the need to raise additional tax revenues. The revenue itself is a transfer payment, not a real economic cost, but for every dollar of tax raised, about 28.75 cents is absorbed by the distortions induced and the administration of the tax system. Tax revenue is also required to finance welfare and disability payments in a budget-neutral setting (since long-term fiscal deficits for consumption are unsustainable).

A study in the United States by Gardner et al (2009) investigated the relationship between visual acuity and DME using data from 584 eyes in 340 placebo-treated patients in the 3-year Protein Kinase C Diabetic Retinopathy Study. The authors found that approximately **73% of eyes evaluated had sustained moderate visual loss that was attributable to DME.** The subsequent vision impairment due to DME imposes a burden on individuals and the health care system, thus having economy-wide impacts. For the patient, the impact of DME is significant on their health-related quality of life as it may limit their capacity to work. Studies have also shown that people with lower levels of vision have lower job satisfaction, less freedom to decide their employment situation, fewer opportunities to develop new skills, less support and recognition, and fears that their health may limit their ability to work until regular retirement age (e.g. Mojon-Azzi et al, 2010). Average employment rates for people who are blind are also significantly lower than the general population (Vision Australia, 2012), resulting in a loss of earnings which, together with taxation losses, comprises productivity losses. In a Canada-based study, Keefe et al (2009) found that composite scores for vision-related quality of life declined with increasing visual acuity loss.

Informal care in the form of day-to-day care by family and friends to provide support for the blind or visually impaired also presents a cost to the economy.

Shane's story

"It's hard, because if I didn't have my eyes I wouldn't be able to see my kids grow up or work," – said Shane, a young father living with DME and type 2 diabetes.

Shane is a father of two primary school aged children and has been living with type 2 diabetes for more than 15 years. At just 39 years of age Shane is also living with DME following an early diagnosis three years ago. Shane's DME was diagnosed following the detection of damage to the back of his eye during a routine eye exam. At this point in his life Shane was still an active member of the community, with a fulltime career as an engineer and a primary carer of his young children.

For Shane, protecting his eyesight means maintaining his independence, continuing in his career as an engineer, and importantly, being an active father. Fortunately, following his diagnosis by an ophthalmologist, Shane was immediately started on anti-VEGF treatment, which has protected and maintained his vision preventing further deterioration of his eyesight or blindness. Today, Shane lives with his young family and is still working full time. Shane travels to Sydney regularly for treatment, which he will need in order to maintain his sight for the rest of his life.

Source: provided by Bayer Australia

4.3.1 Productivity losses

Productivity losses were estimated by taking into account the lower-than-average employment rates for people with vision loss from DME, lost lifetime earnings due to premature deaths attributable to vision loss, and the 'bring forward' of employers' search and hiring costs resulting from replacing employees lost to premature deaths. 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 (i.e. presenteeism).

Short-term impacts of DME were measured using a friction methodology and largely comprise absenteeism costs. The friction methodology measures the cost from the employer's perspective of sustaining production until an employee who has DME returns to work or is replaced (e.g. sick leave and overtime premiums for a temporary replacement worker). As is appropriate in developed countries, a human capital approach was adopted to measure long-term productivity losses. The human capital approach, as opposed to the friction method, measures the cost to society of a contraction in the production possibility frontier due to lower labour inputs overall. A review of available literature was undertaken to determine key parameter inputs, including the change in employment participation and productivity associated with DME.

4.3.1.1 Lower workforce participation

The Vision Australia's Employment Research Survey indicated that only 36% of all people of working age with visual impairment were gainfully employed in 2012 (Vision Australia 2012), compared to 61.6% in the Australian general population (ABS, 2015). This represents a difference of 25.6%.

The age-gender specific employment rates were calculated by dividing the number of employed people by the total number of people in the corresponding groups from 15 to 65 years. The model calculated the difference between the employment rates between people with visual impairment due to DME, and the employment rates if they were not visually impaired by DME. The difference (or excess) between the two scenarios was attributed to DME and its risk factors and impacts. Data on employment rates and average weekly earnings (AWE) for each respective age-gender group were combined to calculate the lost earnings due to reduced employment.

> DME is a major cause of vision impairment in a significant number of people of working age, and the cost of lost earnings due to reduced workforce participation from visual impairment of DME, compared to the general workforce, was estimated as $553.42 million in 2015.

4.3.1.2 Absenteeism from paid and unpaid work

For people with DME who are employed, the condition can adversely affect work performance through absence from work. Such absenteeism is measured by looking at the number of working days missed by people with DME over a 12-month period.

According to Gonder et al (2014), people with DME in Canada took an average of 0.48 additional days away from work over 6 months relative to their counterparts without DME. This study assumed the same amount of absenteeism and applied it to the Australian employed population with DME. Furthermore, for those who do not work, the same number of days was estimated to be lost from their household productivity, valued at 30% of the average wage rate.

> Based on these parameters and AWE for each age-gender group, the cost of absenteeism and lost home production due to DME was estimated as $4.38 million in 2015 for people of working age.

4.3.1.3 Presenteeism

Visual impairment due to DME can also affect a person's ability to function effectively while at work, for the same reasons as it contributes to absenteeism and lower employment participation. A randomised controlled trial by Adepoju et al (2014) found that workers with type 2 diabetes (n=371) had 7,864 days of reduced productivity attributed to their diabetes. While this reduced productivity may be related to VI from ophthalmologic complications of diabetes, the precise level of presenteeism among individuals with DME is not certain. This study took a conservative approach and did not estimate presenteeism.

4.3.1.4 Premature deaths

The number of premature deaths attributable to VI was estimated based on the findings that BMES participants who had VI had higher mortality than participants who had no VI (RR=1.69 for individuals aged <75 years and RR=1.39 for individuals aged ≥75 years) (Karpa et al, 2009). The model calculated the population attributable fraction (see Rockhill et al, 1998 for explanation), and applied it to the population age-sex specific mortality rates.

The model found that if all DME patients never had VI, assuming a causal relationship, 218 DME patients would not have experienced premature deaths. Based on the age-gender distribution of these deaths, and incorporating employment rates and estimates of average lifetime earnings for different age-gender groups, the present value of lost earnings due to premature mortality among those who would otherwise have been employed was estimated at $12.2 million.

> Assuming causal relationship, there were 218 cases of premature deaths due to visual impairment among patients with DME. The cost of lost productivity from premature death due to DME was estimated as $12.2 million in 2015 for people of all ages.

Premature deaths would also lead to additional search and hiring costs for replacement workers. These were estimated as the product of the number of people with DME who died prematurely, the chance of being employed (if they did not die), and the search and hiring costs brought forward by three years – the average staff turnover rates in Australia. The search and hiring cost is estimated as 26 weeks at AWE[11].

> In 2015, additional search and hiring costs to replace individuals who died prematurely from DME-related VI are estimated at $21,400.

4.3.2 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.

[11] Literature estimates of search and hiring costs range from 26 to 104 weeks' salary, covering recruitment, training and lose business costs e.g. Safe WorkAustralia (2012), Pezzullo et al (2006).)

Informal care costs are the value of the care provided by informal friends or family carers. This study analysed the available epidemiological data from Australia and overseas, together with data reported in the Survey of Disability, Ageing and Caring (SDAC) (ABS 2014), to gain estimates of the total number of hours of care provided to people with DME, and the average unit cost of that care.

SDAC data for the year 2012 identified around 18,365 carers who provided care for people with diabetes as their main condition. However, it is uncertain how many of these individuals were caring for patients with diabetic ophthalmologic complications, such as DME. An observational study on the costs of care for people with impaired vision in Australia (Keeffe et al, 2009) found that the median[12] reported carers' hours in a week was 4.6% of the working week (i.e. 1.75 hours per week assuming a 38 hour working week). However, patients with DR only represented 5.2% (n=6) of the total study sample.

Due to a lack of robust estimates, the cost of informal care was conservatively assumed as zero in this study.

4.3.3 Aids and modifications

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 visual impairment from DME may require a variety of aids, special equipment and home modifications to function adequately and enhance their quality of life. Some of these, identified in the study by Lafuma et al (2006), are presented in Table 4.2. This study quantified the excess use of resources per visually impaired person in France, Germany, Italy and the United Kingdom. It found that visually impaired people required home adaptation more often than their non-visually impaired counterparts, ranging from +0.0% to +3.9% for different types of home fittings.[13] The study also found that 0.2% to 33.7% more visually impaired people required various devices than in the non-visually impaired population. Among those requiring home modifications and devices, the average cost per subject in the UK in 2004 amounted to €118.96 and €592.10 for modifications and devices respectively. This corresponds to a total of $2,564 in 2015 Australian dollars. The weighted average additional proportion of visually impaired persons requiring home adaptations and devices was estimated to be 0.31%.

Table 4.2: Aids and appliances

Category	Items
Institutional adaptations	Restroom, Bathroom, Tables, Seats, Bed, Ramps, Door-opening devices, Lift
Home adaptations	Toilets, Kitchen, Bathroom, Tables, Seats, Bed, Ramps, Door-opening devices, Stair lift, etc
Devices for those living in an institution*	Stick, Walking aids, Wheelchair, Guide dog, Optical assistance, computer interface, Software adapted for blindness, Tape recorder

*Please note that these aids and appliances are cited in Lafuma et al (2006). These devices are also of benefit for people in non-institutional setting. Source: Lafuma et al (2006)

[12] The median value was used rather than the mean because of large dispersion of the reported hours.
[13] Note that Italy reported +20% home adaptations among visually impaired person across all categories. This result is likely to be an artefact of the survey design.

Using these estimates, the cost of aids and modifications associated with DME, over and above the non-visually impaired population, is estimated to be $366,600 in 2015.

4.3.4 Transfer costs and DWLs

Transfer payments represent a shift of resources from one economic entity to another. As the act of taxation and redistribution creates distortions and inefficiencies in the economy, transfer payments involve real net costs to the economy.

The Government in Australia provides funding for much of the public sector services, social security (transfer) payments and so on. To achieve a budget neutral position, the government needs to raise sufficient tax revenue. Taxes and transfers (such as subsidies and pensions) do not themselves represent a real economic cost because they are payments from one economic agent to another and do not involve a net use of resources. However, the cost of raising revenue to fund transfer payments is not zero because tax reduces the efficiency with which the economy's resources are used. For example, an increase in income tax rates will increase the relative price of work compared to leisure and therefore create a disincentive to work. Consequently, there is an associated reduction in consumer and producer surplus, which is known as the DWL, or excess burden, of tax.

This section estimates the size of DWLs associated with having to raise additional taxation revenue to replace taxation revenue lost from lower productivity among people with DME (section 4.3.4.1), and welfare and income support payments (section 4.3.4.2). This study did not estimate DWL of having to raise taxes to fund direct healthcare costs associated with DME because direct healthcare costs were not estimated due to a lack of specific data.

4.3.4.1 Lost taxation revenue from lower productivity

Reduced earnings due to reduced workforce participation, absenteeism and premature deaths have an effect on taxation revenue collected by the government. As well as forgone income (personal) taxation, there will also be a fall in indirect (consumption) tax, as those with lower incomes spend less on the consumption of goods and services.

There are two sources of lost tax revenue that result from the lower earnings – the personal income tax forgone and the indirect (consumption) tax forgone. The latter is lost because, as income falls, so does consumption of goods and services. Based on parameters for 2015 from the Deloitte Access Economics macroeconomic model, this study applied an average personal income tax rate of 21.8% and an average indirect taxation rate of 11.1%. In 2015, reduced productivity attributable to DME resulted in $382.4 million of lost potential tax revenue.

Administration of the taxation system costs around 1.25% of revenue raised (derived from total amounts spent and revenue raised in 2000-01, relative to Australian Government department running costs). These distortionary impacts of taxes on workers' work and consumption choices have been estimated to be 27.5% for each tax dollar collected (Lattimore, 1997 and used in Productivity Commission, 2003:6.15-6.16, with rationale). Altogether, the DWL is 28.75% of the value of the taxation forgone.

In 2015, around $60.03 million in DWL is incurred from having to raise $382.4 million of foregone taxation due to lost productivity from people with DME.

4.3.4.2 Welfare and income support payments

Centrelink data by special request shows that there were 12,623 recipients of Disability Support Pension (DSP) who were considered ”blind”. The average payment for DSP, weighted by number of single and coupled recipients, was found to be $18,802. In Australia, “blind” is commonly defined as having visual acuity of 3/60 to 6/60 (see Table 2.3 for conversion). It is uncertain how many of these welfare recipients had DME because the data did not specify the cause of blindness. An indirect estimation method would require ascertaining all other possible causes of blindness in Australia, including glaucoma, macular degeneration, cataracts and congenital causes. To be conservative, this study did not attribute any of these costs to DME.

4.3.5 Summary of indirect costs

Table 4.3 presents the total financial costs of vision loss from DME, other than health system costs. A significant proportion of these is related to the productivity losses associated with DME.

Table 4.3: Summary of indirect economic costs associated with DME in 2015

Cost items	Total costs ($million)
Productivity costs	
Productivity losses due to lower employment	$553.42 million
Absenteeism	$4.38 million
Premature deaths	$12.18 million
Search and hiring costs	$0.02 million
Aids and modifications	$0.37 million
Deadweight loss	$53.93 million
Total other financial costs	$624.30 million

Source: Deloitte Access Economics calculations.

Financial costs, other than health expenditure, associated with DME are estimated to be $624.30 million in 2015.

This study did not include the costs of informal care, lower productivity while at work (i.e. presenteeism) or welfare payments, because of a lack of robust data. The estimate for other financial costs is thus likely to be an underestimate.

4.4 Loss of wellbeing from DME

DME imposes a burden that extends beyond health care systems and broader economic costs. A person with DME will experience a lower quality of life due to morbidities such as vision loss, and premature mortality because of visual impairments.

The 'Burden of Disease' methodology developed by the World Health Organization (WHO), World Bank and Harvard University provides a comprehensive measure of mortality and disability from diseases, injuries and risk factors for populations around the world, first completed in 1990, with projections to 2020 (Murray and Lopez 1996). It uses a non-financial approach, where pain, suffering and premature mortality are measured in terms of Disability Adjusted Life Years (DALYs).

DALYs are a measurement unit that quantify the morbidity aspect as well as the premature death associated with various diseases and injuries (Murray and Acharya 1997). DALY weights are measured on a scale of zero to one, where a zero represents a year of perfect health and a one represents death. Other health states that result from specific diseases or injuries are given a weight between zero and one to reflect the quality of life that is lost due to a particular condition. A disability weight of, for example, 0.195 for people with blindness, is interpreted as a 19.5% loss in the quality of life relative to perfect health. The disability weights are pre-agreed on by a reference group convened at the WHO based on a person trade-off method for measuring health state preferences (Murray and Acharya 1997).

Under the DALY framework, the total burden of disease for an individual with a condition is the sum of the mortality and morbidity components associated with that condition, and includes the years of healthy life lost due to disability (YLDs) and the years of life lost due to premature death (YLL). Aggregating the DALYs of all people with a particular condition produces the total burden of that disease on society.

Table 4.4 presents the disability weights associated with vision loss from various eye conditions, estimated for the Australian burden of disease study and the global burden of disease studies (GBD) 2010. The values range from 0.004 for mild vision loss to 0.266 in severe glaucoma related vision loss. **The disability weight used to measure the additional morbidity burden associated with DME-related vision loss was assumed to equal 0.1275** – the mid-point between the disability weights for vision loss from "other causes" used in the 2003 Australian study. The model assumed that the person with DME-related VI would experience poor vision for the entire year. YLDs associated with DME are estimated as 5,787 DALYs in Australia in 2015.

Table 4.4: Disability weights for vision loss used in 2003 Australian and Indigenous burden of disease studies and global burden of disease studies 2010

2003 Australian weight	GBD 2010 weight
0.266 severe, glaucoma related	0.004 mild
0.228-0.246 macular degeneration	0.033 moderate
0.103-0.136 severe, cataract-related	0.191 severe
0.09-0.24 other causes	0.195 blindness

Source: AIHW 2014b

As outlined in section 4.3.1.4, if all DME patients never experienced VI, 218 deaths among individuals with DME could be avoided. The number of YLLs due to these deaths was estimated for each age-gender group determined via Standard Life Expectancy Table. Applying a discount rate of 3%, the total YLL were estimated to be 1,933 DALYs in 2011-12.

Total DALYs associated with DME is estimated to be 7,720 years in 2015.

The DALY approach is not financial, and thus not directly comparable with monetary costs and benefits associated with a particular condition. In order to make comparisons, a monetary conversion of the loss in healthy life is usually performed. This allows the determination of the total cost of a condition and the comparison of this cost to the benefit from a particular health intervention. The monetary conversion involves applying the value of a statistical life year (VSLY) in perfect health to the total number of DALYs estimated for a particular condition. The VSLY essentially estimates how much society is willing to pay to reduce the risk of premature death, expressed in terms of saving a statistical life year.

Various studies have ascertained VSL and VSLY in different countries (e.g. Viscusi et al, 2011; Access Economics 2008) and the estimated values are dependent on factors such as individual age, income, immigrant status, and the nature of the risk exposure. In Australia, the Office of Best Practice Regulation has provided an estimate of the VSLY of $151,000 in 2007 dollars (Department of Finance and Deregulation, 2007). This corresponds to $187,235 in 2015 value, after accounting for inflation.

Using this estimated VSLY, the total monetary value of the burden of disease of 7,720 DALYs amounts to $1,445.5 million in 2015. It is important to note that this is not a direct cost to the economy in the traditional sense (i.e. that impacts gross domestic product); it is the social value of a loss in the stock of health capital.

4.5 Summary

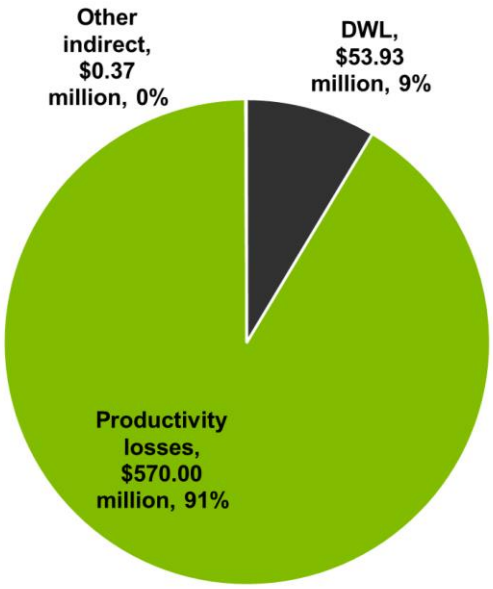
In 2015, the total cost of vision loss associated with DME was estimated to be $2.07 billion, which corresponds to $28,729 per person.

Table 4.5 summarises the total estimated indirect economic costs of DME in Australia. A large part of this estimated cost was related to the loss of wellbeing associated with DME and productivity losses associated with VI resulting from DME in individuals of working age.

Table 4.5: Summary of estimated indirect economic costs of DME in Australia

Cost type	Total cost
Total indirect costs (a)	**$624.30 million**
Productivity losses	$570.0 million
Other indirect	$0.37 million
DWL	$53.93 million
Loss of wellbeing (b)	$1,445.5 million
Total indirect economic cost (a) + (b)	**$2,069.80 million**

Distribution of indirect financial costs only



NOTE: Productivity losses: lower workforce participation, absenteeism from paid and unpaid work, and premature deaths associated with visual impairment among people with DME. **DWLs:** deadweight losses associated with the inefficiency of transfer costs (e.g. raising taxes to pay for public services).

- The estimate may have understated the true economic impact of DME. Because of a lack of robust data, this study did not include the costs associated with:
  - informal care;
  - lower productivity while at work (i.e. presenteeism); and
  - welfare payments (while these are transfers, they have associated deadweight loss).
- Because of a lack of data specific to DME, this study did not include an estimate of direct healthcare costs.

5 Screening and treatment of DME

This chapter discusses current state of screening for DR in Australia and the type and evidence of treatment for DME. It also examines the potential benefits of improving the uptake of screening for DR, and offering anti-VEGF treatments to patients with DME.

5.1 Screening of DR and DME detection

5.1.1 Screening guidelines

As with prevention of other diseases, early detection is an important part of the overall strategy to lessen the disease and economic burden of DR and DME, particularly since effective treatments are available to slow disease progression and visual impairment. In Australia, the National Health and Medical Research Council (NHMRC) and Optometrists Association of Australia (OAA)[14] have published guidelines in relation to the screening and management of DR and maculopathy (NHMRC 2008, OAA 2014).

Both guidelines recommend a multidisciplinary approach in the screening and management of DR involving optometrists, general practitioners, ophthalmologists and the patient's diabetes management team. The recommendations on the method and frequency of screening are broadly consistent:

- **Method of screening and diagnostic investigation**
  - dilated ophthalmoscopy or slit lamp biomicroscopy with suitable lens; or
  - in the absence of a dilated fundus examination, non-mydriatic or mydriatic photography with adequate sensitivity, specificity and low technical failure rate**;**
  - DME is best assessed using fundoscopy with slit lamp biomicroscopy with pupil dilation, grading stereoscopic macular photographs or OCT; and
  - performing fluorescein angiography.
- **Frequencies of screening**
  - **Children with pre-pubertal diabetes**: at puberty;
  - **People with diabetes without DR or other risk factors**: at least every 2 years;
  - **People with higher risk[15] but without DR**: at least every year;
  - **With NPDR:** every 3 to 6 months depending on the DR level; and
  - **With unexplained fall in visual acuity or suspected DME**: refer to an ophthalmologist urgently within 4 weeks.

Recent technology advancement has also allowed **screening using digital photography or telemedicines** to reach remote communities, instead of the standard slit-lamp fundus examination. For example, Ku et al (2013) demonstrated that screening for DR using single-field dilated fundus photography in an Indigenous population met the NHMRC's minimum screening requirements, with adequate sensitivities, specificities and repeatability for DR

[14] Now known as Optometry Australia.
[15] Longer duration of diabetes, poor glycaemic, blood pressure or blood lipid control

detection and referral assessment. However, future research would need to investigate the use of conveniently portable OCT to improve CSME screening and reduce false-negatives.

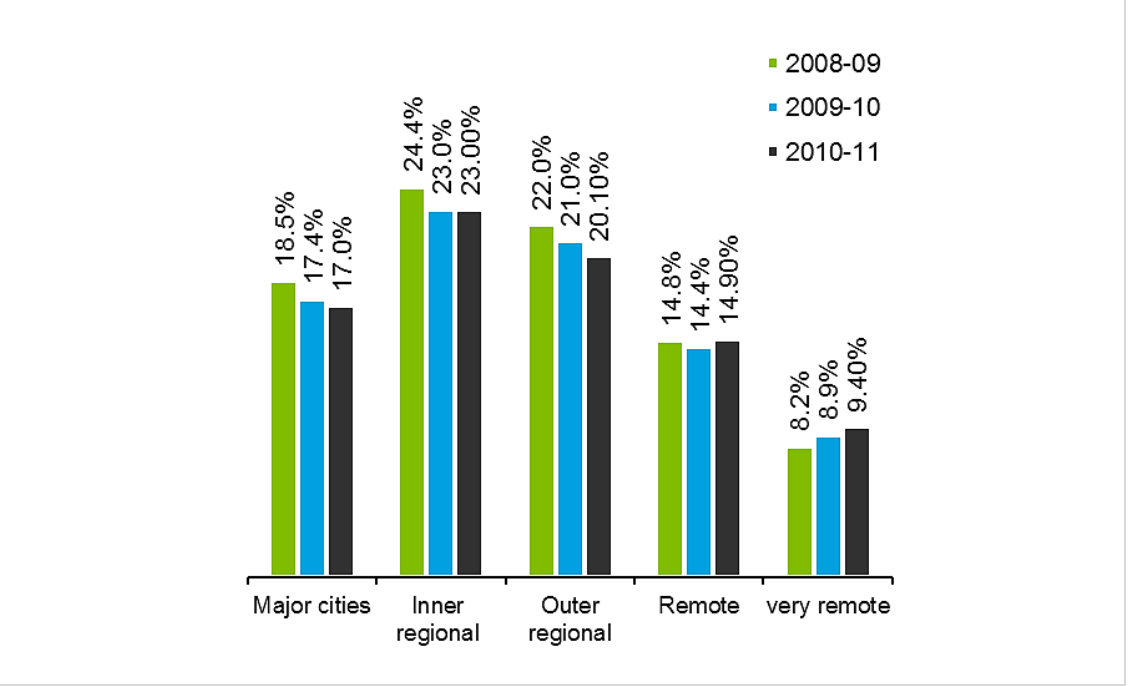
5.1.2 Implementation of screening and effectiveness

In Australia, ophthalmologists and optometrists provide most publicly funded DR screening. In the year to June 2014, Medicare Statistics[16] recorded 190,213 consultations claimed against MBS item 10915[17] for examination of the eyes in diabetes patients by optometrists.

Some of these services were provided as part of the general practice based DR screening, integrated into the Diabetes Annual Cycle of Care of the Commonwealth Government Practice Incentive Programs for diabetes management. In 2012-13, one in four Australians with diabetes had Medicare claims for a completed annual cycle of care (Productivity Commission, 2014), and one of the compulsory components is to carry out a comprehensive eye examination. It is worth noting that the overall screening rates reported for 2008-09 (19.9%), 2009-10 (18.9%) and 2010-11 (18.6%) and by region were much lower than 25% (Chart 5.1).

> Whilst there appears to be an improvement over recent years, the overall screening rate remains suboptimal.

Chart 5.1: Proportion of people with diabetes who had a GP annual cycle of care by region



Source: Productivity Commission (2014) Table 11A.56

[16] medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp

[17] Item 10915: Professional attendance of more than 15 minutes duration, being the first in a course of attention involving the examination of the eyes, with the instillation of a mydriatic, of a patient with diabetes mellitus requiring comprehensive reassessment.

In addition to medical services provided via the Medicare Benefits Scheme, a review by Tapp et al (2015) identified 14 retinal photography screening programs for DR in Australia implemented in a range of settings: urban population, rural and remote communities, regional areas, pathology collection centres, prison, mobile units with or without use of telecommunication technologies (Table 5.2, p.43). Except for the Eye Health Coordinators program that is still ongoing, all other projects were time-limited research projects that aimed to evaluate the feasibility and effectiveness of different screening programs, particularly in rural and remote Australia. The review found that these programs were highly effective (Tapp et al, 2015).

Table 5.1 outlines the estimated diagnostic accuracy of various methods for DR. Evidence suggests that the ability to detect and stage DR among health professionals is significantly variable and that accuracy of diagnosis improves with appropriate education.

Table 5.1: Diagnostic accuracy of DR screening method

Screening method	Sensitivity	Specificity
Slit lamp biomicroscopy after pupil dilation	87.4%	94.9%
Direct and indirect ophthalmoscopy	45%-98%	62%-100%
Mydriatic retinal photography	73%-96%	68%-99%
Non-mydriatic retinal photography†	25%-78%	90%-100%

Note: † CSME may be difficult to detect when few exudates are present. Test accuracy is highly dependent on the severity of DR, with sensitivity as low as 25% for patient with PDR and 78% for DR needing referral.
Source: Mitchell et al (2008)

There is evidence from other countries that implementing a nationwide DR screening program reduces the risk of vision loss among people with diabetes. For example, nationwide DR screening programs in England and Wales that offer annual eye examinations for DR for all people with type 1 and type 2 diabetes over the age of 12 years have been found to be a key factor in reducing vision loss. In an analysis of the national database of blindness certificates of vision impairment, Liew and colleagues (2014) found that “For the first time in at least five decades, diabetic retinopathy/maculopathy is no longer the leading cause of certifiable blindness among working age adults in England and Wales, having been overtaken by inherited retinal disorders”. The authors attributed the positive observation to factors such as the implementation of the national programs and improved glycaemic control.

Other countries that have implemented national diabetic retinopathy screening programs include Denmark, Sweden, Iceland, Scotland, Wales and Northern Ireland while many others have large regional programs with high uptake.

DR screening in England and Wales

A national screening programme for diabetic retinopathy in England was announced in 2003, and implemented between 2003 and 2008. Screening is now offered to all people aged over 12 with type 1 or type 2 diabetes. In 2011-12, over 2.58 million people were identified with diabetes in the UK. Of these people with diabetes, 2.36 million were offered screening and 1.91 million received screening - an uptake of 81%. Before the implementation of the programme, less than half of all people with diabetes received regular testing for retinopathy. It has been estimated that the sight of over 400 people is saved each year because of the screening programme. Indeed, the programme has been so successful that DR is no longer the leading cause of vision loss and blindness in working aged people in England.

Source: http://diabeticeye.screening.nhs.uk/statistics [accessed April 2015]

Table 5.2: Summary of Australian projects that assessed the effectiveness of DR screening programs

Project (First author)	Location	Timeframe	Key outcomes
Mobile DR screening (Karagiannis)	South Australia	1996	Of 47 subjects who attended, 77% had interpretable images
Community DR screening 2 year follow up (Lee)	Victoria	1996-1998	Screening program for people with diabetes able to increase compliance with guidelines
Community DR screening (Centre for Eye Research Australia)	Victoria	1996-2000	None of the participants in the study had previously accessed eye care services on a regular basis, 87% did so after attending screening.
DR screening in rural Victoria (Harper)	Victoria	1998	48% of those who attended the service could not recall a dilated fundus examination in the past 2 years.
DR screening via pathology services (Larizza)	Victoria	2009-2010	Of 289 patients with diabetes who came through the service, 34.3% had not had recommended DR screening; 93.9% (n = 93) of those accepted a screening service. Median photography time was 6 minutes.
Eye Health Coordinators Project (Barry)	5 regions, Western Australia	1998 to date	The state-wide screening program was implemented in 2004. Of those with known diabetes, 58% were regularly screened, surpassing programs in less remote areas.
Regional DR screening program (Murray)	Kimberley region, Western Australia	1999-2004	Screening for DR by Aboriginal health workers can be successfully sustained with regional support.
DR screening in the Kimberley (Mak)	Kimberley region, Western Australia	2000-2001	DR screening in remote Australia is comparable to, or higher than, other urban or rural populations.
Prison DR screening: telemedicines (Barry)	Western Australia	2001	Telemedicine DR screening of inmates reduced travel time and was deemed successful.
DR screening telemedicines (Barry)	Gascoyne, Western Australia	2004	36% of patients required follow-up, 3% had treatment at the remote site and 3% were transferred to Perth.
DR screening: Pilbara Western Desert (Barry)	Pilbara, Western Australia	2005-2006	15.6% of those presenting for DR screening had DR; Outlined technical and practical difficulties.
Telepaediatrics DR screening (Stillman)	Regional hospitals in Queensland	2004	Study demonstrated feasibility of a screening service for DR using a portable digital retinal camera
Pilot DR screening in general practice (Askew)	Queensland	2007-2008	General practice-based DR screening was feasible and acceptable, but photographic quality was an issue.
DR screening in indigenous primary care (Spurling)	Inala, Queensland	2007-2009	Appropriate screening and ophthalmic follow-up increased 6-fold, following the introduction of the retinal camera.

Source: adopted from Tapp et al (2015) Table 1

5.1.3 Challenges of DR screening services in Australia

Despite multiple services offering DR screening services with established efficacy in Australia, current screening for DR and DME has various challenges, including:

- **Low awareness and screening rate, and constrained time and resources in general practice**

  Tapp et al (2015) found that a median of 48% (range 16-85) of people with diabetes who participated in screening programs had not undergone a retinal examination within the recommended timeframe. This estimate is in line with the low utilisation of the Government funded Diabetes Annual Cycle of Care. This may reflect a low awareness about ocular effects of diabetes among the population with diabetes and the general population. In a survey of 2,000 rural and urban GPs across Australia in 2007-2008, 74% of GPs indicated that they did not routinely examine the eyes of their patients with diabetes, instead referring them to an ophthalmologist for assessment (Ting et al, 2011). The low screening rate is in part explicable by the lack of time in general practices. Furthermore, many GPs do not have the equipment required for undertaking screening. There is a short supply of ophthalmology services leading to long waiting times (Health Workforce Australia 2012).

Susan's story

"*I just wish that I had been more aware of the risk of vision loss from diabetes and had my eyes tested – it could have helped save my sight*," – Susan, living with vision impairment due to DME.

Susan was diagnosed with type 2 diabetes at age 60 years. Even though she had a family history of diabetes, she was surprised when she was told she had developed the chronic condition following a hospital admission due to a heavily swollen foot. At that time, her vision started to deteriorate rapidly, but she was not aware that this was related to her diabetes.

After discharge from hospital, Susan was referred to a diabetes specialist who helped her manage her condition. The specialist recommended regular eye tests as part of Susan's treatment plan. On her first visit to an optometrist, she was immediately referred on to an ophthalmologist and treatment for DME commenced.

Since then, Susan has had laser treatment, injections, eye surgery, but has never regained her full vision.

Susan wishes that she had known about the risk of diabetes related vision loss earlier and had regular eye tests.

Susan now volunteers at the Macular Disease Foundation Australia where she gets enormous satisfaction by helping the Foundation, help people like her living with DME.

Source: provided by Macular Disease Foundation Australia

- **Skills and confidence**

  Several commentators and researchers have highlighted the low number of gradable photographs (Ng and Morlet 2013; Askew et al, 2009; Ku et al, 2013). For example, in the study by Askew et al (2009), participating ophthalmologists only deemed 61% of the photographs taken by two GPs as interpretable.

- **Service coordination**

  A number of health professionals are involved in the provision of care for patients with DR and DME, particularly with novel models of services (e.g. at pathology service collection points). Some researchers have suggested promoting a closer relationship between GPs and optometrists in recognition of the central role of optometrists in the delivery of primary eye health care, to encourage more referrals to optometrists rather than solely to ophthalmologists (Jamous et al, 2014). Robust communication is required between screening services, optometrists, GPs and ophthalmologists, especially when there is no centralised system in Australia to monitor screening compliance and outcomes, as in the UK (Scanlon 2008).

- **Lack of reimbursement for OCT**

  A separate issue is the lack of reimbursement for OCT. As noted in Sections 2.2 and 5.1.1, OCT is one of the methods for the assessing and monitoring the severity of DME. However, the Medical Services Advisory Committee (MSAC) rejected a submission for seeking reimbursement for OCT in Australia for patients with DME (MSAC 2013). This means that patients would need to incur out-of-pocket costs for the test when their ophthalmologists or optometrists require information from OCT to inform diagnosis and treatment decisions and to monitor treatment response.

In summary, ophthalmologists and optometrists provide most publicly funded DR screening in Australia. In addition, there are multiple services in Australia offering DR screening services in a range of settings, including mobile units and pathology collection centres. There is significant variability in diagnostic accuracy of screening methods.

Whilst there appears to be an improvement over recent years, the overall screening rate remains suboptimal. The suboptimal screening rate is a result of a combination of factors, including lack of time and resources, lack of skills and confidence, and suboptimal service coordination, as well as lack of public awareness about the ocular effect of diabetes.

5.2 Treatments for DME

Over the past decades, there have been significant advances in the characterisation and management of diabetes mellitus, DR and DME. These include better detection, glycaemic control, surgical procedures, and the discovery of innovative medicines.

5.2.1 Medical management of risk factors

As noted in Section 2.4, a range of modifiable risk factors can have an influence on the development and progression of DR and DME. These include hyperglycaemia, and hypertension and dyslipidaemia. For this reason, optimal medical management of these risk factors should be part of the holistic approach to hindering disease progression. Fenofibrate is now approved in Australia for "the reduction in the progression of DR in patients with type 2 diabetes and existing DR" (Australian Register of Therapeutic Goods ARTG, 2015). However, fenofibrate "does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of DR" (ARTG 2015). An overview of the management of these risk factors is beyond the scope of this report.

5.2.2 Laser therapy

The first treatment with established efficacy for DME management was focal or grid laser photocoagulation. Focal laser photocoagulation involves applying light, small-sized burns to areas of leaking micro-aneurysms and thickening within the macula, with a view to stabilising visual acuity. The ETDRS demonstrated that at three years, treatment halved the risk of moderate visual loss significantly (RR=0.50, 95% CI: 0.47-0.53), and the benefits were most marked in eyes with centrally involved or imminently threatened CSME (Table 5.3). However, few patients experienced significant improvement in visual function, and when improvement did occur, it tended to occur slowly. Focal laser photocoagulation is currently considered the preferred treatment for patients with DME that does not involve the centre of the macula. Patients with DME may also receive pan-retinal laser photocoagulation if they have proliferative DR.

Table 5.3: Randomised controlled trials of laser treatment for DME

Study	Sample size	DME severity	Intervention	Findings
ETDRS 1985	2,244	Bilateral DME (mild-to-moderate NPDR)	Focal argon laser (754 eyes) vs. Observation (1490 eyes)	At three years, treatment reduced moderate visual loss (RR 0.50, 95% CI 0.47-0.53). Benefits most marked in eyes with CSME, particularly if the centre of the macula was involved or imminently threatened.
DRCR network Fong 2007	323	DME No previous treatment	Modified ETDRS laser (162 eyes) vs. mild grid laser (161 eyes)	At one year, no significant difference in OCT central macular thickness or visual acuity (Treatment reduced CMT by 88µm in the modified ETDRS group vs. 49µm in the mild macular grid laser group, p=0.04)

Study	Sample size	DME severity	Intervention	Findings
Olk 1986	92	Diffuse DME ± CSME	Modified grid argon laser vs. observation	Treatment reduced the risk of moderate visual loss 50-70% at 2 yrs. VA loss reduced compared with no treatment at one year (RR 0.84) & at 2 yrs (RR=0.78, CI 0.60- 0.96)
Author unknown 1975	76	Bilateral symmetrical DME	Xenon-arc laser vs. observation	At three years, 8 treated vs. 18 control eyes blind. Prognosis was best in those with initial VA ≥ 6/24

Source: adapted from Mitchell et al (2008)

In the 12 months to June 2014, there were 38,791 retinal photocoagulation procedures, including focal and pan-retinal photocoagulation, undertaken in Australia (Medicare item 42809). Some of these procedures would have been performed for people with DME, although the exact proportion is not reported in publicly available data.

5.2.3 Vitrectomy

Vitrectomy is a surgical procedure that involves the removal of the clear gel in the space between the lens and the retina (i.e. the vitreous humour), as well as any blood if present. This procedure is generally required in more severe cases of PDR. The NHMRC guidelines for the management of DR (Mitchell 1998) noted that most common indications for diabetic vitrectomy are:

- severe non-clearing vitreous bleeding;
- traction retinal detachment recently involving the macula;
- combined traction and rhegmatogenous detachment;
- progressive fibrovascular proliferation; and
- rubeosis iridis and vitreous haemorrhage, with opacity preventing adequate laser.

There are a few studies demonstrating the potential efficacy of vitrectomy in managing cases of chronic or diffuse DME, which are non-responsive to laser therapy, particularly if there is a mechanical tractional element. However, the quality of evidence from these studies is limited by relatively small sample size, short follow-up period, and inconsistent results (Table 5.4).

Table 5.4: Randomised controlled trials of vitrectomy for DME

First author	Sample size	DME severity	Intervention	Findings at 1 year follow-up
Yanyali 2006	20 eyes of 10 patients	Bilateral DME unresponsive to grid laser photocoagulation	Vitrectomy with removal of the internal limiting membrane (ILM) randomly in one eye	Surgery reduced central macular thickness (CMT) by 165.8 ± 114.8µm vs. 37.8 ± 71.2µm in untreated eye (p=0.016). Vitrectomy increased VA by ≥2 lines in 4 (40%) vs. 1 (10%) – not significant
Thomas 2005	40 eyes	DME (VA≤6/12) unresponsive to laser with no associated traction	Vitrectomy + ILM peel vs. further macular laser.	Vitrectomy reduced CMT by 73µm (20%) vs. 29µm (10.7%). Vitrectomy reduced mean BCVA by 0.05 logMAR vs. increased by 0.03 logMAR in controls -- not significant

First author	Sample size	DME severity	Intervention	Findings at 1 year follow-up
Dhingra 2005	20 eyes of 20 patients	DME (VA≤6/12) unresponsive to laser with no associated traction	Vitrectomy + ILM peel vs. observation	Vitrectomy decreased mean CMT (250.6 ± 56.8µm vs. 450 ± 40µm controls). No significant change in logMAR VA
Bahadir 2005	58 eyes of 49 patients	DME (VA≤6/12) unresponsive to laser with no associated traction	Vitrectomy + ILM peel (17 eyes) vs. vitrectomy without ILM peel (41 eyes)	No significant difference between groups in VA outcome. VA increased in both groups (0.391 ± 0.335 in Vitrectomy/ILM and 0.393 ± 0.273 logMAR, p>0.01)

Source: adapted from Mitchell et al (2008)

5.2.4 Anti-VEGF therapy

As explained in Section 2.1, the increased VEGF levels in DR are a potent stimulus for abnormal growth of new blood vessels and vascular permeability that causes leakage of fluid into the retinal tissue. Anti-VEGF medicines block the effects of VEGF and slow the vision loss linked to AMD and DME.

A number of pivotal trials have demonstrated the efficacy and safety profile of these medicines. A recent Cochrane review confirmed the efficacy and safety profile of anti-VEGF treatments in patients with DME (Virgili et al, 2014). This review included 18 randomised controlled trials that involved participants with central DME and moderate vision loss. It found clear evidence that anti-VEGF medicines provide a benefit compared to grid laser photocoagulation in clinical trial populations at one or two years. Key findings from this review include:

- quality of the evidence was judged to be high, because the effect was large, precisely measured and did not vary across studies;
- people treated with anti-VEGF were more likely to gain ≥3 lines of vision at one year (RR=3.6, 95% CI: 2.7-4.8) compared to people who received grid laser photocoagulation;
- people treated with anti-VEGF were less likely to lose ≥3 lines of vision at one year (RR=0.11, 95% CI: 0.05-0.24) compared to people who received grid laser photocoagulation;
- an estimated 28% of participants with DME may gain ≥3 lines of vision with anti-VEGF therapy compared to 8% of participants using photocoagulation. This means that for every 100 participants treated with anti-VEGF, 20 additional people (95% CI: 13-29) will markedly improve their vision after one year; and
- on average, people treated with anti-VEGF had 1.6 lines better vision (95% CI: 1.4 to 1.8) after one year compared to laser photocoagulation. To achieve this result, patients received 7-9 injections in the first year and 3-4 injections in the second, with larger studies adopting either as-needed regimens with monthly monitoring or fixed regimens.

In addition, there is now an effectiveness comparative trial of the VEGF therapies for DME, which has been sponsored, conducted and recently published by the Diabetic Retinopathy Clinical Research Network (DRCRnet 2015). Six hundred and sixty adults with DME were

randomly assigned to three anti-VEGF therapies at 89 clinical sites. The study drugs were administered as often as every 4 weeks, according to a protocol-specified algorithm and the primary outcome was the mean change in visual acuity at 1 year.

5.2.5 Other drug treatments

This report only includes treatments approved for use in DME by the Therapeutic Goods Administration (TGA) in Australia. The authors acknowledge there are other pharmacological therapies sometimes used to treat patients with DME in clinical practice. One of these products is an oncology product intended for intravenous use. This treatment is 'off label' in Australia and in other countries. 'Off label' in this context means the TGA and other regulatory agencies have not approved the treatment for ophthalmic use, nor is it formulated or manufactured for this use. No regulatory authority in the world has established the safety and efficacy profile of this product for intraocular injection. Corticosteroids are also not approved by the TGA for use in DME and are therefore used off-label in Australia. Some overseas regulatory authorities, however, have evaluated their safety and efficacy in DME and therefore have approved their use in this condition.

5.3 Potential benefits from screening for, and treatment of, DME

In view of the benefits of screening patients with diabetes for DR and DME, and the established efficacy and safety profile of anti-VEGF treatments, this section presents a concise assessment of the potential economic benefits of two potential changes to the current provision of services:

- increasing screening coverage in patients with diabetes, while providing treatment for those confirmed to have vision-impairing DME; and
- providing treatment to people with known vision-impairing DME in Australia.

Please note that this modelling study did not model the benefits of screening program in detecting early stages of DR. Early detection of DR would allow preventative measures to avoid or delay subsequent occurrence of DME.

5.3.1 Existing literature on cost effectiveness of laser treatment and vitrectomy in Australia

There is limited information publicly available on the cost effectiveness of laser treatment and vitrectomy in Australia. A targeted review of the literature identified several cost-effectiveness studies from other countries, although the findings across the studies are not consistent.

A recent modelling study comparing the cost effectiveness of treatment of clinically significant DME in the United States showed that laser therapy alone was more costly and

less effective over a patient's lifetime in comparison with anti-VEGF treatment options[18] (Pershing et al, 2014, Figure 2). The modelling showed that lifetime costs and quality-of-life-adjusted survival of patients receiving laser therapy alone were similar to those who received no treatment (Pershing et al, 2014; Figure 2). In contrast, an older modelling study by Sharma et al (2000) showed that grid laser was associated with a relatively low cost per QALY gained (over no laser) of US$3,655 over an extended 40-year time horizon. The inconsistency in the findings of cost-effectiveness studies of laser in DME partly reflects the different analytical and modelling approaches applied in those studies.

International evidence has found early vitrectomy to be a cost-effective treatment of vitreous haemorrhage in DR. The study by Smiddy (2011) reported vitrectomy to cost around one-fifth of the cost of ranibizumab, but saved a similar number of lines of vision, in one year. However, no formal cost-effectiveness of vitrectomy versus another treatment was reported. A modelling study in the U.S. by Sharma and colleagues (2001) concluded that early vitrectomy after vitreous haemorrhage in patients with DR was highly cost effective over a lifetime horizon. The authors noted that "even at the extreme sensitivity values, the cost per QALY of early vitrectomy treatment remained under [US]$10,000" (p.230).

Due to the inconsistencies of the methods and findings in the available literature on the cost effectiveness of laser treatment and vitrectomy in DR and DME, these treatments have not been further analysed in this report.

5.3.2 Increase screening coverage in patients with diabetes

As found by Tapp et al (2015), a median of 48% (range 16-85) of individuals with diabetes mellitus in rural and urban Australia had not undergone retinal examination within the recommended timeframe. This suggests that, of the 1.73 million people with diabetes in 2015 in Australia, an estimated 830,000 people may not currently undertake retinal examinations as recommended by the NHMRC guidelines. A subset of these people might have DME and could have received effective management if detected earlier through routine screening, rather than being detected at a later time-point, possibly with more severe diabetic eye disease and often a worse treatment outcome.

5.3.2.1 Method

A decision-analytic model was constructed to evaluate the benefits of increasing screening coverage to this group of the population with diabetes, compared to the current practice. The model first evaluated the additional number of people that would be screened if 10%, 25%, 50% and 100% of the modelled population were screened. It then assessed the probability of DME in the screened population, and the proportion that would be detected according to the sensitivity and specificity of screening procedures. The model then assessed the likelihood of treatment among people with confirmed DME. Finally, by applying the efficacy of anti-VEGF medicines in improving VA and preventing VA loss, the

[18] The anti-VEGF options considered in the Pershing et al 2014 modelling study included off label pharmacological therapies. The findings of this modelling study are therefore not directly applicable in the context of this report.

model assessed the potential savings in economic costs associated with the improved coverage.

Table 5.5 lists the model parameters. It is worth noting that the estimated prevalence of DME among the screened population is based on a conservative assumption that people with more severe form of DME would self-refer for medical care rather than present for screening. For this reason, the prevalence of DME is assumed to be lower than the estimated prevalence across the entire population (i.e. 4.2%), which includes people with DME of all severity. The estimate was based on the data provided by Thomas et al (2012) on the prevalence of maculopathy with background DR detected among the 91,393 people with type 1 and type 2 diabetes who attended community based National Diabetic Retinopathy Screening Service for Wales from 2005 to 2009.

Table 5.5: Model parameters

Parameter	Value (range)	Source
DME prevalence in the screened population*	1.51% (1.4%-4.2%)	Thomas et al, 2015
Sensitivity of screening procedure	73.3% (59.5%-72.6%)	Prescott et al, 2014
Specificity of screening procedure	70.9% (66.8%-79.0%)	Prescott et al, 2014
Post screening treatment rate	87.0% (33.0%-93.0%)	Tapp et al, 2015
Percentage of people receiving anti-VEGF	65%	Assumed[19]
Treated | Gaining VA ≥3 lines at 1 year	27.6% (20.7%-36.8%)	Virgili et al, 2014
Treated | Losing VA ≥3 lines at 1 year	1.3% (0.6%-2.8%)	Virgili et al, 2014
Not treated | Gaining VA ≥3 lines at 1 year	0.8% (not reported)	Virgili et al, 2014
Not treated | Losing VA ≥3 lines at 1 year	11.5% (not reported)	Virgili et al, 2014
Non-health system cost per DME case	$8,755	Estimate from Chapter 4
Non-health system cost per DME case with lost wellbeing	$28,729	Estimate from Chapter 4
Changes in disability weight due to improved VA and preventing VA lost	0.17	See Table 4.4

*The prevalence of DME among the screened population is conservatively lower than the overall population prevalence, on the assumption that people with more severe forms of DME would self-refer for medical care rather than present for screening.

In assessing the potential benefits of expanding screening, the model made a number of assumptions:

- The benefits and costs related to eye diseases other than DME (e.g. glaucoma) detected through screening were not included in the assessment;
- False positive cases would be ruled out following referral to an ophthalmologist and would therefore not receive subsequent treatment;
- All patients would receive anti-VEGF treatment and not laser coagulation;
- The healthcare costs after screening may increase after screening because treatment would be offered to patients. However, improvement in vision or reduction in the

[19] 65% is assumed as the maximum to account for clinical eligibility and access to services etc.

probability of vision loss may offset the increase in healthcare costs. Given the level of uncertainty, the findings were presented without incorporating healthcare costs.

- The model examined the potential benefits within one year and did not model the altered population profile of disease progression from early detection through screening.

5.3.2.2 Findings

The model found that screening 10% of people with diabetes not currently undertaking retinal examination would identify 918 new cases of DME. An additional 9,179 cases would be detected if retinal examination were provided to all people with diabetes not being screened (Table 5.6). Because of the relatively low estimated sensitivity and specificity of the screening process, a considerable number of people would be tested positive despite not being affected by DME (i.e. false positives) or vice versa (i.e. false negatives). While subsequent assessment by an ophthalmologist would prevent these people with false positive results from receiving further treatments, assessment of screening program costs would need to take into account the costs of consultations associated with these referrals.

Table 5.6: Summary of findings, by coverage of people not currently being screened

Screening rate / Output parameter	+10%	+25%	+50%	+100%
Number of individuals detected with DME (true positive)	+918	+2,295	+4,589	+9,179
Number of false positives	+23,785	+59,464	+118,927	+237,854
Number of people with VA improvement ≥3 lines at 1 year	+139	+348	+696	+1,393
Number of people with worsened VA	-53	-132	-265	-529
Reduction in DALYs	32	79	159	317
Savings in non-health care costs	$1.67 million	$4.16 million	$8.33 million	$16.65 million
Savings in economic costs (non-health care) + VSLY	$7.60 million	$19.01 million	$38.02 million	$76.03 million

The model found that screening of, and subsequent anti-VEGF treatment for, people with confirmed DME accessing treatment (assumed to be 65%) would improve vision in an estimated 139 to 1,393 people, while reducing the number of people with worsened VA (53-529 people). Accordingly, there are significant reductions in DALYs (32-317 years), savings in non-health care costs ($1.68-$16.83 million), and social benefits of $76.03 million. The benefits would be even greater if non-DME eye disease and future streams of benefits from early detection of DR were considered.

As demonstrated by Heraghty and Cummins (2012) in raising awareness of macular degeneration, public awareness about diabetic eye disease in general, and DME specifically, is achievable through a multi-layered approach. This approach includes education programs, national advertising and health promotion campaigns, awareness week, and mobile screening units.

5.3.3 Providing anti-VEGF treatment to people with known vision-impairing DME

Section 4.1.3 estimated that 45,400 people with DME in Australia have vision impairment in 2015. These people may be eligible for anti-VEGF treatment if the medicines were available via the PBS. Table 5.7 presents the findings of a model that assessed the scenarios where 10%, 25%, 50% or 65% of the people with known vision-impairing DME gained access to anti-VEGF treatment. The model used the same values for parameters outlined in Table 5.5, where relevant.

The model found that providing anti-VEGF treatment to eligible people with known vision-impairing DME would improve vision (3 lines or more) in 1,218-7,916 people, and in addition, prevent vision loss in up to 3,009 people. These benefits would translate into a significant reduction in the costs associated with productivity losses and other non-healthcare costs of up to $15.62 million. The benefits would also reduce lost wellbeing, avoiding up to 1,803 DALYs. In monetary terms, this corresponds to a total saving of between $54.33 million to $353.13 million.

Table 5.7: Summary of findings, by treatment coverage of people with known DME

Treatment rate Output parameter	10%	25%	50%	65%
Number of people treated	4,539	11,347	22,695	29,503
Number of people with VA improvement ≥3 lines at 1 year	+1,218	+3,044	+6,089	+7,916
Number of people with worsened VA	-463	-1,157	-2,315	-3,009
Reduction in DALYs	277	693	1,387	1,803
Savings in non-health care costs	$2.40 million	$6.01 million	$12.02 million	$15.62 million
Savings in economic costs (non-health care) + VSLY	$54.33 million	$135.82 million	$271.64 million	$353.13 million

In summary, if approximately two thirds of people with DME were eligible and be treated with anti-VEGF therapy, the savings potentially associated with improvement in vision and wellbeing would amount to $353.13 million.

5.4 Other considerations

5.4.1 Barriers to screening services and treatment

In November 2005, the Australian Health Ministers' Conference endorsed the *National Framework for Action to Promote Eye Health and Prevent Avoidable Blindness and Vision Loss* (Australian Health Ministers' Conference 2005). This document sets out five key action

areas for the promotion of eye health and the prevention of avoidable blindness in Australia:

- reducing the risk of eye disease and injury;
- increasing early detection;
- improving access to eye health care services;
- improving the systems and quality of care; and
- improving the underlying evidence base.

The discovery of intra-vitreal treatment for eye diseases, including anti-VEGF for aged related macular degeneration, central retinal vein occlusion, branch retinal vein occlusion and DME, has changed the landscape for treatment of eye disease and prevention of blindness. However, a lack of routine examination of eyes in high-risk patients, such as those with diabetes, continues to be a challenge (Ng and Morlet 2013). Section 5.1.2 outlines a number of challenges to enhancing the delivery of screening. While some of these challenges would require considerable efforts (e.g. increase awareness and service coordination), some barriers could be removed if the Government were to commit more resources to raising awareness of the importance of regular eye tests for those with diabetes and the importance of early detection (e.g. using the multilayered approach outlined by Heraghty and Cummins, 2012). Likewise, providing expeditious access to registered treatments with established efficacy, safety profile and value for money would also improve the prognosis of patients with DME and lessen the considerable economic and disease burden of DME.

5.4.2 Potential impact on the NDIS

The National Disability Insurance Scheme (NDIS) is a national scheme designed to help improve delivery and access to disability services. The aim of the initiative is to create a disability support service focusing on the individual needs and choices of people with disability, including people with disability due to visual impairment from eye diseases, such as DME.

The scheme would provide eligible people with financial support to give them greater control over decisions relating to their care. The current eligibility criteria for the NDIS include:

- **Age:** the scheme covers people aged between 0 and 65 years old.[20]
- **Disability requirement:** clients are assessed based on the impact of their disability on their functional capacity to communicate, interact socially, learn, navigate their home and manage personal care and affairs.
- **Early intervention requirement:** early intervention supports will be available to achieve a benefit that would help mitigate the effects of impairment to alleviate or prevent the deterioration of functional capacity, or strengthen informal supports.

[20] People with disability who enrolled in the NDIS before 65 years old can choose to continue to receive support from the NDIS or to be transferred to aged care system after they have turned 65. People who acquire a disability after they turn 65 will receive their supports through the Commonwealth Government's aged care system.

Currently, the NDIS is implemented at five trial sites at Barwon in Geelong, Tasmania, the Hunter region, Adelaide and Canberra. At the end of March 2014, the average package cost across the first four sites was $34,019 per participants, with a skew towards those requiring high frequency of disability support who had an average package cost of $150,000 per annum (Joint Standing Committee on the NDIS, 2014).

While further evidence is needed to quantify the efficacy of anti-VEGF therapy in preventing vision loss in the long term, it is likely that treating individuals with vision-impairing DME now would prevent or delay some cases of disability due to vision-impairment that would otherwise require support from the NDIS. Assuming 1,000 people from the 2015 cohort of people with vision-impairing DME would be saved from severe disability were they to receive treatment today, there would be at least $34 million in financial savings per year to the NDIS.

While the NDIS is still in the early phases of implementation, investment in preventing vision impairment through undertaking effective screening and providing treatment with established safety profile and efficacy now will reduce future reliance on the NDIS for support.

Appendix A: Type 1 and type 2 diabetes

Table A.1: Comparing type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Other name	Juvenile diabetes Insulin-dependent diabetes mellitus	Adult-onset diabetes Non- insulin-dependent diabetes mellitus
Typical age of onset	Usually younger than 30 years of age, but can occur at any age	Usually older than 40 years, but can occur at any age
Cause	Autoimmune response causing failure of insulin secreting beta cells in the pancreas	Impaired function of beta cells and glucose regulation
Insulin level	Low or none	Normal, decreased or increased
Onset	Quick onset generally within a few weeks or months	Slow onset over several years with gradual rise in blood sugar
Treatment	Insulin	Blood glucose lowering drugs insulin may be used

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