Retinal photography with a non-mydriatic retinal camera in people with diabetes

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Assessment report

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee that has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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This assessment examines the evidence to support listing of retinal photography with a non-mydriatic retinal camera (RP-NMRC) on the Medicare Benefits Schedule (MBS). The service would be used exclusively in primary care settings for the detection of diabetic retinopathy (DR) among patients with diabetes. The target population are people with diabetes who do not currently follow the National Health and Medical Research Council's (NHMRC's) recommendations to see an eye specialist. In Indigenous Australians this should occur every year, and every 2 years in the non-Indigenous population.

RP-NMRC

RP-NMRC is a non-invasive technique for imaging the retina and optic disc. Non-mydriatic retinal cameras use infrared light to image the retina without requiring chemical eye drops to dilate the pupils. RP-NMRC is thought to avoid the discomfort that may be associated with chemical dilation of the pupils (mydriasis), and may be performed by a technician or photographer without medical qualifications. For these reasons RP-NMRC may be preferable and/or more accessible compared with other methods used to detect DR. However, it must be emphasised that RP-NMRC is not intended to replace a comprehensive eye examination (CEE) by an optometrist or ophthalmologist. Rather, RP-NMRC is considered to be a replacement for the care that the target population is currently receiving—i.e. ophthalmoscopy with mydriasis undertaken by a GP (secondary comparator), or no eye examination (primary comparator).

Current arrangements for public reimbursement

Outside the research setting, RP-NMRC is usually provided by an ophthalmologist or optometrist, concurrent with CEE. The cost of the photography is borne by the patient. Existing MBS items for 'retinal photography'[1] relate to a distinct procedure, correctly defined as fluorescein angiography, to inform the treatment of severe DR following initial diagnosis.

[1] MBS item numbers 11215 and 11218

Health professionals in some Aboriginal Community Controlled Health Services (ACCHSs) provide RP-NMRC and screen clients in a manner that is similar to the current proposal (Murray et al. 2005).

Clinical need

Control of blood glucose, blood pressure and blood lipids in people with diabetes is considered essential for the primary prevention of DR (Schiffelers et al. 2007). Where primary prevention measures fail, detecting changes in the retina and associated structures enables early identification of DR. Monitoring is accepted as necessary for the management and/or treatment of DR once changes to the retina have occurred. If unmanaged, DR progresses through a series of changes, culminating in macular oedema and haemorrhaging of the delicate retinal microvasculature. Advanced disease results in permanent and severe loss of peripheral and central vision (AAO 2008; Curtis, Gardiner & Stitt 2009; NHMRC 2008).

The current Australian guidelines for the management of DR recommend 2-yearly vision assessments and retinal examinations of people with asymptomatic diabetes (i.e. those without visual impairment). For Indigenous Australians, the recommendation is that yearly examinations should be conducted (NHMRC 2008). Currently, only half of non-Indigenous Australians with diabetes comply with NHMRC screening guidelines (Harper et al. 1998; Taylor, H et al. 2009). Similarly, up to 44% of Indigenous Australians have not had a diabetic eye examination in the previous year (Ku et al. 2013).

Existing procedures/tests

A CEE involves visual acuity testing and an ocular fundus examination, usually through dilated pupils.

The presence or severity of DR may be assessed using slit lamp biomicroscopy (SLBM), ophthalmoscopy or retinal photography (RP) (NHMRC 2008). The handheld direct method of ophthalmoscopy is the standard in clinical use but, due to poor diagnostic accuracy, many optometrists and ophthalmologists prefer to use binocular indirect ophthalmoscopy (BIO) and SLBM. SLBM is in wide clinical use throughout optometric practices, but very few GP or diabetes clinics have access to it. More recently, retinal cameras have been developed. Non-mydriatic retinal cameras are well established in clinical practice across the UK, Scandinavia, USA and Singapore. Many clinicians in Australia, predominantly optometrists, independently

screen for DR using RP, and some public hospitals and health services use RP-NMRC to screen for DR under an ophthalmologist's supervision[2].

If a visual acuity deficit is observed, appropriate management is determined; if the patient is presenting to an optometrist or GP, they may be referred to an ophthalmologist.

Results of assessment

Safety

No studies on the comparative safety of RP-NMRC were identified. Among a case series of 75 patients who had RP-NMRC *with mydriasis*, a single case of angle-closure glaucoma was reported (Maberley et al. 2002).

A systematic review of 28 original studies found that the risk from mydriasis in the *general population* is low (Pandit & Taylor 2000). For all mydriatic agents combined, the rate of acute glaucoma was 1 in 18,020. Mydriasis may or may not be used with RP-NMRC, unlike CEE where it is always used. With regard to the comparator of no examination or ophthalmoscopy with mydriasis undertaken by a GP, RP-NMRC would appear to have a slightly elevated risk if mydriasis is used as part of the procedure. When RP-NMRC does not involve mydriasis, its use as an opportunistic screening test may reduce the safety risks associated with mydriasis in those patients who are test-negative and do not require a subsequent CEE.

RP-NMRC was found to be highly acceptable to most patients. Up to one-fifth of patients experienced some level of discomfort during the procedure, with very few experiencing severe discomfort associated with the flash on older Polaroid systems. Digital systems are associated with discomfort in less than 3% of patients (Taylor, DJ et al. 1999). One Australian study that interviewed 11 Indigenous diabetes patients found that 10 were positive towards RP-NMRC (Spurling et al. 2010).

Effectiveness

No direct evidence was identified that reported on the effectiveness of RP-NMRC. Studies that reported on diagnostic accuracy and change in management were therefore included for a synthesis of indirect evidence using the linked evidence approach.

[2] Personal communication, HESP (ophthalmologist)

Thirty-one diagnostic accuracy studies were included, of which 23 contributed data to meta-analyses to determine the overall accuracy of RP-NMRC. These studies needed to use RP-NMRC for the detection of *any DR* and *DR requiring urgent referral*. Subgroup analysis was conducted according to whether or not chemical mydriasis was used, the number of fields photographed, publication year and study sample size.

Accuracy to detect any DR

Meta-analysis was undertaken for 13 studies that compared RP-NMRC with SLBM and/or CEE to detect *any level* of DR. Unreadable images (UIs) were considered a positive result. Overall pooled results showed that RP-NMRC can accurately confirm the presence of any DR (sensitivity 91.2%, 95%CI 81.7, 96.1; positive likelihood ratio (LR+) 3.88, 95%CI 2.79, 5.40) with a trade-off in ability to *rule out* DR (specificity 76.5%, 95%CI 67.4, 83.6; negative likelihood ratio (LR–) 0.11, 95%CI 0.05, 0.24). However, it should be noted that in 7 of the studies in this analysis, the photographs were read by ophthalmologists or retinal specialists. RP-NMRC is principally being proposed for use by those with lesser training, such as GPs or other professionals in community or rural primary care settings.

For the detection of any DR by RP-NMRC, an analysis conducted according to use or non-use of mydriasis showed no appreciable difference: sensitivity 89.4% (95%CI 72.2, 96.5) versus 91.7% (95%CI 79.2, 97.0), respectively; specificity 74.2% (95%CI 63.5, 82.7) versus 74.4% (95%CI 61.2, 84.2), respectively. There was improved sensitivity with those fundus cameras that utilised multiple fields (96.6%, 95%CI 87.0, 99.2) rather than one field (82.7%, 95%CI 70.9, 90.3). Similar differences according to publication year were observed, with greater sensitivity of RP-NMRC in studies published after 2000, probably due to imaging with multiple fields as opposed to a single field.

There were no studies identified that reported on the relative accuracy of RP-NMRC versus ophthalmoscopy by a GP, with CEE as the reference standard—as specified *a priori.*

Accuracy to detect DR requiring urgent referral

In the meta-analyses for detection of severe non-proliferative diabetic retinopathy (NPDR) or worse, requiring urgent referral, UIs were regarded as a negative result as they do not constitute a need for urgent referral. The pooled findings suggest that RP-NMRC is more likely to confirm the presence of severe NPDR or worse than it is to confirm the presence of any DR (specificity 98.1%, 95%CI 95.4, 99.2 versus 76.5%, 95%CI 67.4, 83.6), but is less sensitive (76.3%, 95%CI 60.2, 87.3 versus 91.2%, 95%CI 81.7, 96.1). The HSROC curve analysis similarly showed an excellent level of detection of severe NPDR or worse by RP-NMRC (AUC = 0.96, 95%CI 0.94, 0.98), with SLBM and/or CEE as the reference standard. The mean false negative rate for NPDR was high (24%) but is not expected to have a

substantial negative impact on patient health, as the majority of false negative patients are likely to have less-severe disease, which would still result in referral to an ophthalmologist. Similarly, the low false positive rate (2%) is not expected to be of clinical consequence in terms of patients' eye health.

As in the detection of any level of DR, mydriasis *did not* improve the detection of DR requiring urgent referral. In the subgroup analysis by number of fields, wide confidence intervals (CIs) preclude any meaningful conclusions.

In contrast to the detection of *any* DR, there was no threshold effect for the detection of DR requiring urgent referral based on number of fields. This is potentially because advanced DR should be more readily detected with single-field photography than early disease, where small changes may not be present in all photographed fields.

Change in management

Evidence was sought on whether RP-NMRC has the potential to increase rates of referral to CEE and whether it increases compliance with these referrals. The body of evidence reported on outcomes such as attendance at screening, rates of compliance with recommended screening, rates of compliance with recommended follow-up ophthalmological appointments, and referral rates for follow-up and management.

Compared with a traditional eye health surveillance model (self-organised CEE), opportunistic RP-NMRC in a primary healthcare setting was found to result in significantly greater compliance across the three studies included for this comparison (Leiner et al. 2009; Mansberger et al. 2013; Spurling et al. 2010) (OR 1.21, 95%CI 1.08, 1.35; OR 12.3, 95%CI 7.20, 20.9; OR 86.8, 95%CI 36.8, 204.9, respectively). As the RP-NMRC screening was opportunistic, set in primary care, and the studied populations typically had poor access to health care, these results are considered highly applicable to the assessment target population. It is clinically significant that the Australian study by Spurling et al. (2010) found that, on referral by a GP, more Indigenous patients attended follow-up with an eye specialist after RP-NMRC than after traditional surveillance (90% vs 15% of patients, respectively; $p<0.001$).

In a comparison of two concurrent screening models, both conducted at hospital-based eye screening clinics, Tu et al. (2004) found that the proportion of patients attending an RP-NMRC appointment was statistically significantly higher than that attending a CEE appointment with an optometrist (OR 1.22, 95%CI 1.07, 1.40), although compliance was poor in both groups (50% vs 45%). Two case series that reported on compliance with annual or 2-yearly RP-NMRC screening, following an invitation to do so, reported similar compliance rates—87% and 89%, respectively (Lee, SJ et al. 2000; Leese et al. 2005).

Overall conclusion with respect to comparative effectiveness

RP-NMRC is a more effective tool for triaging patients with diabetes for further assessment with CEE than no eye examination or ophthalmoscopy delivered in primary care. Patients who receive a false negative result from RP-NMRC, like those who do not have an eye examination or who receive a false negative result from ophthalmoscopy in primary care, are at risk of blindness as they will not be referred to an eye specialist for a CEE following screening, and treatment may be delayed until their disease is symptomatic. It is likely, however, that the false negative rate with RP-NMRC will be smaller than not having an examination at all. Patients who receive a false positive result for DR by RP-NMRC are not likely to be negatively affected (except with regard to inconvenience), as they will be referred to an eye specialist for a CEE, at which point DR will be excluded.

Other relevant organisational considerations

The Department of Health requested that consideration be given to alternative (non-MBS) funding arrangements in the evaluation of RP-NMRC.

Any prospective reimbursement scheme would need to ensure that non-mydriatic retinal cameras are placed in areas where they can be used efficiently, i.e. where this technology is likely to be used with reasonable frequency and where it is unlikely to replace the 'gold standard' for detection/grading of DR, CEE by an optometrist or ophthalmologist. As such, it is suggested that separate grant funding for retinal cameras should be considered for the proposed RP-NMRC service.

Training and accreditation will be important determinants of the success and cost-effectiveness of any RP-NMRC service. Collaboration among key stakeholders, including government, relevant clinical craft groups (e.g. RANZCO, OAA, ACO, RACGP) and educational institutions, should ensure that appropriate training programs and quality assurance mechanisms are implemented and reviewed as required.

Non-mydriatic retinal cameras are portable and easily transported to rural or remote settings for use by non-medical staff who have been accredited via appropriate technical training (Heaven, Cansfield & Shaw 1993). A number of studies have demonstrated that retinal photography is a viable option for screening for DR in rural and remote communities (Ku et al. 2013; Lee, SJ et al. 2001; Murray et al. 2005). In addition, access to eye-care services for Indigenous people is likely to be improved if these services can be delivered within culturally appropriate facilities (Turner et al. 2011). The provision of RP-NMRC within these communities is not only likely to increase compliance with recommended screening

for DR, but would also reduce unnecessary travel for those patients in whom no signs of DR are detected.

Economic and financial considerations

Economic evaluation

A modelled economic evaluation is presented to compare the costs and outcomes of RP-NMRC testing with those for the situation in which no testing is performed (primary comparator is no eye examination). In this scenario RP-NMRC would be used as a triage test; that is, patients with evidence of DR would be referred for a CEE by either an ophthalmologist or an optometrist, whereas patients without evidence of DR would return for another screening eye examination (RP-NMRC) in 1 or 2 years. The model is a cost-utility analysis, capturing the health outcomes associated with prompt diagnosis and treatment, compared with either delayed diagnosis and treatment, or failure to diagnose. A cost-effectiveness analysis (cost per case of blindness prevented) is also presented.

The structure of the economic model is a Markov model incorporating seven main health states: no retinopathy, non–sight-threatening DR (non-STDR), early sight-threatening DR (STDR), advanced STDR (AdvSTDR), treated DR, treated DR, blind and dead. STDR is defined as DR of a severity requiring urgent referral for CEE and treatment. Early STDR includes severe NPDR and low-grade PDR with only mild vision loss, whereas advanced STDR is assumed to be of a severity to result in moderate visual impairment. Due to variations in testing frequencies and timing of treatment between diagnosed and undiagnosed patients, an additional four health states, relating specifically to patients diagnosed with DR, were required: non-STDR (diagnosed), STDR (diagnosed), treated DR (early) and AdvSTDR (post-treatment) (see Figure 14).

In the RP-NMRC arm, transitioning to a diagnosed heath state is dependent on the diagnostic accuracy of RP-NMRC. In comparison, in the ‘no testing’ arm of the model, patients are presumed to progress to the AdvSTDR health state before undergoing eye testing due to deteriorating vision. The economic evaluation is conducted from the perspective of the Australian healthcare system. The model has a 40-year time horizon, capturing lifetime costs and outcomes.

For the secondary comparators—ophthalmoscopy with mydriasis performed by a GP, or CEE performed by an ophthalmologist/optometrist—the comparator arm of the model is similar in structure to that for RP-NMRC. The incremental effectiveness of the alternative strategies is entirely dependent on the relative accuracy of the respective testing methods.

Two populations have been assessed—the broad Australian diabetic population and the Indigenous Australian diabetic population—and the frequency of testing, epidemiological characteristics of DR and mortality rates have been altered accordingly.

Primary comparison: RP-NMRC versus no testing

The results for the primary comparison of RP-NMRC versus no testing are presented in Table 1.

Table 1 Primary comparison of RP-NMRC versus no testing

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Broader Australian population					
RP-NMRC	$52,381	$1,054	10.964	0.071	$14,875
No testing	$51,327		10.894		
Indigenous population					
RP-NMRC	$52,020	$2,005	9.925	0.162	$12,379
No testing	$50,015		9.763	-	-

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

A conservative approach has been taken, with the use of inputs that tend to favour the comparator over RP-NMRC screening. In the primary scenario for the comparison of RP-NMRC with no testing, a low DR incidence and slow progression rates were used, minimising the benefits of early diagnosis resulting from regular testing. The resulting estimated incremental cost per quality-adjusted life-year (QALY) is approximately $14,870 in the broader Australian population and $12,380 in the Indigenous population, and the incremental cost per blindness prevented is approximately $51,600 and $46,600, respectively. If a more rapid rate of progression is assumed, the incremental cost-effectiveness ratio (ICER) per QALY gained reduces to $6,440 and $5,200 in the broader Australian population and the Indigenous population, respectively.

Key uncertainties in the primary comparison of RP-NMRC and no testing

The cost of treatment is a major source of uncertainty in the economic model. In the base-case analysis it is assumed that all patients are treated with laser photocoagulation, at an average cost of $2,214. However, intra-vitreal injection of anti-vascular endothelial growth factor (VEGF) is increasingly being used as the primary treatment for patients with clinically significant macular oedema, even though no anti-VEGF agents are listed on the Pharmaceutical Benefits Scheme (PBS) for this indication. In the primary scenario, if the average treatment cost is increased to $24,250 (the estimated cost of anti-VEGF treatment), the incremental cost per QALY gained increases to approximately $42,500.

Secondary comparison: RP-NMRC versus standard medical assessment

While RP-NMRC was more effective than dilated ophthalmoscopy performed by a GP, it was also the more expensive strategy, with an ICER of approximately $26,000 in both the broader population and the Indigenous population. However, the results of a national survey of Australian GPs (Ting et al. 2011) suggest that the proportion of clinicians using ophthalmoscopy as a triage test is low. Therefore, the relevance of dilated ophthalmoscopy performed by a GP as a comparator for RP-NMRC is limited.

In comparison with CEE performed by either an ophthalmologist or an optometrist, regular testing by RP-NMRC was marginally less expensive than CEE but also slightly less effective in terms of QALYs gained. Given that CEE is more accurate than RP-NMRC, and is more likely to detect other non–DR-related lesions, it would be inappropriate for RP-NMRC to be substituted for CEE in patients currently receiving this service.

Overall conclusion with respect to comparative cost-effectiveness

The economic evaluation suggests that RP-NMRC is likely to be a cost-effective option for diagnosing DR in patients with diabetes who would not otherwise receive regular eye examinations. The sensitivity analyses confirm that the results of the economic model comparing RP-NMRC testing with the primary comparator (no testing) are reasonably robust. The model is most sensitive to the cost of treatment and the quality-of-life weight applied to the AdvSTDR health state, but the ICER remains below $45,000/QALY gained in all modelled scenarios.

The introduction of RP-NMRC will only be effective if provision is made to ensure compliance with regular testing, appropriate follow-up of results, and prompt treatment of STDR when indicated.

Financial/budgetary implications

An epidemiological approach has been used to estimate the financial implications of the introduction of RP-NMRC. The costs associated with increased use of CEE, resulting from the additional cases of DR diagnosed by RP-NMRC, have also been estimated.

The financial implications to the MBS (inclusive of safety net implications) resulting from the proposed listing of RP-NMRC are summarised in Table 2.

Table 2 Total costs to the MBS associated with RP-NMRC testing for DR and associated CEE, inclusive of safety net implications

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
RP-NMRC						

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Number of services	59,965	87,391	112,547	109,543	109,241	110,131
Non-Indigenous population	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922
Indigenous population	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Total	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE						
Number of services	16,938	36,542	57,391	70,334	79,158	85,452
Non-Indigenous population	$1,152,026	$2,579,714	$4,114,880	$5,112,242	$5,789,415	$6,269,936
Indigenous population	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total cost						
Non-Indigenous population	$2,882,207	$5,142,709	$7,458,325	$8,383,307	$9,044,408	$9,543,858
Indigenous population	$1,075,249	$1,964,113	$2,708,794	$2,902,423	$2,992,449	$3,058,136
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

If the new listing for RP-NMRC testing is approved, within 3 years the cost to the MBS is likely to exceed $10 million per year. The cost attributable to CEE initially increases markedly as more patients are diagnosed with DR and require ongoing monitoring for disease progression. This rapidly becomes the major source of the cost to the MBS. The main sources of uncertainty are the proportion of patients with diabetes who are not receiving regular eye examinations and the likely uptake of RP-NMRC testing in this population. If the proportion of patients not receiving regular eye examinations increases from 23%, as in the base-case, to 40% by 2020–21, the estimated cost to the MBS will increase to $19.65 million.

The total cost associated with RP-NMRC testing alone will increase to approximately $4.5 million by 2020–21. The majority of the cost to patients results from the out-of-pocket cost for CEE performed by an ophthalmologist to monitor patients who have been diagnosed with DR as a result of RP-NMRC testing. Due to the high rate of bulk-billing by GPs for patients with chronic diseases such as diabetes, the total cost to patients for undergoing RP-NMRC testing is minimal[3].

Depending on the uptake of RP-NMRC, the provision of an alternative funding mechanism *for the initial set-up* costs associated with RP-NMRC testing would potentially result in savings to the MBS of $5–$9 million over the first 6 years of listing on the MBS. Assuming an

[3] In the 2014–15 Federal Budget the introduction of a patient co-payment for previously bulk-billed patients was proposed for GP, pathology and imaging services. If this legislation is introduced, previously bulk-billed patients may incur a fee of $7 for RP-NMRC services.

initial set-up cost of $50,000 at each RP-NMRC testing site, as proposed in the justification of the proposed MBS fee, these potential savings are sufficient to fund approximately 100–180 cameras.

Glossary and abbreviations

Abbreviation	Full term
ACCHS	Aboriginal Community Controlled Health Service
ACO	Australian College of Optometrists
AdvSTDR	advanced sight-threatening diabetic retinopathy
AHTA	Adelaide Health Technology Assessment
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ATSI	Aboriginal and Torres Strait Islander (people)
AUC	area under the curve
AusDiab	Australian Diabetes Obesity and Lifestyle (study)
BIO	binocular indirect ophthalmoscopy
CEE	comprehensive eye examination
CERA	Centre for Eye Research Australia
CI	confidence interval
CSMO	clinically significant macular oedema
DAP	decision analytic protocol
DR	diabetic retinopathy
DRG	diagnosis-related group
DRS	Diabetic Retinopathy Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
GP	general practitioner
HESP	Health Expert Standing Panel
HSROC	hierarchical summary receiver–operator characteristic
ICER	incremental cost-effectiveness ratio
KRDRS	Katherine Region Diabetic Retinopathy Study
LR+	positive likelihood ratio
LR–	negative likelihood ratio
MBS	Medicare Benefits Schedule
MO	macular oedema
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council

Abbreviation	Full term
NPV	negative predictive value
NPDR	non-proliferative diabetic retinopathy
NS	not stated
OAA	Optometrists Association Australia (now Optometry Australia)
PASC	Protocol Advisory Subcommittee (of MSAC)
PBS	Pharmaceutical Benefits Scheme
PDR	proliferative diabetic retinopathy
PoC	point of care
PPV	positive predictive value
PRP	panretinal photocoagulation
QAAMS	Quality Assurance for Aboriginal and Torres Strait Islander Medical Services
QALY	quality adjusted life-year
RACGP	Royal Australian College of General Practitioners
RANZCO	Royal Australian and New Zealand College of Ophthalmologists
RCT	randomised controlled trial
RP	retinal photography
RP-NMRC	retinal photography with a non-mydriatic retinal camera
SLBM	slit lamp biomicroscopy
STDR	sight-threatening diabetic retinopathy
UIs	unreadable images
VEGF	vascular endothelial growth factor

Introduction

This assessment report is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

Adelaide Health Technology Assessment (AHTA), School of Population Health, University of Adelaide, has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of retinal photography with a non-mydriatic retinal camera (RP-NMRC), for identification of diabetic retinopathy (DR) in patients in the primary care setting. This evaluation has been undertaken in order to inform MSAC's decision-making regarding public funding of the intervention.

The proposed use of RP-NMRC in Australian clinical practice was outlined in a decision analytic protocol (DAP) that guided the evaluation undertaken by AHTA. The DAP was released for public comment on 7 October 2013 and closed for comments on 15 November 2013. On 22 November the Protocol Advisory Subcommittee (PASC) chair responded that all issues raised in the feedback would be most appropriately considered in the assessment, and the DAP was finalised without further PASC deliberation.

Rationale for assessment

RP-NMRC has been requested for MBS listing for detection of DR in the primary care setting among patients with diabetes. The target population are people with diabetes who do not currently follow the National Health and Medical Research Council's (NHMRCs) recommendations to see an eye specialist. In Indigenous Australians this should occur every year, and every 2 years in the non-Indigenous population. The applicant has claimed that successful listing of the technology in the target population and setting will lead to improved management of DR. The application submitted to MSAC indicated that the proposed Medicare service is not intended to replace or be used in conjunction with regular comprehensive eye examinations (CEEs), but to address populations that are less likely to seek regular eye health examinations from optometrists or ophthalmologists.

Background

Diabetic retinopathy

Under the considerations of the present assessment, RP-NMRC is intended for the detection of DR in the primary care setting among patients with diabetes who have not had a CEE in the past 2 years if non-Indigenous, or the past year if Indigenous. RP-NMRC is not intended as a general screening tool.

RP-NMRC

RP-NMRC is a non-contact, non-invasive imaging technique that provides digital images of the retina and optic disc using a fundus camera. Whereas early fundus photography used bright visible light, newer technologies incorporate infrared-sensitive video cameras, enabling image acquisition without the use of mydriatic agents to dilate the pupil. During a typical photographic session the viewing field[4] is centred on the fovea (central retina) in a darkened room, which allows normal physiological dilation of the pupils to occur and aids in capturing a readable image. Images are taken with the aid of a flash, which causes immediate pupil constriction. Therefore, it is usual to leave an interval of at least 5 minutes between imaging a patient's first and second eye, as this allows pupil recovery from the first flash. Photographs can be interpreted by an optometrist, an ophthalmologist or a specifically trained reader, either locally or remotely via electronic link / telemedicine. However, because RP-NMRC cannot provide a complete view of the retina, it primarily enables *detection* of DR rather than definitive severity grading for retinopathy[5]. Accordingly, detection of DR usually indicates referral to an optometrist or ophthalmologist for a comprehensive assessment. Non-mydriatic retinal cameras are portable and easily transported to rural or remote settings for use by non-medical staff who can be accredited through appropriate technical training (Heaven, Cansfield & Shaw 1993; NHMRC 2008; Williams, GA et al. 2004).

Retinal cameras for use without mydriasis are currently rarely found outside optometrist and ophthalmologist practices. Therefore, the provision of RP-NMRC within the primary healthcare setting (i.e. GP clinics, diabetes clinics or Indigenous health clinics) will usually

[4] Typically a fundus camera will cover 45–60 degrees in one exposure. Special software may be used to combine multiple frames to achieve a coverage of up to 140 degrees, while ultra-wide field retinal capture imaging can cover up to 200 degrees in a single exposure (Soliman et al. 2012).

[5] HESP advice (ophthalmologist, optometrist) is that a limited level of grading may be achieved but, even with an ideal photograph, subtle changes may be missed. Photographs of poorer quality may conceal diffuse and/or more-severe disease.

require an initial capital outlay that will vary depending on the choice of camera. Costs for a range of cameras are shown in Table 3. Health Expert Standing Panel (HESP) members also advise (personal correspondence 17 June 2014) that non-mydriatic retinal cameras that are adequate within a primary care context, where ease of use and portability are likely to be important (Leferink 2011), may be purchased for as little as $8,000 to $16,000. However, HESP also advised that any camera within the hands of an inadequately trained operator will result in poor technical performance. Training issues are discussed under 'Other relevant considerations'.

Table 3 Capital equipment costs for non-mydriatic retinal photography, effective as of July 2013

Non-mydriatic retinal camera	Cost (Australian dollars)
Canon CR2	$26,400
Canon CR2 Plus	$30,800
Canon CR2 Plus AF	$38,500
Cobra CSO-272	$15,990
Horus handheld (MIS-901890)	$9,500
Kowa 500	$26,500
Kowa 800	$25,500
Kowa 900	$32,900
Nidek AFC330	$28,600
Topcon TRC-NW8	$34,450

Source: correspondence with multiple suppliers via HESP (optometrist), 30 July 2013

In addition to capital costs, several professional services are required to deliver RP-NMRC and provide follow-up for patients, depending on whether evidence of DR is found. Acquisition of images, under the proposed listing, may be conducted by appropriately trained technicians and health workers, or GPs. However, if the taking of photographs is conducted by non-medical staff, reading by an optometrist, ophthalmologist or possibly a GP would be required, to enable claiming of an MBS item. Any sign of DR would then indicate a requirement for CEE to determine suitable treatment. The only publicly funded treatment for DR is laser photocoagulation (MBS item number 42809). Anti-vascular endothelial growth factor (VEGF) agents are not currently approved on the Pharmaceutical Benefits Scheme (PBS) for the treatment of DR; however, the procedure of administering such agents by an intra-vitreal injection is funded through the MBS (item number 42738). That is, the provision of the service is covered by the MBS, and the anti-VEGF is an out-of-pocket cost to the patient.

Intended purpose

RP-NMRC is proposed to be used in populations less likely to seek regular eye health examinations from optometrists or ophthalmologists. Its use would therefore replace 'no testing,' i.e. no regular eye examinations. The PASC also recommended that the evaluation

compare RP-NMRC with standard medical assessment, i.e. fundus examination through dilated pupils using slit lamp biomicroscopy (SLBM) by an optometrist or ophthalmologist, or ophthalmoscopy by a GP. In populations who would otherwise have attended regular CEEs, RP-NMRC would possibly be used in place of, or in addition to, regular CEEs. As a triage test RP-NMRC would screen diabetes patients; for those in whom DR is detected a referral to CEE would be made, and in instances where no DR was evident a CEE would not be considered necessary.

Any Medicare service provider who routinely provides healthcare services to people with diabetes could order or perform RP-NMRC (see Table 5), or could use accredited imagers to perform RP-NMRC under their supervision. Medicare service providers would be responsible for determining the level of presenting vision in each eye, and would report on the quality of the images, the degree of DR (possible only with images of good quality) and the necessity of referral for further ophthalmic assessment (mandatory when images cannot be graded; see NHMRC guidelines).

Prior to any patient undergoing RP-NMRC, it has been proposed that visual acuity should first have been determined in the primary care setting (i.e. GP, Indigenous health or diabetes clinic). In this assessment visually impaired people with diabetes will be considered ineligible for publicly funded RP-NMRC as they are more appropriately managed by referral to CEE. Conversely, it is intended that persons with diabetes assessed as free from visual impairment constitute the eligible population for RP-NMRC. In the DAP produced to guide this assessment it was determined that RP-NMRC should be reserved exclusively for use in primary care settings, but that the interpretation of the photograph and claiming of the MBS item should be restricted to optometrists and medical practitioners (GP or ophthalmologist), so that current MBS claiming rules are satisfied. In instances where the photographs are taken by a technician and then read by a medical practitioner (i.e. the photographer and reader are not the same person), an internal arrangement will need to be made regarding division of the fee for the service provided, as only medical practitioners are able to claim MBS fees. The imager would be responsible for maintaining the camera and image quality, and the certified reader would be required to identify DR where present and provide a report, including an appropriate referral timeframe, to the patient's medical practitioner responsible for the diabetes care plan/management.

Clinical need

As the most common complication of diabetes, DR is a chronic, sight-threatening eye disease that occurs in 25–44% of people with diabetes in any time period. Ninety per cent of

people with diabetes will have retinopathy after 25 years (NHMRC 2008)[6]. DR is directly related to poor control of blood glucose, blood pressure and blood lipids (Schiffelers et al. 2007). Without intervention, DR progresses from thickening of the basement membrane that lines retinal blood vessels through a series of changes in the microvasculature, resulting in macular oedema (MO). At this stage central vision typically deteriorates while the peripheral vision is maintained. These early stages of DR are referred to as non-proliferative diabetic retinopathy (NPDR), characterised by retinal vascular microaneurysms[7], blot haemorrhages and 'cotton wool' spots. As disease progresses further, damaged cells release VEGF, which stimulates growth of new blood vessels on the surface of the retina or optic nerve in order to supply sufficient nutrients. This vasculature is extremely delicate and prone to leakage and rupture, which may in turn cause vitreous haemorrhage[8], scarring of the retina or retinal detachment. This condition, known as proliferative diabetic retinopathy (PDR), is characterised by an increased number of microaneurysms and haemorrhages, and may cause severe loss of both central and peripheral vision (AAO 2008; Curtis, Gardiner & Stitt 2009; NHMRC 2008).

Regular screening to detect DR is considered essential (NHMRC 2008), as this enables timely treatment in order to minimise the degree of permanent vision loss. The current Australian NHMRC guidelines for the management of DR recommend 2-yearly and yearly vision assessments for non-Indigenous and Indigenous Australians with diabetes, respectively, and retinal examinations in asymptomatic patients with diagnosed diabetes (i.e. those without visual impairment) at the same frequency. The supporting evidence underwriting these guidelines indicates that treatable retinopathy is commonly asymptomatic, and it is considered that timely treatment is the key to preventing partial/complete loss of vision. Further, the NHMRC (2008) recommends that:

'… ophthalmologists, optometrists and other trained medical examiners should use dilated ophthalmoscopy or slit lamp biomicroscopy with a suitable lens (e.g. 78 D), to detect presence and severity of DR … with adequate sensitivity and specificity. In the absence of a dilated fundus examination by a trained examiner … non-mydriatic (or mydriatic) photography with adequate sensitivity, specificity and low technical failure rate [are recommended] to detect presence of DR'.

[6] The AusDiab study (n=11,247) reported, more conservatively, that 22% of people with type 2 diabetes had DR and 6% of newly diagnosed people with diabetes had DR (Tapp et al. 2003).

[7] That is, focal dilation of retinal capillaries occurring in diabetes mellitus, retinal vein obstruction and absolute glaucoma.

[8] That is, haemorrhage into the vitreous humour, the transparent gel that fills the inner portion of the eyeball between the lens and the retina.

However, only 50% of non-Indigenous Australians with diabetes are compliant with these guidelines (Harper et al. 1998; Taylor, H et al. 2009). Similarly, it was found that 44% of Indigenous Australians have not had a diabetic eye screening in the previous year (Ku et al. 2013).

Existing tests/procedures for detection of diabetic retinopathy

A CEE involves visual acuity testing and an ocular fundus examination, usually through dilated pupils. Diagnosis of DR is accomplished by imaging the retina of the eye through the pupil. Various instruments may be used for this purpose. Ophthalmoscopes are instruments containing an arrangement of lenses and a source of illumination that allows direct visualisation of the eye's interior. The handheld direct ophthalmoscope is a standard type in clinical use, but studies have reported low diagnostic accuracy for this instrument (Siu et al. 1998); hence, many optometrists and ophthalmologists prefer to use binocular indirect ophthalmoscopy (BIO) and SLBM with indirect lenses.

Clinical examinations to assess the presence or severity of DR may use SLBM, ophthalmoscopy or retinal photography (RP) (NHMRC 2008). SLBM has the added advantage of a stereoscopic view, which allows an appreciation of depth. SLBM is in wide clinical use, predominantly throughout optometric practice, but very few GP or diabetes clinics have access. Retinal cameras use newer technology that consists of an optical system designed to focus on the ocular fundus. An image-capture device such as a digital camera is mounted on top of the optical system. Non-mydriatic retinal cameras have been well established in clinical practice across the UK, Scandinavia, USA and Singapore, and several pilot projects have used these cameras in Australia (Aung et al. 2009; Harper et al. 1998; Phiri et al. 2006). Advice from the ophthalmologist member of HESP indicated that there are many clinicians in Australia, mostly optometrists, who independently screen for DR using retinal photography, and some public hospitals and health services use RP-NMRC to screen for DR under an ophthalmologist's supervision. It was further advised that Optometrists Association Australia (OAA) (now Optometry Australia) conducted a survey of their members, with the finding that approximately 60% had retinal fundus cameras. No evidence has been identified which provides estimates on the uptake of non-mydriatic retinal cameras by GPs, however the applicant has advised that the use of RP-NMRC by GPs is limited. The applicant has also advised that there are a few large diabetes clinics in Queensland that use RP-NMRC to screen for DR and a number of non-mydriatic retinal cameras have been provided to several Aboriginal Health Services over the years, but noted that most are out of use due to lack of sustainable funding *specifically* for RP-NMRC.

Marketing status of retinal cameras

Numerous non-mydriatic retinal cameras have been registered with the Therapeutic Goods Administration on the Australian Register of Therapeutic Goods (ARTG) (Table 4).

Table 4 Retinal cameras listed on the ARTG

ARTG no.	Product description	Product category	Sponsor
156438	To take digital photographs of the fundus to study potential eye disorders and store images for further comparisons and reference	Medical Device Class IIa	BOC Ophthalmic Instruments
140423	To take digital photographs of the retina for optical and medical analysis	Medical Device Class IIa	BOC Ophthalmic Instruments
119011	To study and record images of the fundus	Medical Device Class I	BOC Ophthalmic instruments
144145	For use to photograph the fundus of the eye	Medical Device Class I	Canon Australia
152527	For use to photograph the fundus of the eye	Medical Device Class I	Canon Australia
108114	Photographing eye	Medical Device Class I	Canon Australia
161816	For use to photograph the back of the eye	Medical Device Class I	Canon Australia
164706	This medical device is intended to observe image and record retinal fundus through the pupil without contact with subject's eye	Medical Device Class I	Canon Australia
98728	Photograph the human retina	Medical Device Class I	Canon Australia
129300	Fundus imaging in non-mydriatic and mydriatic mode	Medical Device Class IIa	Carl Zeiss
94352	Fundus imaging	Medical Device Class I	Carl Zeiss
131015	A camera designed to photograph/record images of the ocular fundus	Medical Device Class IIa	Device Technologies Australia
220554	Portable digital fundus/ophthalmic camera	Medical Device Class IIa	Designs for Vision
142066	Wide-field paediatric retinal imaging	Medical Device Class I	Designs for Vision
107405	For taking an image of the fundus of the eye	Medical Device Class I	Designs for Vision
218764	A specialised camera used to record magnified images of the ocular fundus and retina, and images of the back of the inside of the eye, through the pupil, using a spectrum of light not visible to the eye	Medical Device Class IIa	IQ Medical
189846	A dedicated kind of camera used to record magnified images of the ocular fundus (back or rear of the inside of the eye) through the pupil	Medical Device Class I	Opticare Pty Ltd
133323	The device is a digital fundus imaging system intended for use by optometrists and ophthalmologists. The device mounts to the tonometer adapter of an optional slit lamp stand. The device is intended to capture an image of a patient's fundus after they are correctly positioned on the chinrest of the stand. After capture, images are intended to be downloaded from the camera to a computer. Included software enables the images to be sorted and annotated as required by the practitioner.	Medical Device Class I	Scan Optics

ARTG no.	Product description	Product category	Sponsor
194727	Camera used to record images of the ocular fundus	Medical Device Class IIa	Spectrum Surgical Pty Ltd
203775	To take digital photographs of the eye-fundus	Medical Device Class I	Zone Medical Pty Ltd

Source: Therapeutic Goods Administration, accessed 25 March 2014, https://www.ebs.tga.gov.au/.

Current reimbursement arrangements

RP-NMRC is usually provided by an ophthalmologist or optometrist, concurrent with a CEE. The cost of photography is an out-of-pocket expense for patients. The existing MBS items for 'retinal photography'[9] relate to a procedure known as fluorescein angiography, which is specifically used to assess severe retinopathy in order to guide treatment[10], and is distinct from RP-NMRC.

Health professionals in some Aboriginal Community Controlled Health Services (ACCHSs) provide RP-NMRC screening for their clients in a manner resembling the current proposal (i.e. using a transportable camera and accessing remote areas) (Murray et al. 2005).

Proposal for public funding

The proposed MBS item is summarised in Table 5. The applicant suggested restricting the item to those who have not had a CEE within the past 2 years (if non-Indigenous) or year (if Indigenous). As CEE frequency would be difficult to ascertain, PASC decided this restriction should not be placed on the use of the item. The proposed service is intended for use in patients who would not regularly attend an optometrist or ophthalmologist for a CEE (i.e. for whom the alternative to RP-NMRC would likely be no eye examination).

Table 5 Proposed MBS item descriptor for retinal photography in people with diabetes

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS And Group A10 – OPTOMETRIC SERVICES
MBS [item number (Note: this will be assigned by the Department if listed on the MBS)] Bilateral retinal photography with a non-mydriatic retinal camera for initial or repeat assessment for presence or absence of diabetic retinopathy in people with medically diagnosed diabetes. Fee: $50.00 Explanatory notes: A fee may not be charged for an assessment where a previous medical diagnosis of diabetic retinopathy applies at the time of presentation, or for patients with visual impairment. Visual impairment is defined as distance vision of less than 6/12 in either eye, or a difference of more than two lines of vision between the two eyes at the time of presentation. Presenting

[9] MBS item numbers 11215 and 11218

[10] HESP (ophthalmologist) advice via personal correspondence, 5 April 2013

distance vision means unaided distance vision or the vision obtained with the current spectacles or contact lenses, if normally worn for distance vision.

A fee may be charged for repeat assessment on the condition that two calendar years have elapsed since the previous presentation for retinal photography (except for Indigenous Australians where a restriction of one calendar year applies).

This item is intended for the provision of retinal photography with a non-mydriatic retinal camera. Use of mydriasis by medical practitioners only is permitted if adequate photographs cannot be obtained through an undilated pupil (see note below regarding referral requirements).

Item usage is restricted to retinal photography within the primary care settings (eg general practitioner, Indigenous health and diabetes clinics) and cannot be co-claimed on the same day with any other eye procedure by optometrist or ophthalmologist.

Claiming of a fee is permissible for an ophthalmologist or optometrist for remote interpretation of images taken in primary care settings, but not for retinal photography performed exclusively within optometric and ophthalmological practice.

Detection of any diabetic retinopathy must be followed by referral to an optometrist or ophthalmologist.

Where images are of inadequate quality for detection of diabetic retinopathy by the attending medical practitioner, referral to an optometrist or ophthalmologist for further assessment is indicated. The fee must not be charged when a referral is required due to inability to obtain photographs of adequate quality for grading.

Imaging procedure by a non-medical operator must be followed by referral if (a) it is not possible to obtain an image of adequate quality through undilated pupils; (b) diabetic retinopathy is detected.

Charging of a fee must be accompanied by a report detailing the presence or absence of diabetic retinopathy, based on photos of readable quality.

The application also proposed a change to two current MBS descriptors (Table 6). These items are commonly referred to as fluorescein angiography. The proposed changes are shown in Table 7. Given the requested changes relate to semantics, they are not considered further in this evidence-based assessment. It is likely that this will be addressed by the relevant policy area in the Department of Health.

Table 6 Current MBS item descriptors for 11215 and 11218

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
MBS 11215 RETINAL PHOTOGRAPHY, multiple exposures of 1 eye with intravenous dye injection Fee: $123.00 Benefit: 75% = $92.25 85% = $104.55
MBS 11218 RETINAL PHOTOGRAPHY, multiple exposures of both eyes with intravenous dye injection Fee: $151.95 Benefit: 75% = $114.00 85% = $129.20

Table 7 Proposed changes to MBS item descriptors for 11215 and 11218

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
MBS 11215 RETINAL ANGIOGRAPHY, multiple exposures of 1 eye with intravenous dye injection Fee: $123.00 Benefit: 75% = $92.25 85% = $104.55
MBS 11218 RETINAL ANGIOGRAPHY, multiple exposures of both eyes with intravenous dye injection Fee: $151.95 Benefit: 75% = $114.00 85% = $129.20

Approach to assessment

A DAP was developed prior to commencement of this assessment, and was approved by the Protocol Advisory Subcommittee (PASC) of MSAC. The guiding framework of the DAP was used throughout this assessment. The purpose of a DAP is to describe in detail a limited set of decision options associated with the possible public funding of a proposed medical service. A DAP also accurately captures current clinical practice and reflects likely future practice with the proposed medical service. A research protocol was also developed prior to undertaking the assessment, and outlined the methodology to be used in the systematic literature review.

Objective

The objective of this assessment was to carry out a structured assessment of RP-NMRC for the detection of DR among people with diagnosed diabetes. By itself, a diagnostic or triage test does not impact health outcomes; thus, the focus of the assessment is the impact of RP-NMRC on subsequent referral to CEE and compliance with CEE as a result of increased testing for the detection of DR. To achieve this, the following outcomes were selected in accordance with a linked evidence approach:

Safety

- physical and psychological harms from DR testing
- mydriasis-related harms (associated primarily with the comparators)

Diagnostic accuracy

- measures of test performance (e.g. sensitivity, specificity, negative and positive predictive values, false positive and false negative rates)
- measures of test concordance (e.g. kappa measures, agreement measures), should test performance data be limited or absent
- rate of unreadable photographs or inability to make a diagnosis

Subgroup analyses of the above diagnostic accuracy measures, according to the area of medical specialisation of the reader, would have been performed, if there were sufficient data on the accuracy of readers other than ophthalmologists / retinal specialists. Given the absence of these data, the concordance in diagnosis among readers was reported.

Effectiveness (based on change in management)

- change in rate of appropriate referral for CEE—for DR and non-DR ocular disorders and vision impairment/loss, separately and combined
- reduction in unnecessary referral
- compliance with referral to CEE

The research protocol specified that the potential consequences of non–DR-related ocular findings would be included as part of this review, although it was noted that these are not of primary interest for this assessment. Given that none of the identified papers that reported on non-DR disorders were found to be eligible for inclusion, it has not been possible to evaluate the potential impact of such findings.

Given that the effectiveness of treatment for DR is already established, and RP-NMRC will not broaden the spectrum of patients being treated, an assessment of treatment effectiveness in DR patients identified by RP-NMRC has not been included and is not required for MSAC's purposes.

Clinical pathway

A flowchart can help define the place of a new intervention in the clinical management of a patient. Figure 1 shows the current management algorithm for the detection of DR in patients with diabetes who are not vision impaired, in the absence of RP-NMRC in the primary healthcare setting. Figure 2 shows the proposed management algorithm, with the addition of RP-NMRC.

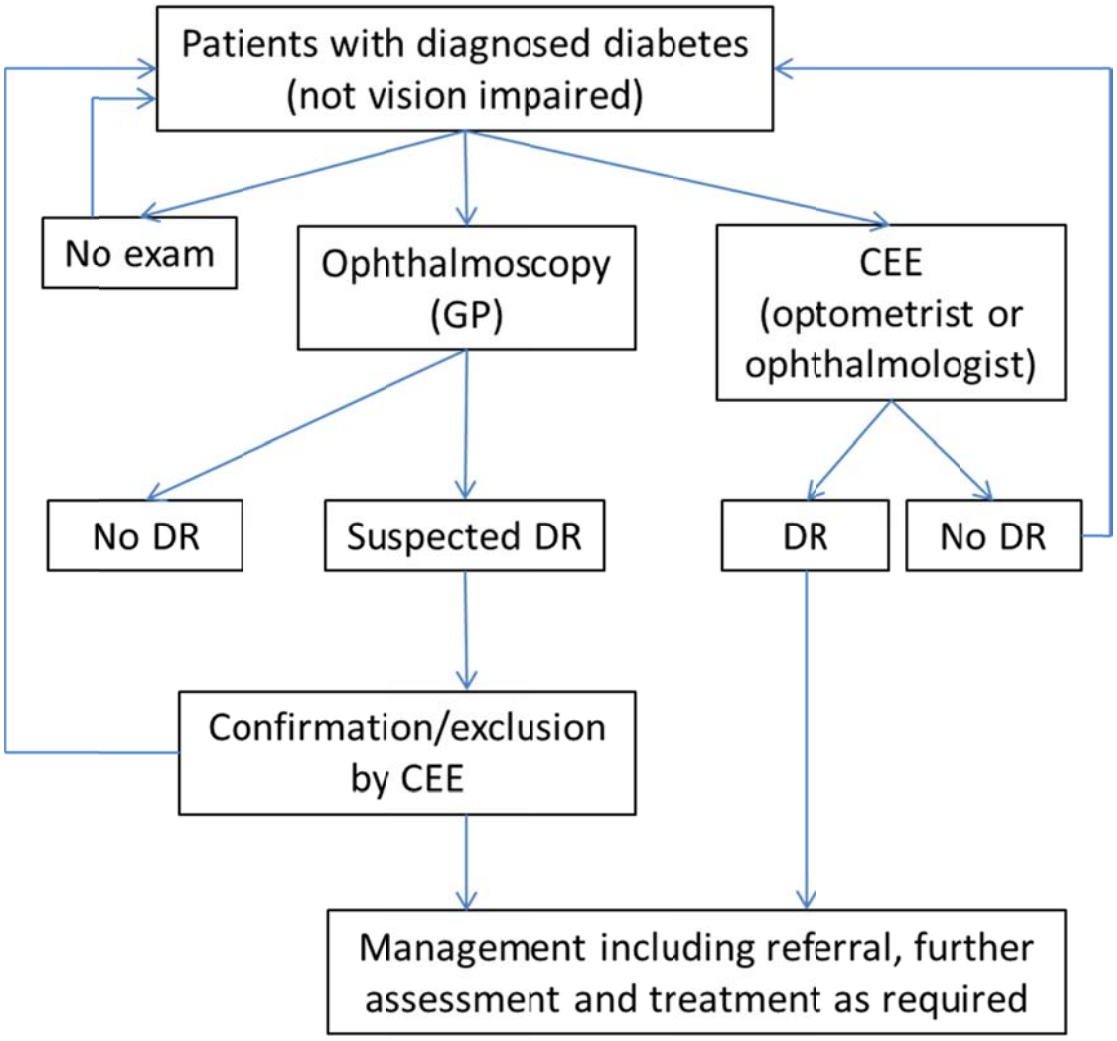


Figure 1 Management algorithm for detection of diabetic retinopathy in patients with diabetes in the absence of the proposed service, i.e. retinal photography using a non-mydriatic retinal camera

CEE = comprehensive eye examination; DR = diabetic retinopathy; GP = general practitioner

Note: CEE by an optometrist or ophthalmologist will include fundus examination with mydriasis using an ophthalmoscope or a slit lamp biomicroscope, and may also involve retinal photography. Examination conducted by a GP through an ophthalmoscope may also involve instillation of a mydriatic in the eyes. Either service option should be repeated every 2 years among non-Indigenous, and yearly among Indigenous, persons with diabetes (as per NHMRC guidelines on DR). 'No exam' means no eye examination beyond visual acuity testing.

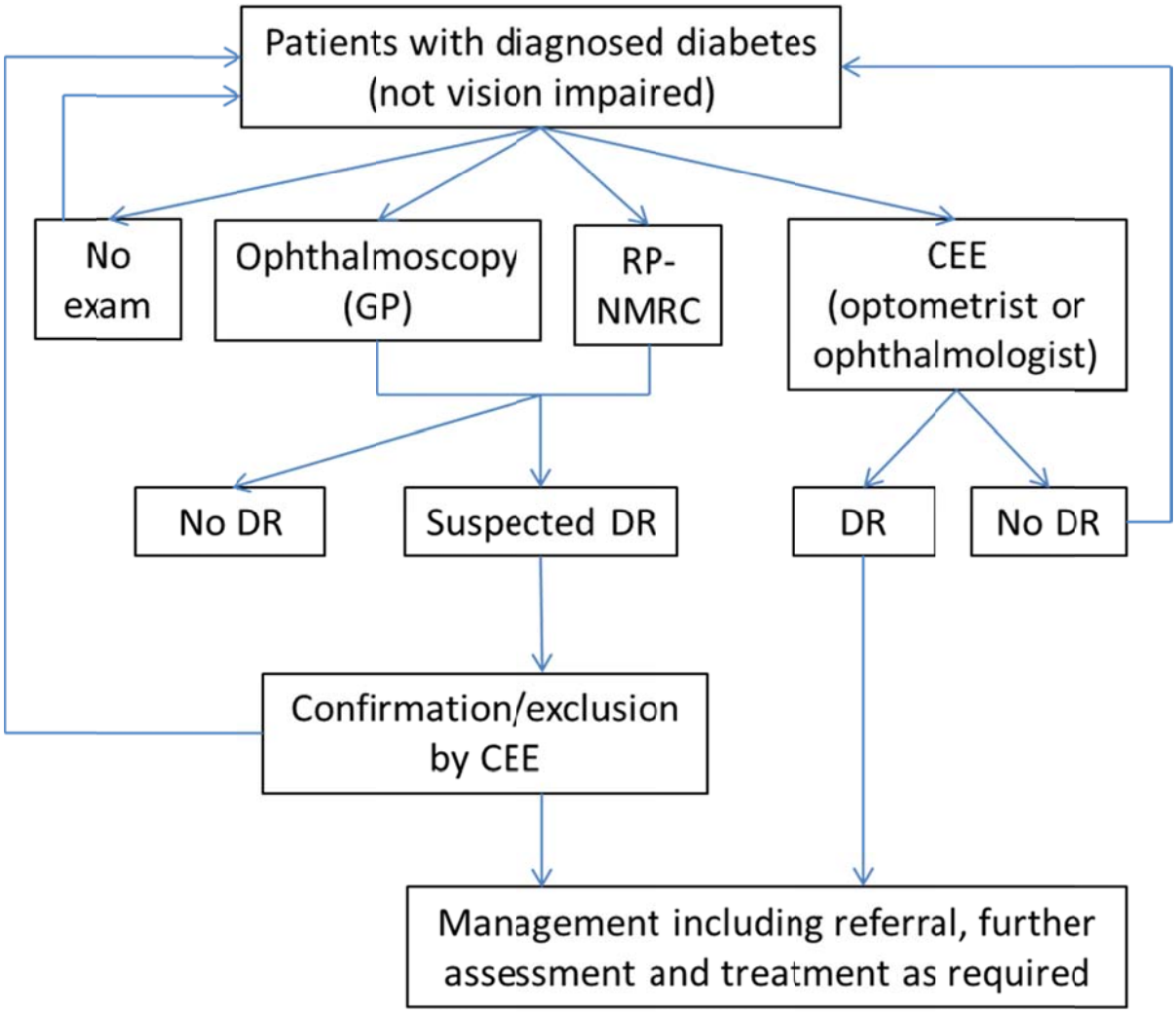


Figure 2 Management algorithm for detection of diabetic retinopathy in patients with diabetes, with the proposed service available, i.e. retinal photography using a non-mydriatic retinal camera

CEE = comprehensive eye examination; RP-NMRC = retinal photography with a non-mydriatic retinal camera; DR = diabetic retinopathy; GP = general practitioner

Note: CEE by an optometrist or ophthalmologist will include fundus examination with mydriasis using an ophthalmoscope or a slit lamp biomicroscope, and may also involve retinal photography. Examination conducted by a GP through an ophthalmoscope may also involve instillation of a mydriatic in the eyes. NHMRC guidelines on DR recommend CEE and ophthalmoscopy are repeated every 2 years among non-Indigenous, and yearly among Indigenous, persons with diabetes(as per NHMRC guidelines on DR). Maximum frequency for the proposed RP-NMRC service is the same as recommended for comparator services among the respective populations. 'No exam' means no eye examination beyond visual acuity testing.

Comparators

The primary comparator is the one that RP-NMRC is most likely to replace, which is proposed by the applicant to be no regular eye examination. PASC has specified standard medical examination as an additional comparator—this can include ophthalmoscopy by a GP and CEE performed either by an ophthalmologist or optometrist, which includes visual acuity testing and an ocular fundus examination through pupils dilated with mydriatic drops. The proposed RP-NMRC service would operate in conjunction with regular CEEs if a patient's photographs show evidence of DR. That is, as a triage test, RP-NMRC would identify instances where DR is and is not present, and hence indicate whether or not referral to CEE is required. In summary, the comparators for the assessment of RP-NMRC are:

- no eye examination
- standard medical assessment, including:
  a) ophthalmoscopy with mydriasis by a GP; and/or
  b) CEE by an optometrist or ophthalmologist (includes SLBM of the fundus without mydriasis).

The MBS items associated with the provision of comparator services are shown in Table 8. Note that MBS item numbers 10900, 10913 and 10916 are for claiming by optometrists, whereas items 23 and 104 are reserved for GP and specialist (i.e. ophthalmologist) consultations, respectively.

Table 8 MBS item descriptors for provision of comparator services

Category 1 – PROFESSIONAL ATTENDANCES
MBS 10900 COMPREHENSIVE INITIAL CONSULTATION Professional attendance of more than 15 minutes duration, being the first in a course of attention - not payable within 24 months of an attendance to which item 10900, 10905, 10907, 10912, 10913, 10914 or 10915 applies Fee: $71.00 Benefit: 85% = $60.35 (See para O6 of explanatory notes to this Category)
MBS 10913 Professional attendance of more than 15 minutes duration, being the first in a course of attention, where the patient has new signs or symptoms, unrelated to the earlier course of attention, requiring comprehensive reassessment within 24 months of an initial consultation to which item 10900, 10905, 10907, 10912, 10913, 10914 or 10915 at the same practice applies Fee: $71.00 Benefit: 85% = $60.35 (See para O6 of explanatory notes to this Category)
MBS 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. Fee: $71.00 Benefit: 85% = $60.35 (See para O6 of explanatory notes to this Category)

MBS 10916 BRIEF INITIAL CONSULTATION Professional attendance, being the first in a course of attention, of not more than 15 minutes duration, not being a service associated with a service to which item 10931, 10932, 10933, 10940, 10941, 10942 or 10943 applies Fee: $35.55 Benefit: 85% = $30.25 (See para O6 of explanatory notes to this Category)
MBS 23 CONSULTATION AT CONSULTING ROOMS Professional attendance at consulting rooms Fee: $36.30 Benefit: 100% = $36.30 (See para A5 of explanatory notes to this Category)
MBS 104 SPECIALIST, REFERRED CONSULTATION – SURGERY OR HOSPITAL (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) INITIAL attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply Fee: $85.55 Benefit: 75% = 64.20 85% = $72.75

The reference standard

The nominated reference standard is CEE performed by an ophthalmologist or optometrist. Given that CEE is also one of the comparators, resources used and item numbers claimed for a CEE by these service providers are discussed in the preceding section ('Comparators').

Review questions

The following research questions were formulated according to the information provided in the application from the Centre for Eye Research Australia (CERA), and were revised and accepted by PASC.

Research questions:

- What is the effectiveness of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing?
- What is the safety and acceptability of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing?
- What is the cost-effectiveness of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing?

Sub-questions (for a linked evidence approach):

Accuracy

- What is the accuracy of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing in people with diagnosed diabetes?

Change in management

- Does the availability of RP-NMRC result in a change in the number of patients with diabetes undergoing a CEE?

Additional policy question (not for systematic review):

- What are the risks and benefits of funding capital equipment separately to the MBS item numbers for the procedure?

Diagnostic assessment framework

This assessment uses the theoretical framework outlined in the MSAC *Guidelines for the Assessment of Diagnostic Technologies* (MSAC 2005).

This means that evidence of the clinical effectiveness of RP-NMRC requires either:

- evidence of the effectiveness of RP-NMRC from high-quality comparative studies (direct evidence) evaluating whether the use of RP-NMRC affects patient health outcomes differently when compared with standard medical assessment or no eye examination. Randomised controlled trials (RCTs) provide the highest quality evidence for this comparison. Or, if this is not available;

- evidence of effectiveness from comparative studies evaluating whether RP-NMRC results in changes to clinical management, linked with applicable evidence of the accuracy of RP-NMRC in the diagnosis of DR compared with standard medical assessment (or no eye examination)[11]. This is called 'linked evidence'.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period between 1985 and February 2014, as RP-NMRC was first available in 1985. Searches were conducted via the databases described in Appendix C. Search terms are described in Table 9.

[11] Note: PASC agreed that a third linkage step investigating the impact of treatment of diagnosed patients on health outcomes is not required (i.e. no research question asking whether patients receiving RP-NMRC benefit from any subsequent change in management was considered necessary). The rationale is that the effectiveness of DR treatment is already established, and RP-NMRC as a triage test will not broaden the spectrum of patients being treated.

Table 9 Search terms used (PubMed platform)

Element of clinical question	Search terms
Population	"Diabetes Mellitus"[MeSH Terms]
Intervention	(("Retina"[Mesh] OR "Diabetic Retinopathy"[Mesh] OR "Mydriasis"[Mesh]) AND "Photography"[Mesh])) OR ((retina*[tiab] OR fundus*[tiab] OR retinopathy[tiab]) AND (photograph*[tiab] OR imaging[tiab] OR camera[tiab]) AND (mydria*[tiab] OR nonmydria* OR dilat*[tiab] OR undilat*[tiab]))
Limits	Search period: 1985 – 2/2014 Language: English / German

MeSH = Medical Subject Heading

Study selection criteria

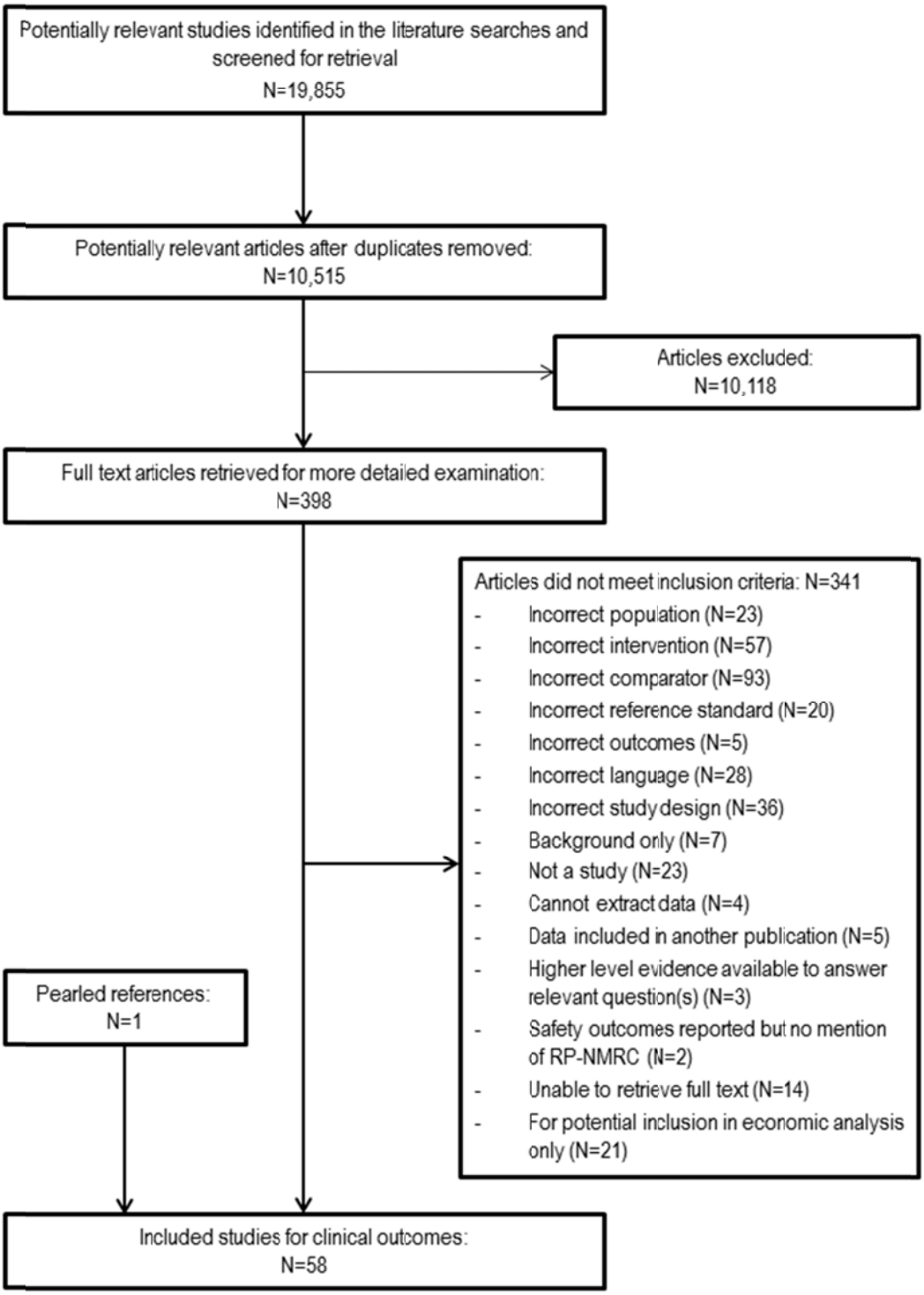
In general, studies were excluded from the review if they:

- did not provide information on the pre-specified target population;
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes;
- were in a language other than English or German and were of a lower level of evidence than the studies in English or German; or
- did not have an eligible study design.

If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included.

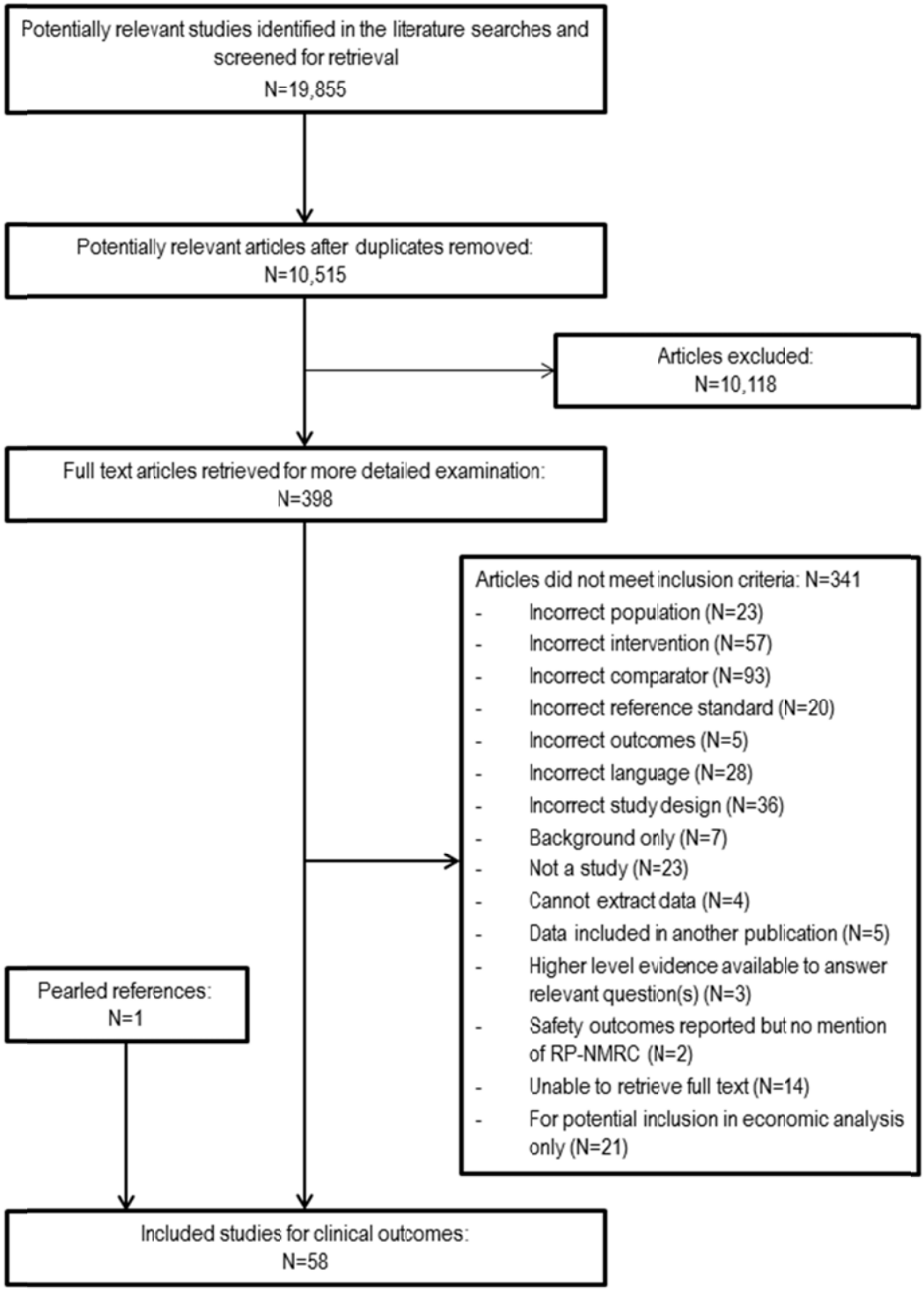
Search results

A PRISMA flowchart is shown in



Source: Liberati et al. (2009)

Figure 3, outlining the number of papers considered at each stage of the systematic review.



Source: Liberati et al. (2009)

Figure 3 Summary of the process used to identify and select studies for the review

Data extraction and analysis

A profile of key characteristics was developed for each included study (see Table 92). Each study profile described the level of evidence, design and quality of the study, authors, publication year, location, criteria for including/excluding patients, study population characteristics, type of intervention, comparator intervention and/or reference standard (where relevant), and outcomes assessed. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed in Appendix F. Definitions of all technical terms and abbreviations are provided in the 'Glossary and abbreviations' section. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies.

Assessing diagnostic accuracy

To assess the diagnostic accuracy of RP-NMRC, where possible the sensitivity, specificity, negative and positive predictive values (NPV, PPV) and likelihood ratios (LR+, LR–) were calculated with corresponding 95% confidence intervals (CIs). Data were extracted into a classic 2×2 table (Table 10), in which the results of the index diagnostic test were cross-classified against the results of the reference standard (Armitage, Berry & Matthews 2002; Deeks 2001), and Bayes' Theorem was applied:

Table 10 Diagnostic accuracy data extraction for RP-NMRC

		CEE		
		Disease +	*Disease –*	
RP-NMRC	*Test +*	true positive	false positive	Total test positive
	Test –	false negative	true negative	Total test negative
		Total with DR	Total without DR	

CEE = comprehensive eye examination; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Primary measures

Test sensitivity was calculated as the proportion of people with DR (as determined by the reference standard) who tested positive using RP-NMRC:

Sensitivity (true positive rate) = number with true positive result / total with DR

Test specificity was calculated as the proportion of people without DR (as determined by the reference standard) who had a normal test result using RP-NMRC:

Specificity (true negative rate) = number with true negative result / total without DR

A PPV is the proportion of positive test results that are true positives, and the NPV is the proportion of negative test results that are true negatives. These values reflect the probability that a positive (or negative) test corresponds with having (or not having) DR. However, its value depends on the prevalence of DR in the target population being tested.

PPV = number true positives / total test positives

NPV = number true negatives / total test negatives

When a 95%CI was not provided, it was calculated by exact binomial methods.

Positive and negative likelihood ratios (LRs) measure the probability of the test result in patients with DR compared with those without DR.

LR+ = sensitivity / 1–specificity

LR– = 1–sensitivity / specificity

A likelihood ratio of 1 means that the test does not provide any useful diagnostic information, whereas LR+ >5 and LR– <0.2 can suggest strong diagnostic ability (MSAC 2005).

Summary measures

Diagnostic test accuracy meta-analysis was undertaken to assess the accuracy of RP-NMRC in the diagnosis of DR, relative to SLBM and/or a CEE by an ophthalmologist, using Stata version 12 (Stata Corporation 2013). Only studies that provided raw (2×2) data could be included in a meta-analysis. Hierarchical summary receiver–operator characteristic (HSROC) curves were generated using the 'metandi' command. This fits the model based on the method developed by Rutter & Gatsonis (2001), which uses multiple-level mixed effects logistic regression ('xtmelogit'). Summary estimates for sensitivity, specificity, LR+ and LR– were calculated. CIs were computed assuming asymptotic normality after a log transformation for variance parameters and for LR+ and LR–. Forest plots and LR scattergrams were generated using the 'midas' command, which requires a minimum of four studies for analysis and calculates summary operating sensitivity and specificity (with confidence and prediction contours in SROC space), also using 'xtmelogit'. Heterogeneity was calculated using the formula:

$$I^2 = 100\% \times (Q - df)/Q$$

where Q is Cochran's heterogeneity statistic and df is the degrees of freedom (Higgins et al. 2003).

In addition to the overall analysis of results for the ability of RP-NMRC to detect any DR versus no DR, subgroup analyses were performed for results according to the degree (level) of DR (urgency of referral), whether or not chemical mydriasis was used with RP-NMRC, the number of fields used for retinal image acquisition, and the year the study was published.

Where meta-analysis could not be performed, the median (range) sensitivity and specificity values were presented.

Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the systematic review (strength of the evidence).

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results for primary outcomes in individual studies—used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Stage 1: Strength of the evidence

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

Table 11 Evidence dimensions

Type of evidence	Definition
Strength of the evidence:	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design [a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 12

These dimensions (Table 11) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention; the last two each require expert clinical input as part of their determination.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results. The impact of bias on the *execution* of the study is also assessed, and is discussed below. The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (Table 12).

Table 12 Designations of levels of evidence according to type of research question (including table notes)

Level	Intervention [a]	Diagnostic accuracy [b]
I [c]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard [d], among consecutive persons with a defined clinical presentation [e]
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard [d], among non-consecutive persons with a defined clinical presentation [e]
III-2	A comparative study with concurrent controls: ▪ non-randomised, experimental trial [f] ▪ cohort study ▪ case-control study ▪ interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	A comparative study without concurrent controls: ▪ historical control study ▪ two or more single arm studies [g] ▪ interrupted time series without a parallel control group	Diagnostic case-control study [e]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) [h]

Source: Merlin, Weston & Tooher (2009)

Explanatory notes:

[a] Definitions of these study designs are provided in NHMRC (2000; pp. 7–8) and in the accompanying Glossary.

[b] These levels of evidence apply only to studies assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient

management and health outcomes (MSAC 2005; Sackett & Haynes 2002). The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or alternative screening methods.

[c] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity, and thus are rated on the likelihood that the results have been affected by bias rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies and study designs might contribute to each different outcome.

[d] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al. 2011).

[e] Well-designed population-based case-control studies (e.g. screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease, are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin & Miller 2002).

[f] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C, with statistical adjustment for B).

[g] Comparing single-arm studies, i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C, but where there is no statistical adjustment for B).

[h] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within RCTs, in which case lower levels of evidence may be the only type of evidence that is practically achievable; both physical and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a 'level of evidence' should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

Sources: Adapted and modified from Bandolier editorial (1999); NHMRC (1999); Phillips et al. (2001)

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Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 13.

Table 13 Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population

The likelihood that the execution of the identified research was affected by bias was also critically appraised. The appraisal of intervention studies was undertaken using the Downs and Black (1998) checklist. This validated checklist was used for trials and cohort studies. Uncontrolled before-and-after case series were assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al. 2001). The quality of studies of diagnostic accuracy was assessed using the QUADAS-2 tool (Whiting et al. 2011).

Stage 2: Precision, size of effect and clinical importance

Small CIs and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Similarly, studies need to be appropriately powered to ensure that a real difference between groups will be detected in the statistical analysis.

For intervention studies it was important to assess whether statistically significant differences between patients receiving RP-NMRC and standard medical assessment were also clinically important. The size of the effect needed to be determined, as well as whether the 95%CI included only clinically important effects.

The outcomes being measured in this report were assessed as to whether they were appropriate and clinically relevant (NHMRC 2000).

Stage 3: Assessment of the body of evidence

Appraisal of the body of evidence was conducted in accordance with NHMRC's recommendations on clinical practice guideline development (NHMRC 2009). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence-base—which includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results—whether the better quality studies had results of a similar magnitude and in the same direction, i.e. homogenous or heterogeneous findings
- the potential clinical impact—appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test
- the generalisability of the evidence to the target population
- the applicability of the evidence—integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 14).

Table 14 Body of evidence matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base [a]	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias, or an SR or several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency [b]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as target population	Population(s) studied in the body of evidence are similar to target population	Population(s) studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population [c]	Population(s) studied in body of evidence differ from target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: adapted from NHMRC (2009)

SR = systematic review; several, more than two studies

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)

[b] If there is only one study, rank this component as 'not applicable'.

[c] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

Expert advice: Health Expert Standing Panel (HESP)

HESP is a panel of experts collated from various medical fields who are nominated by their associated professional body or by applicants (see Appendix A). HESP members are engaged to provide practical, professional advice to evaluators relevant to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees. Their role is limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and that consumer interests are accounted for. HESP members' advice is used to inform the deliberations that MSAC presents to the Federal Minister for Health.

Results of assessment

Is it safe?

Summary—What is the safety and acceptability of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing?

There was no literature that reported safety outcomes related to the use of RP-NMRC without mydriasis. There was also a paucity of literature investigating adverse events associated with the use of mydriasis for comparator tests, with one case series indicating that mydriasis-related angle-closure glaucoma attack is rare in the relevant population.

RP-NMRC was found to be highly acceptable to the majority of patients across the included studies. The included studies suggested that up to one-fifth of patients experienced some level of discomfort during the procedure, with very few experiencing severe discomfort associated with the high-power flash used on older Polaroid systems. Current digital systems were found to be associated with 'any level of discomfort' in no more than 3% of patients. Compared with assessment by an ophthalmologist, patients considered the duration of RP-NMRC more acceptable. The majority of patients across studies were satisfied with RP-NMRC, preferred it to an examination by an ophthalmologist, and expressed that they would return for yearly screening. One Australian study that interviewed a small sample of Indigenous diabetes patients found that 90% were very positive about the use of RP-NMRC in their local Indigenous health service.

Studies were included to assess the safety of RP-NMRC according to criteria outlined *a priori* in Box 1.

Box 1 PICO criteria for the safety and acceptability of RP-NMRC in patients with diabetes

Selection criteria	Inclusion criteria
Population	Patients with a diagnosis of diabetes and no visual impairment
Intervention	RP-NMRC
Comparators	Standard medical assessment, including: a) ophthalmoscopy by a GP, with mydriasis; and/or b) CEE by an ophthalmologist or optometrist (includes ophthalmoscopy or SLBM of the fundus with mydriasis) No eye examination
Outcomes	- Potential physical and psychological harms from testing - Patient acceptability (e.g. reluctance to undergo mydriasis)
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series or systematic reviews of these study designs
Search period	1985 – February 2014
Language	Studies in languages other than English or German were only translated if they represented a higher level of evidence than that available in the English or German language evidence-base

Systematic review question	What is the safety and acceptability of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing?

CEE = comprehensive eye examination; DR = diabetic retinopathy; GP = general practitioner; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SLBM = slit lamp biomicroscopy

Safety of RP-NMRC

No studies were identified that reported on the comparative safety of RP-NMRC versus standard medical assessment or no eye examination. One case series mentioned the rate of angle-closure glaucoma after the use of mydriasis when used in conjunction with RP-NMRC (Maberley et al. 2002) (Table 15). Of the 75 patients who underwent RP-NMRC with mydriasis, one patient had angle-closure glaucoma 4 hours later.

Table 15 Adverse events after RP-NMRC

Study Level and quality	Study N	Intervention—RP-NMRC	Results
Maberley et al. (2002) Canada Level IV High-quality case series	N=75/100 diabetes patients	Setting Mobile screening unit in remote area Camera Topcon TRC-NW5SF, digital 1 x 45° image per eye Photographer Ophthalmic photographer or minimally trained healthcare worker Reader Retinal specialist at retinal research unit Mydriasis First 15 patients without Remaining 75 patients with mydriasis	1/75 (1.3%) who had dilation presented 4 hours later with angle-closure glaucoma

NS = not stated; RP-NMRC = retinal photography with a non-mydriatic retinal camera

An exploration of adverse events related to mydriasis, found from studies not specific to RP-NMRC, is given in the 'Discussion' section.

Acceptability of RP-NMRC

Two studies (Massin et al. 2005; Taylor, DJ et al. 1999) provided comparative data on the acceptability of RP-NMRC relative to examination by an ophthalmologist (Table 16). Both studies were classified as having poor reporting but good external generalisability (see Table 94 in Appendix E). The cohort study (Massin et al. 2005) could not be ruled out as being at risk of confounding due to poorly documented patient characteristics that may have differed between intervention and comparator groups.

The results of Massin et al. (2005) and Taylor, DJ et al. (1999) may be seen in Table 16. Comparing digital RP-NMRC, Polaroid RP-NMRC and ophthalmoscopy, digital RP-NMRC was

found to cause the least discomfort, with only 4 out of 154 patients reporting some discomfort (Taylor, DJ et al. 1999). The Polaroid system caused a lot of discomfort in 2, and some discomfort in 27 out of 176 patients due to the flash, which was of a higher power than the digital systems used (300W vs 10W). Ophthalmoscopy caused a lot of discomfort in 5, and some discomfort in an additional 32 out of 178, patients.

Visual impairment was considered to be less from RP-NMRC than from an examination by an ophthalmologist ($p<0.001$), and the duration of testing was more acceptable ($p<0.001$) (Massin et al. 2005).

Table 16 Acceptability of RP-NMRC versus eye examination by ophthalmologist

Study	Study population	Intervention—RP-NMRC	Comparator	Outcome	RP-NMRC	Eye examination by ophthalmologist	Comparison
Massin et al. (2005) France Level III-2 Quality 15/26 (poor)	N=834 diabetes patients	Setting Primary care Camera Topcon TRC-NW6S 5 x 45° images per eye Photographer Orthoptist Reader Trained ophthalmologists Mydriasis None	Dilated eye fundus examination with ophthalmologist	Duration of testing acceptable Visual impairment induced by flash absent or mild Accessibility not difficult or only slightly difficult Ready to have next annual screening examination with RP-NMRC	96% 86% 82% 99.1%	82% 66% 93% NA	Chi^2, p<0.001 Chi^2, p<0.001 Chi^2, p<0.001 NA
Taylor, DJ et al. (1999) UK Level II Quality: 19/26 (moderate)	N=118 diabetes patients	Setting GP-based mobile retinal screening clinic Camera Topcon/Imagenet system, Canon CR5/Ris-Lite system and 45° CR4NM Polaroid photography Photographer NS Reader Experienced grader Mydriasis Yes	Ophthalmoscopic review	Discomfort level: 'some' or 'a lot'	Polaroid: 29/176 (16.4%) Digital: 4/154 (2.6%)	37/178 (20.8%)	RR=0.79 [95%CI 0.51, 1.23] RR=0.13 [95%CI 0.05, 0.35]

GP = general practitioner; NA = not applicable; NS = not stated; RP-NMRC = retinal photography with a non-mydriatic retinal camera; RR = relative risk

A further 8 studies provided non-comparative data on the acceptability of RP-NMRC; and 1 study, which included patients undergoing RP-NMRC, assessed the acceptability of mydriasis (see Table 17, Table 18; and Table 95 in Appendix E).

RP-NMRC was found to be acceptable or very acceptable among 98.6% of patients studied by Boucher et al. (2005). Patients reported being satisfied with RPNRMC in 98.6% to 100% of cases (Boucher, Nguyen & Angioi 2005; Cavallerano, JD et al. 2005) and gave an overall rating of 8.6±3.2 on a 10-point Likert scale[12] (Newman et al. 2012). Patients preferred RP-NMRC over examination by an ophthalmologist in 82% to 92.3% of cases (Boucher, Nguyen & Angioi 2005; Cavallerano, JD et al. 2005), and 88.5% to 93% responded that they would return for RP-NMRC testing yearly (Boucher, Nguyen & Angioi 2005; Cavallerano, JD et al. 2005; Massaro, Curry & Quillen 2010). Some discomfort was reported when a Polaroid system was used (Mohan et al. 1988), with the level of discomfort great enough to prevent 4.7% of the Indian sample returning for yearly screening. Given the comparative evidence that digital RP-NMRC causes less discomfort than Polaroid systems (Taylor, DJ et al. 1999), it is unlikely that the discomfort reported by Mohan et al. (1988) would be applicable to the systems used currently.

The most relevant of the included case series to the MBS target population was performed in an Indigenous Health Service in south-western Brisbane. This study sought to determine the acceptability of the service to patients (Spurling et al. 2010). Semi-structured interviews were conducted with 11 participants from the 124 people screened with RP-NMRC. The participants were selectively chosen by clinic staff as being likely to participate in an interview with an unknown researcher. It is not known if or how this selection process may have biased the sample chosen. Of those interviewed, the majority (10/11) were very positive about the experience. These participants felt that RP-NMRC was convenient as it occurred at the same time as other aspects of their diabetes care, there were no lengthy waiting times, and there was free and easy parking. The Indigenous Health Service was also considered to be culturally appropriate, providing a safe environment for the clients where they were treated with respect. The remaining participant was concerned about being screened by a non-eye specialist, and about the inexperience of the practice staff. The interviews conducted were only concerned with the convenience and acceptability of the RP-NMRC within the Indigenous Health Service. From the article identified, it is unknown what the attitudes were towards attending optometrists or ophthalmologists.

[12] 0 = worst eye examination experience; 10 = best eye examination experience

Table 17 Acceptability of RP-NMRC in non-comparative studies

Study Level and quality	Study population	Intervention—RP-NMRC	Outcome measures	Results
Boucher, Nguyen & Angioi (2005) Canada Level IV Quality: 3/6 (medium)	N=291 patients with diabetes (85.9% type 2)	Setting Regional health centre Camera Topcon TRC-NW5S; digital Photographer NS Reader Ophthalmologists Mydriasis None	Patients' acceptance of screening through RP-NMRC imaging: Very acceptable Acceptable Satisfied with the screening experience Would prefer it over traditional examination for next screening Expressed future compliance with this screening Preference over a standard examination by an ophthalmologist Believed standard examination by an ophthalmologist was irreplaceable	 264/291 (90.8%) 23/291(7.8%) 287/291 (98.6%) 277/291 (95.1%) 265/291 (91.2%) 239/291 (82%) 18%
Cavallerano, JD et al. (2005) USA Level IV Quality: 4/6 (medium)	N=52 patients with diabetes (63% type 2)	Setting Diabetes centre Camera Digital video NM retinal imaging system Photographer Certified imagers Reader Certified readers Mydriasis None	Overall experience with non-mydriatic retinal photographic imaging: Very satisfied Satisfied Not satisfied Would return for non-mydriatic retinal imaging on a yearly basis: Definitely yes Maybe Definitely no If both imaging techniques provide similar medical information, would replace pupil dilation and examination by eye doctor with RP-NMRC Strongly agree Agree Strongly disagree No answer	 37/52 (71.2%) 15/52 (28.8%) 0 46/52 (88.5%) 5/52 (9.6%) 1/52 (1.9%) 29/52 (55.8%) 19/52 (36.5%) 3/52 (5.8%) 1/52
Kurji et al. (2013) Kenya Level IV Quality: 3/6 (medium)	N=57 diabetes patients, of whom 26 could be contacted for telephone survey	Setting Multidisciplinary diabetes clinic Camera Topcon TRC NW100; digital Photographer	Patients preferred teleophthalmology over in-person examination for future screenings Satisfied with teleophthalmology screening	5-point Likert scale (± SD, where >3.25 is favourable) 3.42 ± 1.52 4.15 ± 0.97

Study Level and quality	Study population	Intervention—RP-NMRC	Outcome measures	Results
		Trained nurses Reader Trained ophthalmologist Mydriasis NS		
Leese et al. (1992) UK Level IV Quality: 3/6 (medium)	N=312 diabetes patients	Setting Mobile van Camera Canon CR4 45NM Polaroid Photographer NS Reader Hospital physicians, with doubtful films assessed by ophthalmologists Mydriasis NS	Favourable response Unfavourable comments No adverse or appreciative comments	49% 7% 41%
Massaro, Curry & Quillen (2010) USA Level IV Quality: 4/6 (medium)	N=87 diabetes patients	Setting Primary care setting Camera Canon CR-DG Photographer Certified ophthalmic photographers Reader Ophthalmologist Mydriasis None	Think digital retinal scan is beneficial Would get a digital scan annually to check for retinopathy	94% positive response 93% positive response
Mohan et al. (1988) UK Level IV Quality: 3.5/6 (medium)	N=85 diabetes patients (165 eyes)	Setting Hospital diabetes clinic Camera CR3-45NM; Polaroid	Some discomfort during photographs Discomfort sufficient to decline yearly examination	13/86 (15.1%) Indians 2/79 (2.5%) Europeans 4/86 (4.7%) Indians

Study Level and quality	Study population	Intervention—RP-NMRC	Outcome measures	Results
		Photographer Not stated Reader Author—specialty not stated Mydriasis None		
Newman et al. (2012) USA Level IV Quality: 3/6 (medium)	N=274 diabetes patients screened with new point-of-care system	Setting Primary care centre Camera Retasure DRI system; digital Photographer Trained individual Reader Remote retinal specialist Mydriasis None	Favourable comments about convenience of getting procedure done at point of care, and economic benefit of having it done at primary care appointment	Mean satisfaction on 10-point Likert scale 8.6 ± 3.2
Spurling et al. (2010) Australia Level IV Quality: 4/6 (medium)	N=11 Indigenous diabetes patients, chosen for their likelihood of agreeing to talk to unknown researcher	Setting Indigenous health unit (primary care) Camera Canon CR-DGi Photographer GPs with 4 hours training Reader GPs with 4 hours training Mydriasis Used if photo uninterpretable by GP	Very positive about RP-NMRC in Indigenous Health Service	10/11 (90.9%)

BMI = body mass index; DMO = diabetic macular oedema; DR = diabetic retinopathy; GP = general practitioner; NM = non-mydriatic; NPDR = non-proliferative DR; NS = not stated; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SD = standard deviation

One study compared attitudes towards mydriasis between patients who were having routine annual dilated direct fundoscopy and those attending for RP-NMRC testing. Attitudes towards mydriasis were ascertained, both in those who were used to receiving it for the purposes of fundoscopy and those who had undergone RP-NMRC without mydriasis. In both groups the majority of patients considered it would be acceptable to use mydriasis if it improved the quality of photographs. Those who had experienced the use of mydriasis at a previous direct fundoscopy were more likely to consider that it was acceptable than those who were used to receiving RP-NMRC without mydriasis (85% vs 56%). Of those who had experience with mydriasis, its worst aspect was considered to be the discomfort associated with instilling the drops (48%), followed by the inconvenience of blurred vision (41%).

Table 18 Acceptability of mydriasis

Study	Study population	Intervention—RP-NMRC	Outcome	Not used to mydriasis	Used to mydriasis
Murgatroyd et al. (2006) Scotland Level IV Quality: 1/6 (poor)	N=292 patients attending a diabetes clinic with previous experience of mydriasis N=103 patients attending mobile RP-NMRC screening	Setting Diabetes clinic and mobile DR screening Camera NS Photographer NS Reader NS Mydriasis Group 1 only, type NS	Feelings towards mydriasis if it improves quality of photographs Mydriasis discourages attendance Worst aspect of mydriasis	Acceptable: 58/103 (56%) Unhappy: 43/103 (42%) 27/103 (26%) Waiting: 4/103 (4%) Blurred vision: 65/103 (63%) Discomfort: 29/103 (28%)	Acceptable: 247/292 (85%) Unhappy: 22/292 (8%) 3/292 (1%) Waiting: 76/292 (26%) Blurred vision: 120/292 (41%) Discomfort: 48/292 (48%)

DR = diabetic retinopathy; NS = not stated, RP-NMRC = retinal photography with a non-mydriatic retinal camera

Is it effective?

Direct evidence of diagnostic effectiveness

Summary—What is the effectiveness of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing in people with diagnosed diabetes?

The current evidence-base does not enable any direct conclusions regarding whether the use of RP-NMRC in the relevant population improves patient health compared with standard care or no eye examination.

No direct evidence was identified for the effectiveness of RP-NMRC testing. Studies meeting the inclusion criteria for a linked analysis of effectiveness are reported in the following section.

To be eligible for inclusion in the assessment of direct effectiveness, studies were required to satisfy the criteria outlined *a priori* in Box 2.

Box 2 PICO criteria to determine the effectiveness of RP-NMRC in patients with diabetes compared with standard medical assessment or no eye examination beyond visual acuity testing (direct)

Selection criteria	Inclusion criteria
Population	Patients with a diagnosis of diabetes and no visual impairment
Intervention	RP-NMRC (followed by a CEE in those with signs of DR)
Comparators	Standard medical assessment, including: a) ophthalmoscopy by a GP, with mydriasis (followed by a CEE in those with signs of DR); or b) CEE by an ophthalmologist or optometrist (includes ophthalmoscopy or SLBM of the fundus with mydriasis) No eye examination
Outcomes	- Vision impairment/loss - Progression or stabilisation of symptoms of DR - Quality of life
Study design	Randomised or non-randomised controlled trials, cohort studies, case-control studies, comparative studies without concurrent controls, pre-test/post-test case series or systematic reviews of these study designs
Search period	1985 – February 2014
Language	Studies in languages other than English or German were only translated if they represented a higher level of evidence than that available in the English or German language evidence-base
Systematic review question	What is the effectiveness of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing in people with diagnosed diabetes?

CEE = comprehensive eye examination; DR = diabetic retinopathy; GP = general practitioner; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SLBM = slit lamp biomicroscopy

Linked evidence

Is RP-NMRC accurate?

Summary—What is the diagnostic accuracy of RP-NMRC?

Meta-analyses of studies investigating the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE showed that there was little or no difference among studies based on the use of chemical mydriasis with RP-NMRC for any of the subgroups investigated. However, the use of mydriasis did greatly reduce the number of unreadable images (UIs) obtained, from a median of 19.3% (range 11–36%) to a median 5.3% (range 2.5–8.3%).

The HSROC curve showed a very good level of detection of any DR by RP-NMRC compared with SLBM and/or CEE among all studies (AUC = 0.89 [95%CI 0.86, 0.92]). The LR scattergram strongly indicated that a negative test result is likely to be accurate, suggesting that RP-NMRC would be useful for exclusion of any DR (false negative rate = 9%) Thus, RP-NMRC would be a useful test to triage patients for further examination by an ophthalmologist.

Subgroup analysis for the detection of any DR based on the number of fields in the eye that were photographed showed that the sensitivity increased from 83% (95%CI 71, 90) to 97% (95%CI 87, 99), and the specificity decreased from 79% (95%CI 69, 86) to 66% (95%CI 52, 77), when more than one field was photographed, although the 95%CIs were overlapping. This is reflected in the HSROC curve, which shows a threshold effect based on the number of fields photographed. In the LR scattergram the summary LR+ and LR– values move from the lower right quadrant to the lower left quadrant when more than one field is photographed. This indicates that multiple-field RP-NMRC can be successfully used as a triage as it is highly likely that patients without DR, who would not require any further investigations by an ophthalmologist for DR, would be correctly identified (LR– <0.1). In fact, only 1 in 33 patients tested with multiple-field RP-NMRC would receive a false negative test result. Thus, multiple-field RP-NMRC would be a very useful test to triage patients for further examination by an ophthalmologist.

In the detection of severe non-proliferative DR (NPDR) or worse, subgroup analysis showed that studies detecting proliferative DR (PDR) were more sensitive (84.7% 95%CI 70.5, 92.8) than those detecting moderate or severe NPDR or worse (67.4% 95%CI 47.1, 82.7). The specificity was approximately 98% for both groups. The HSROC curve showed an excellent level of detection of severe NPDR or worse by RP-NMRC (AUC = 0.96 95%CI 0.94, 0.98), and a threshold effect based on the severity of DR. The LR scattergram showed that the summary LR+ and LR– values fall in the upper right quadrant for a moderate or severe NPDR cut-off point, and move towards the left to lie in the 0.1–0.2 range for a cut-off point of PDR. This indicates that the ability of the test to correctly identify patients increased as the cut-off point increased in disease severity. Thus, RP-NMRC is useful for both confirmation and exclusion of PDR.

However, it should be noted that in nearly all the studies included above the photographs were read by ophthalmologists or retinal specialists, as opposed to GPs or other professionals with minimal training in a community or rural primary care setting. Six studies reported on agreement among different readers. Agreement between GP readers and retinal specialists ranged between kappa values of 0.40 to 0.95 (the majority of measures being toward the higher limit). The kappa value for agreement between non-physician readers and retinal specialists was 0.66, and between trained imagers and trained readers 0.95.

Studies were included to assess the accuracy of RP-NMRC according to criteria outlined *a priori* in Box 3.

Box 3 PICO criteria for the accuracy of RP-NMRC in patients with diabetes

Selection criteria	Inclusion criteria
Population	Patients with a diagnosis of diabetes and no visual impairment
Intervention	RP-NMRC
Comparator	Standard medical assessment, including: a) ophthalmoscopy by a GP, with mydriasis; and/or b) CEE by an ophthalmologist or optometrist (includes ophthalmoscopy or SLBM of the fundus with mydriasis) No eye examination
Evidentiary standard	CEE (includes ophthalmoscopy or SLBM of the fundus) by an optometrist or ophthalmologist, with mydriasis
Outcomes	- Measures of test performance (e.g. sensitivity, specificity, negative and positive predictive values, false positive and false negative rates) - Diagnostic yield of DR and non-DR outcomes - Measures of test concordance (e.g. kappa measures, agreement measures), in the absence of or with limited test performance data - Rate of unreadable photographs or inability to make a diagnosis
Study design	All study designs in the 'Diagnostic accuracy' column of Table 12, which have a reference standard (level I to III-3) or comparative diagnostic yield (level IV). Non-comparative studies of diagnostic yield were excluded
Search period	1985 – February 2014
Language	Studies in languages other than English or German were only translated if they represented a higher level of evidence than that available in the English or German language evidence-base
Systematic review question	What is the diagnostic accuracy of RP-NMRC compared with standard medical assessment or no eye examination beyond visual acuity testing in people with diagnosed diabetes?

CEE = comprehensive eye examination; DR = diabetic retinopathy; GP = general practitioner; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SLBM = slit lamp biomicroscopy

No studies were identified that compared the diagnostic accuracy of RP-NMRC and ophthalmoscopy by a GP with SLBM/CEE (the evidentiary standard). However, 1 study did report on the accuracy of RP-NMRC compared with ophthalmoscopy by a GP where the latter procedure was used as a reference standard (O'Hare et al. 1996). In isolation the results of this study (Table 92) cannot be used to make meaningful conclusions with respect to the diagnostic accuracy of RP-NMRC[13].

A total of 30 studies that assessed the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE by an ophthalmologist (which is also the evidentiary standard) met the inclusion criteria in Box 4. Summaries of the diagnostic accuracy outcomes for each study are presented in Table 92 in Appendix C. The study profiles are provided in Table 96 in Appendix E. Twenty-three studies reported 2x2 data that could be used in a meta-analysis;

[13] While ophthalmoscopy by a GP was nominated *a priori* as a comparator for this review, it is not a reliable/appropriate reference standard by which to judge the accuracy of RP-NMRC. Rather, the relative accuracy of RP-NMRC versus ophthalmoscopy by a GP against CEE, nominated as the reference standard *a priori*, is required.

14 studies included UIs and 9 did not. Twelve studies reported the results per patient, including 6 of 8 studies that did not provide 2x2 data; the other studies reported the results per eye examined. The studies also varied in the use of chemical mydriasis and in the number of fields per eye that were photographed (Table 92, Table 96). The effects of these differences on the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE are discussed below.

Meta-analysis of studies that reported 2x2 data (including UIs) for the detection of any DR

Meta-analysis was performed using 2x2 data from 13 studies that compared RP-NMRC with SLBM and/or CEE to detect any DR, provided that the UIs were included. This is important because a median of 8% (range 0–21.5%) of patients/eyes in these 13 studies had UIs, which would result in a referral to an ophthalmologist in clinical practice. Thus, UIs were treated as a positive result in the meta-analysis. When the study provided data with and without the use of chemical mydriasis, the 'without' results were used in the meta-analysis, as this was the most clinically relevant outcome in the context of this assessment.

Table 19 Summary statistics for subgroup analysis of diagnostic accuracy for referral of any detectable DR plus UIs by RP-NMRC compared with SLBM and/or CEE

Subgroup		Sensitivity [95%CI]	Specificity [95%CI]	LR+ [95%CI]	LR– [95%CI]
Overall	(k = 13)	91.2% [81.7, 96.1]	76.5% [67.4, 83.6]	3.88 [2.79, 5.40]	0.11 [0.05, 0.24]
Chemical mydriasis:					
without	(k = 7)	91.7% [79.2, 97.0]	74.4% [61.2, 84.2]	3.58 [2.26, 5.66]	0.11 [0.04, 0.30]
with	(k = 7)	89.4% [72.2, 96.5]	74.2% [63.5, 82.7]	3.47 [2.42, 4.78]	0.14 [0.05, 0.40]
Publication year:					
pre-2000	(k = 7)	84.1% [68.1, 92.9]	82.3% [71.4, 89.7]	4.75 [2.68, 8.14]	0.19 [0.09, 0.43]
post-2000	(k = 6)	96.1% [86.5, 99.0]	68.2% [55.7, 78.7]	3.03 [2.16, 4.26]	0.06 [0.02, 0.19]
By study size:					
<400 eyes	(k = 5)	92.5% [71.9, 98.4]	81.7% [67.4, 90.6]	5.05 [2.70, 9.44]	0.09 [0.02, 0.40]
>400 eyes	(k = 8)	91.0% [73.7, 97.3]	81.2% [69.0, 89.4]	4.84 [2.83, 8.30]	0.11 [0.03, 0.35]
By number of fields photographed:					
1 field	(k = 8)	82.7% [70.9, 90.3]	78.5% [68.7, 85.9]	3.85 [2.50, 5.90]	0.22 [0.12, 0.39]
2–7 fields	(k = 5)	96.6% [87.0, 99.2]	65.5% [52.0, 76.0]	2.80 [2.00, 3.93]	0.05 [0.01, 0.19]

CI = confidence interval; k = number of studies; LR+ = positive likelihood ratio; LR– = negative likelihood ratio

Included studies: Cavallerano, AA et al. (2003); Chia & Yap (2004); Diamond et al. (1998); Freyberger et al. (1995); Lee, VS et al. (1993); Lin et al. (2002); Maberley et al. (2002); Mohan et al. (1988); Mollentze, Stulting & Steyn (1990); Moriarty et al. (1993); Penman et al. (1998); Scanlon et al. (2003a), (2003b)

The summary measures for sensitivity, specificity, LR+ and LR– for the detection of any DR by RP-NMRC compared with SLBM and/or CEE are shown in Table 19. Subgroup analysis was also undertaken to investigate the effect of chemical mydriasis, publication year, sample size and the number of fields photographed on these summary measures (Table 19). There

was little or no difference among studies based on the use of chemical mydriasis or study size. The increase in sensitivity and decrease in specificity seen for RP-NMRC compared with SLBM and/or CEE when more than one field was photographed and for studies published after 2000 are discussed below.

The forest plot for the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE for the 7 studies that did not use chemical mydriasis for RP-NMRC, and thus most closely resembled the proposed intervention, is shown in Figure 4. These studies are ranked by number of fields in the eye that were photographed and then by publication date. The high level of heterogeneity (I^2 >95%) is to be expected in meta-analyses of diagnostic test accuracy (Macaskill, Walter & Irwig 2001).

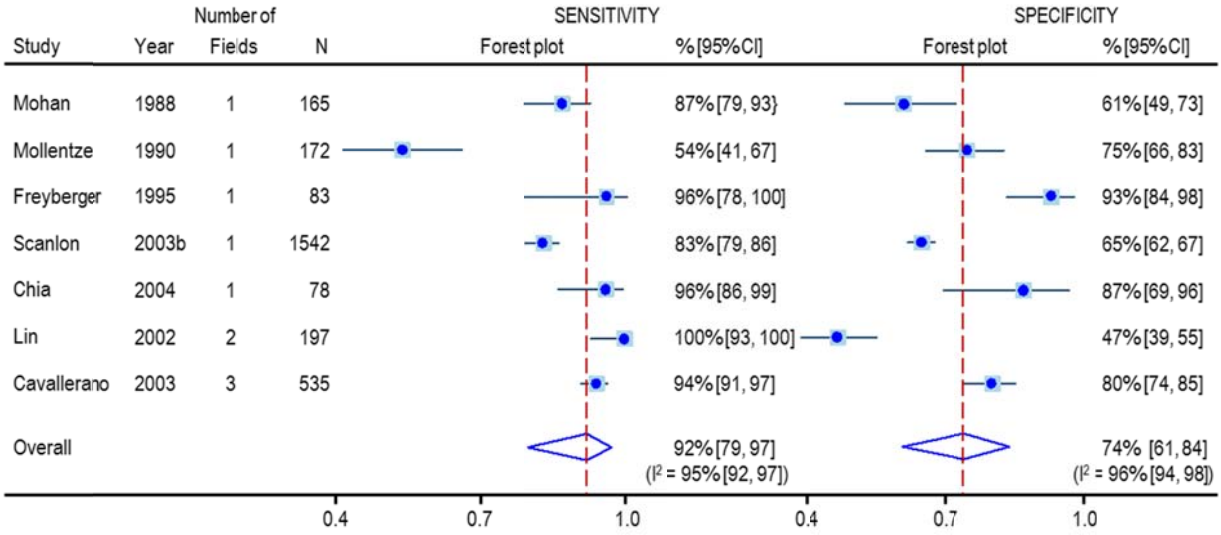


Figure 4 Forest plot of sensitivity and specificity for detection of any DR by RP-NMRC compared with SLBM and/or CEE for studies that did not use chemical mydriasis

CI = confidence interval

The mean sensitivity (91.2% [95%CI 79.2, 97.0]) and mean specificity (74.4% [96%CI 61.2, 84.2]) were similar to the results obtained when studies that used chemical mydriasis were included in the meta-analysis (Table 19; 91.2% [95%CI 81.7, 96.1] and 76.5% [95%CI 67.4, 83.6], respectively). The HSROC curve (Figure 5), which depicts the relationship between true positives and false positives by plotting sensitivity against 1 – specificity, shows a very good level of detection of DR by RP-NMRC among all studies (AUC) of 0.89 [95%CI 0.86, 0.92]). The HSROC curve also shows that there was no threshold effect between studies that used chemical mydriasis and those that did not. The mean false negative rate was 8.8% (1 – sensitivity) and the mean false positive rate was 25.6% (1 – specificity). The implications of these findings are considered in the 'Discussion' section (see 'Detection of any DR including UIs').

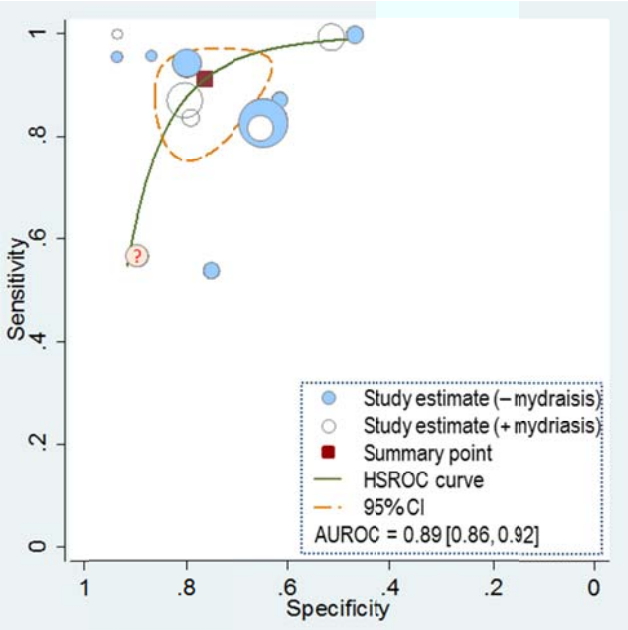
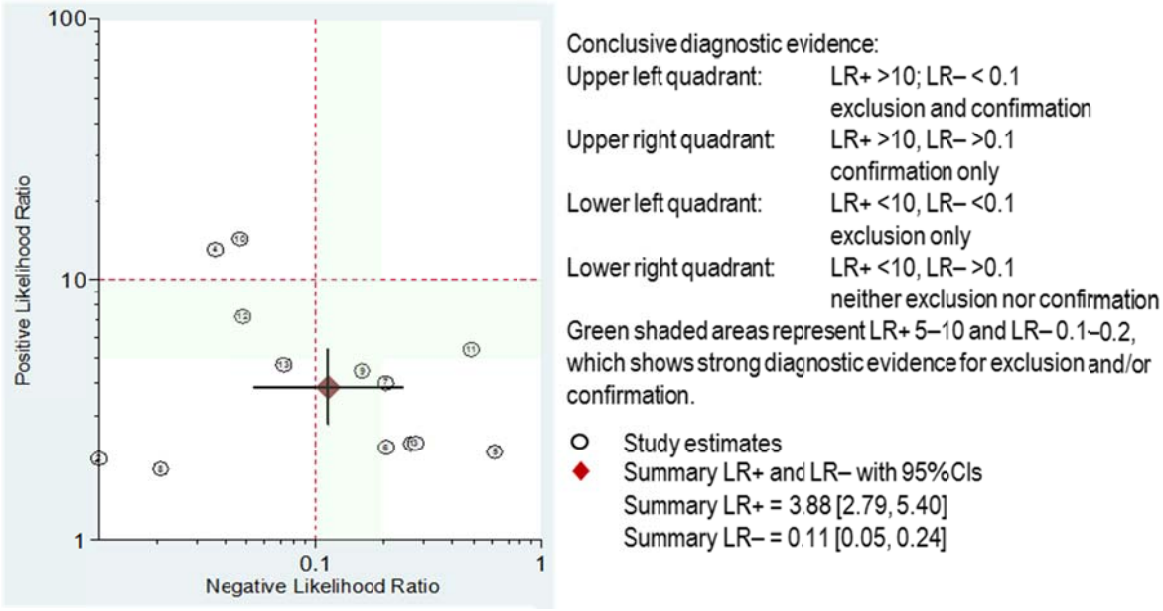


Figure 5 HSROC curve for all studies investigating sensitivity and specificity of RP-NMRC versus SLBM and/or CEE in the detection of any DR according to the use of mydriasis

AUROC = area under ROC curve; CI = confidence interval; HSROC = hierarchical summary receiver–operator characteristic curve

LR scattergrams plot LR+ against LR–, where the likelihood of correctly identifying DR increases along the x-axis and the likelihood of correctly eliminating the presence of DR decreases along the y-axis. The summary LR+ and LR– values for studies investigating the ability of RP-NMRC (with or without the use of chemical mydriasis) to detect any DR compared with SLBM and/or CEE fall within the lower right quadrant of the graph (



). This quadrant represents LR+ and LR– values (<10 and >0.1, respectively) that are inconclusive with respect to the probability of the test either correctly confirming or

excluding DR. However, as the LR– value lies in the 0.1–0.2 range, it still strongly indicates that a negative test result is likely to be accurate, suggesting that the test would still be useful for exclusion (false negative rate = 9%). Thus, RP-NMRC would be a useful test to triage patients for further examination by an ophthalmologist.

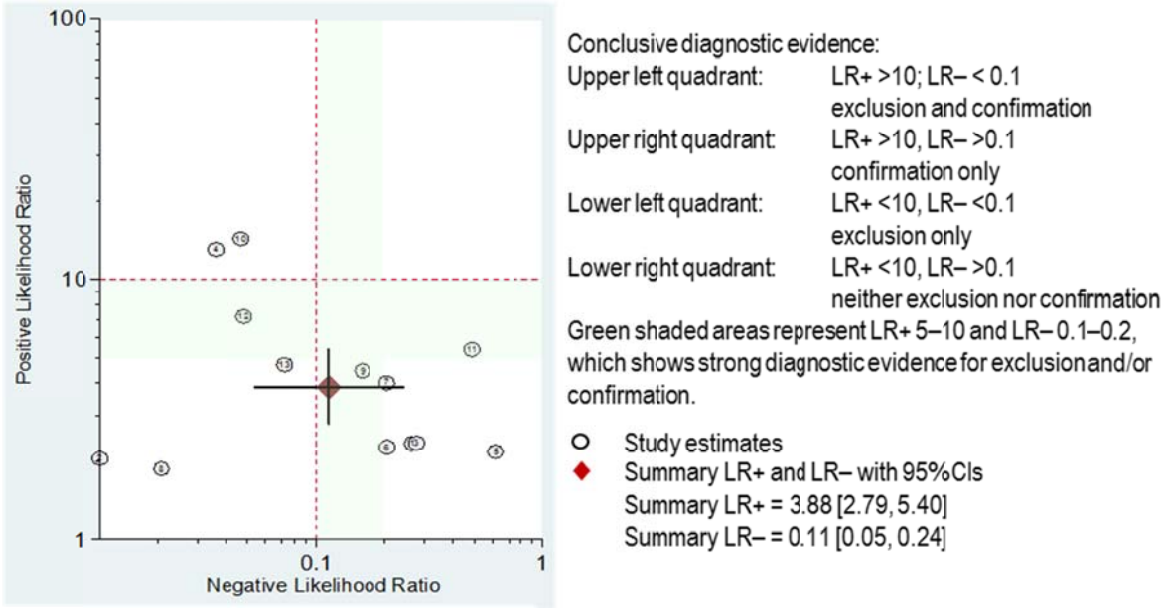


Figure 6 Likelihood ratio scattergram for detection (and referral) of any DR plus any UIs by RP-NMRC compared with SLBM and/or CEE

LR+ = positive likelihood ratio; LR– = negative likelihood ratio

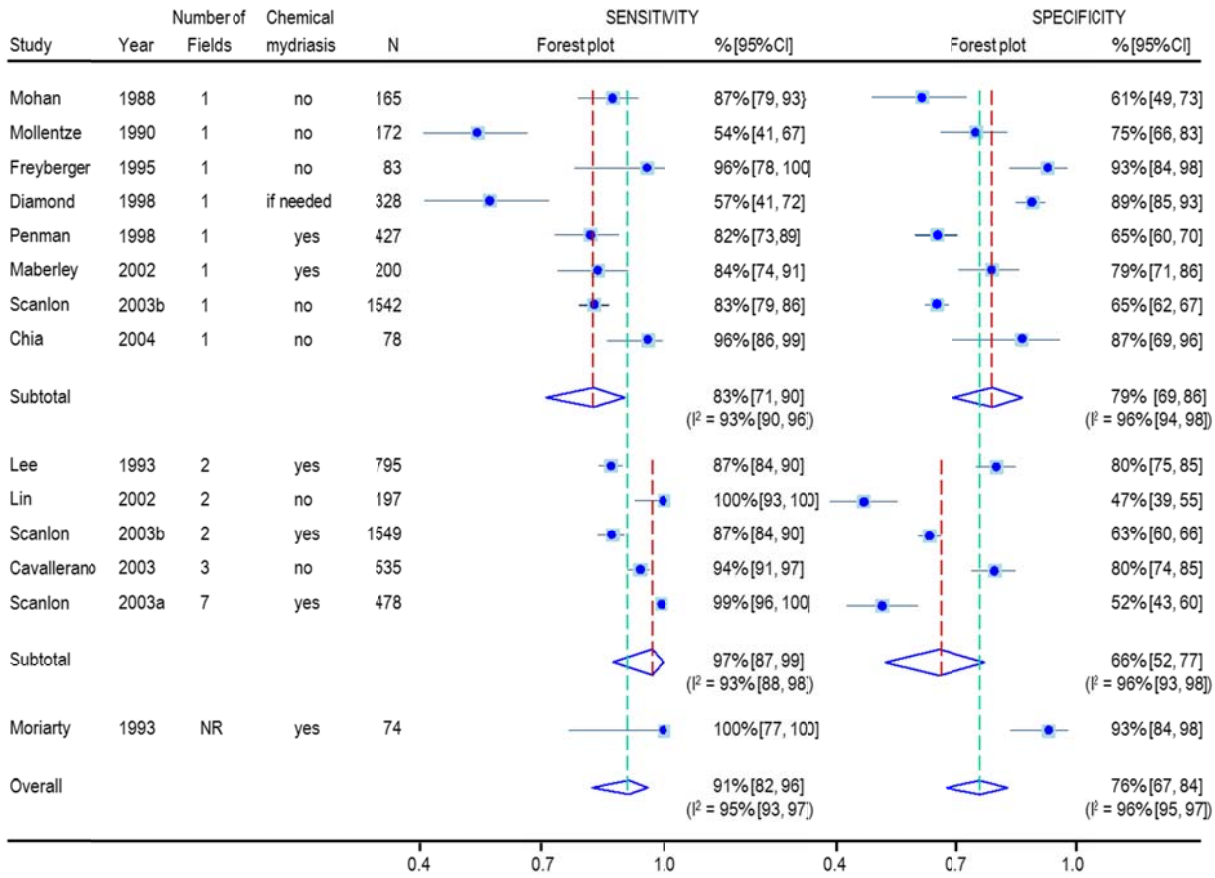


Figure 7 Forest plot of sensitivity and specificity for detection of any DR by RP-NMRC compared with SLBM and/or CEE according to the number of fields photographed

CI = confidence interval

Subgroup analysis for the detection of any DR based on the number of fields in the eye that were photographed showed that the sensitivity increased from 82.7% (95%CI 70.9, 90.3) to 96.6% (95%CI 87.0, 99.2), and the specificity decreased from 78.5% (95%CI 68.7, 85.9) to 65.5% (95%CI 52.0, 76.0), when more than one field was photographed, although the 95%CIs were overlapping (Table 19; Figure 7). The HSROC curve shows a threshold effect based on the number of fields photographed, with sensitivity increasing and specificity decreasing when more fields are photographed (Figure 8). LR scattergrams show that the summary LR+ and LR– values move from the lower right quadrant to the lower left quadrant when more than one field is photographed (Figure 9). This indicates that multiple-field RP-NMRC can be successfully used as a triage as it is highly likely that patients without DR who would not require any further investigations by an ophthalmologist would be correctly identified (LR– <0.1). In fact, only 1 in 33 patients tested with multiple-field RP-NMRC would not receive a referral to an ophthalmologist despite having DR. The similar effect seen for subgroup analysis based on publication date is likely to be due to the number of fields photographed, as only 1 study published before 2000 photographed more than one field (Figure 7).

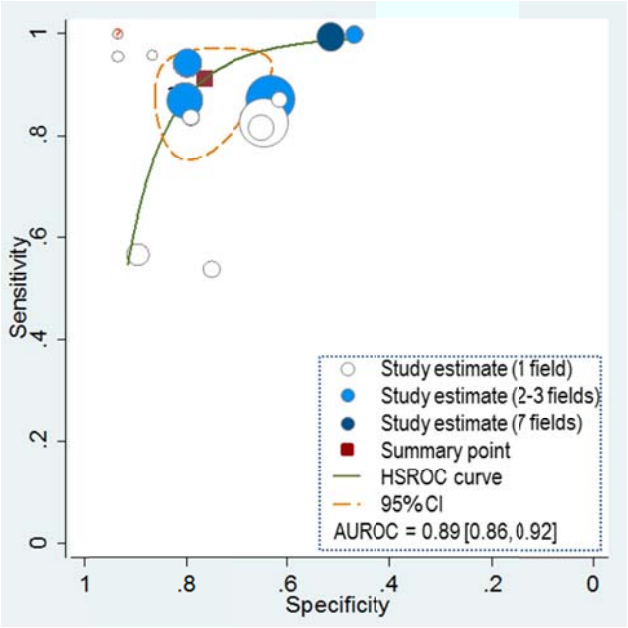
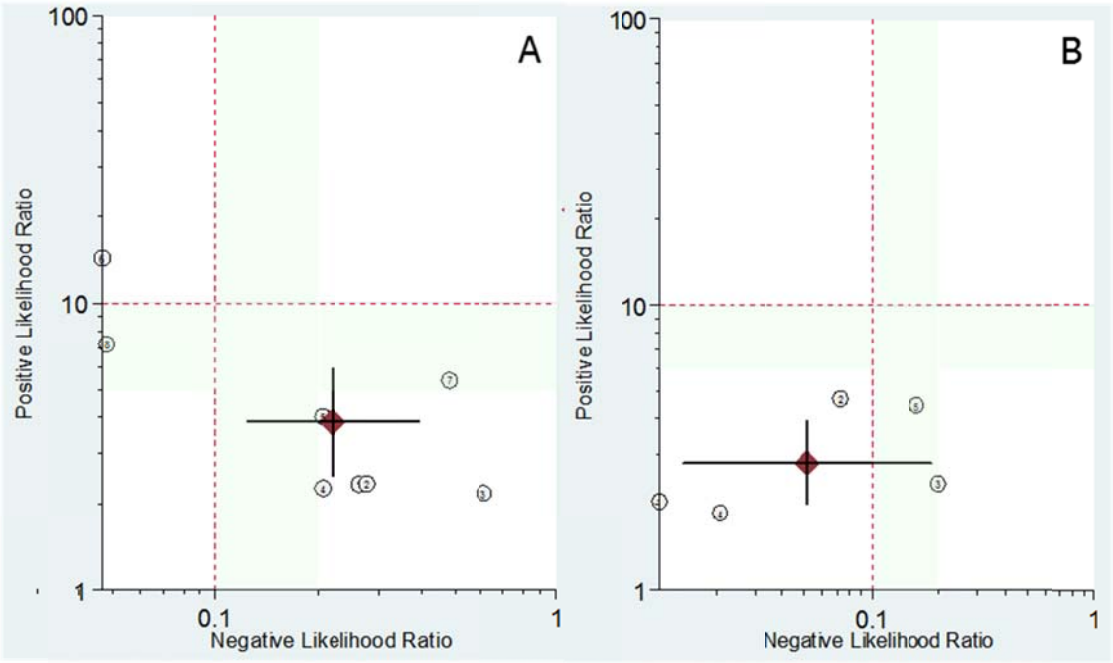


Figure 8 HSROC curve for all studies investigating sensitivity and specificity of RP-NMRC versus SLBM and/or CEE in detection of any DR according to the number of fields photographed

AUROC = area under ROC curve; CI = confidence interval; HSROC = hierarchical summary receiver–operator characteristic curve



Conclusive diagnostic evidence:

Upper left quadrant:	LR+ >10; LR– <0.1	exclusion and confirmation
Upper right quadrant:	LR+ >10, LR– >0.1	confirmation only
Lower left quadrant:	LR+ <10, LR– <0.1	exclusion only
Lower right quadrant:	LR+ <10, LR– >0.1	neither exclusion nor confirmation

Green shaded areas represent LR+ 5–10 and LR– 0.1–0.2, which shows strong diagnostic evidence for exclusion and/or confirmation.

◆ Summary LR+ and LR- with 95% CIs ○ Study estimates

A. Summary LR+ = 3.85 [2.50, 5.90] Summary LR– = 0.22 [0.12, 0.39]

B. Summary LR+ = 2.80 [2.00, 3.93] Summary LR– = 0.05 [0.01, 0.19]

Figure 9 Likelihood ratio scattergrams for detection (and referral) of any DR plus any UIs by RP-NMRC compared with SLBM and/or CEE according to the number of fields photographed: (A) 1 field; (B) 2–7 fields

CI = confidence interval; LR+ = positive likelihood ratio; LR– = negative likelihood ratio

Meta-analysis of studies that reported 2x2 data (including UIs) for urgent referrals for severe NPDR or worse (UIs not considered urgent)

Meta-analysis was performed using 2x2 data from studies that compared RP-NMRC with SLBM and/or CEE in the detection of advanced DR that would require an urgent referral, provided that any UIs were included. However, the UIs were treated as a negative result in the meta-analysis as it was not expected that they would result in an urgent referral. When the study provided data with and without the use of chemical mydriasis, the 'without' results were used in the meta-analysis, as this was the most clinically relevant outcome.

Of the 11 studies that reported 2x2 data for urgent referrals, 5 had the cut-off point at severe NPDR or worse, as recommended by the NHMRC (NHMRC 2008). One had a reduced cut-off point that included moderate NPDR and 5 had a cut-off point of PDR. Additionally, 4 of these studies included maculopathy. The pooled sensitivity, specificity, LR+ and LR– for

detection of severe NPDR or worse by RP-NMRC compared with SLBM and/or CEE are shown in Table 20. Subgroup analyses were undertaken to investigate the effect of chemical mydriasis, publication year, sample size, the number of fields photographed and the cut-off point on these summary measures (Table 20). As seen for the detection of any DR, there was little difference between studies that did or did not use chemical mydriasis with RP-NMRC. The apparently improved results seen in studies with less than 400 eyes is likely due to the small sample size (n=1,041), compared with studies that included more than 400 eyes (n=3,777), as the CIs are extremely large. Similarly, the 95%CIs for studies using 1-field RP-NMRC are also very wide, but the reason for this is unclear. The decrease in sensitivity and less favourable LR– when a lower cut-off is used is discussed below.

Table 20 Summary statistics for subgroup analysis of diagnostic accuracy for detecting severe NPDR and worse by RP-NMRC compared with SLBM and/or CEE

Subgroup		Sensitivity [95%CI]	Specificity [95%CI]	LR+ [95%CI]	LR– [95%CI]
Overall	(k = 11)	76.3% [60.2, 87.3]	98.1% [95.4, 99.2]	39.57 [16.22, 96.52]	0.24 [0.14, 0.43]
Chemical mydriasis:					
without	(k = 6)	72.8% [45.2, 89.7]	96.8% [93.0, 98.6]	22.87 [9.94, 52.61]	0.28 [0.12, 0.66]
with	(k = 7)	78.6% [65.9, 87.5]	97.7% [92.0, 99.4]	34.89 [9.85, 123.67]	0.22 [0.13, 0.36]
Publication year:					
pre-2000	(k = 5)	81.9% [63.6, 92.2]	98.3% [95.3, 99.4]	49.16 [19.21, 125.82]	0.18 [0.09, 0.40]
post-2000	(k = 6)	79.9% [49.1, 94.2]	97.9% [91.8, 99.5]	38.70 [8.42, 177.9]	0.21 [0.07, 0.64]
By study size:					
<400 eyes	(k = 6)	91.8% [42.4, 99.4]	99.3% [97.3, 99.8]	135.26 [36.54, 500.6]	0.08 [0.01, 1.00]
>400 eyes	(k = 5)	73.0% [61.2, 82.2]	95.2% [91.0, 97.5]	15.18 [7.91, 29.12]	0.28 [0.19, 0.42]
By number of fields photographed:					
1 field	(k = 5)	88.1% [34.5, 99.0]	98.1% [95.1, 99.3]	46.34 [14.47, 148]	0.12 [0.01, 1.26]
2–7 fields	(k = 6)	70.8% [55.2, 82.6]	97.8% [90.2, 99.5]	31.53 [7.81, 127.39]	0.30 [0.19, 0.47]
By cut-off:					
PDR	(k = 5)	84.7% [70.5, 92.8]	97.9% [96.2, 98.8%	39.91 [20.76, 76.72]	0.16 [0.08, 0.32]
Moderate–severe NPDR	(k = 6)	67.4% [47.1, 82.7]	98.4% [91.2, 99.7]	42.63 [7.57, 240.13]	0.33 [0.19, 0.58]

CI = confidence interval; k = number of studies; LR+ = positive likelihood ratio; LR– = negative likelihood ratio

Included studies: Cavallerano, AA et al. (2003); Chia & Yap (2004); Harding et al. (1995); Lee, VS et al. (1993); Lin et al. (2002); Maberley et al. (2002); Mollentze, Stulting & Steyn (1990); Moriarty et al. (1993); Penman et al. (1998); Scanlon et al. (2003a), (2003b)

The forest plot for the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE for the 11 studies that provided data for urgent referrals (in increasing order relative to the severity of disease deemed to be urgent) is shown in Figure 10. RP-NMRC is more specific for the detection of severe NPDR or worse compared with any DR (98.1% [95%CI 95.4, 99.2] versus 76.5% [95%CI 67.4, 83.6]), but is less sensitive (76.3% [95%CI 60.2, 87.3] versus 91.2% [95%CI 81.7, 96.1]). The mean false negative rate was found to be high (24%), whereas the

false positive rate was only 2% (see 'Discussion' section, 'Detection of severe NPDR or worse including UIs requiring non-urgent referral', for further details).

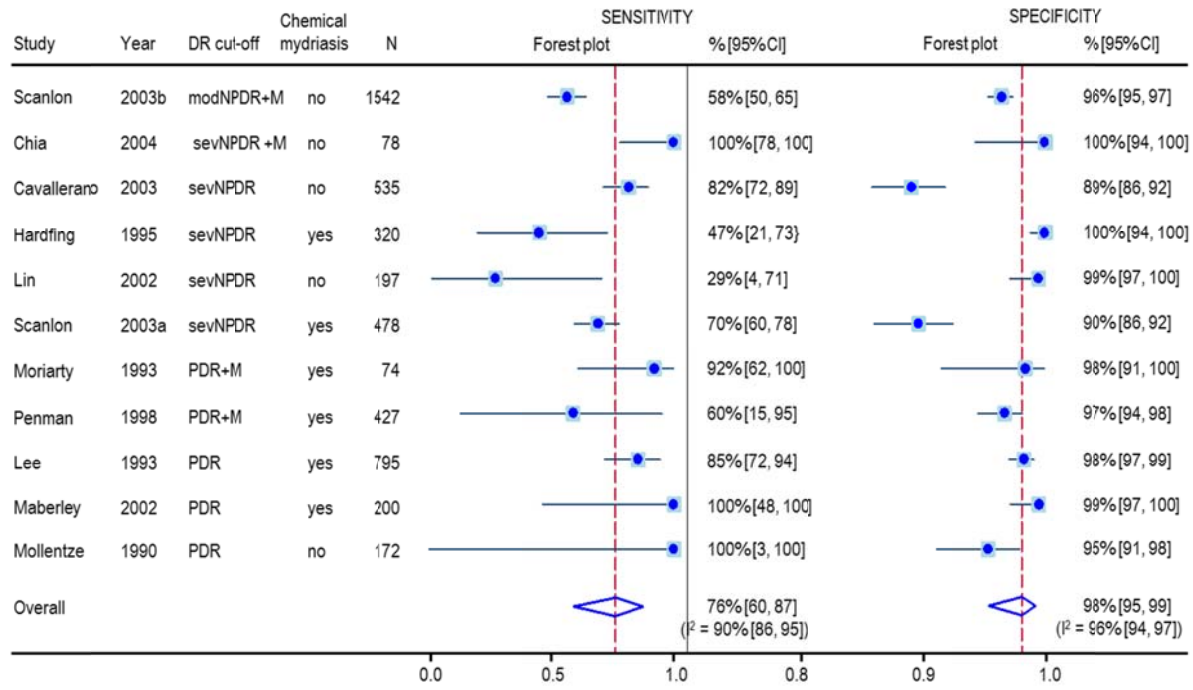
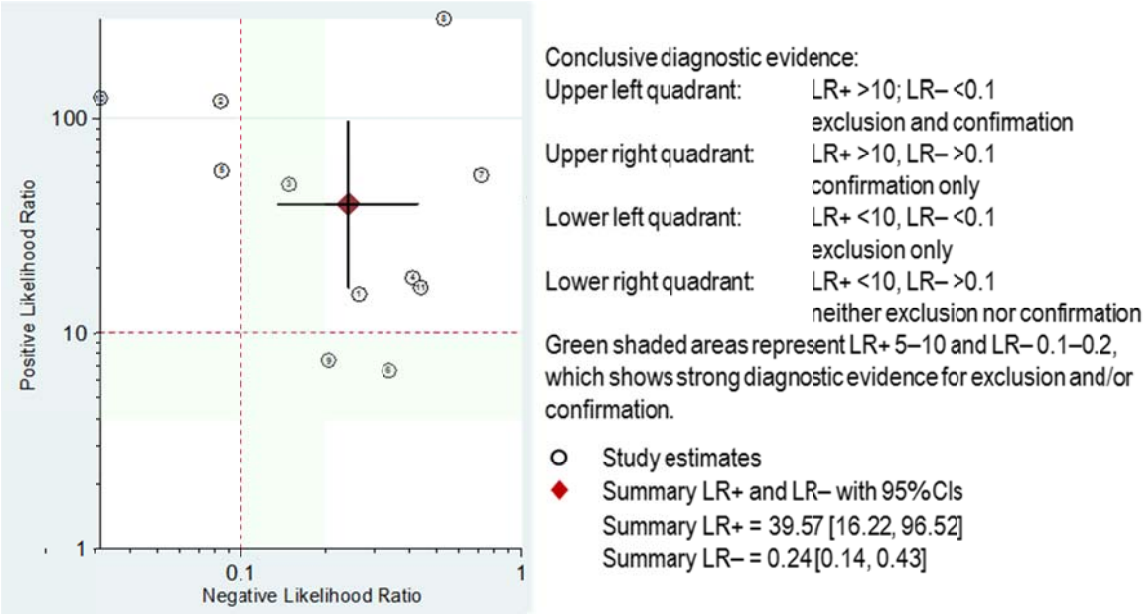


Figure 10 Forest plot of sensitivity and specificity for detection of severe NPDR or worse (requiring an urgent referral to an ophthalmologist) by RP-NMRC compared with SLBM and/or CEE, in order of severity of disease

CI = confidence interval; DR = diabetic retinopathy; mod = moderate; NPDR+M = non-proliferative diabetic retinopathy plus maculopathy; sev = severe; PDR+M = proliferative diabetic retinopathy plus maculopathy

The LR scattergram shows that the summary LR+ and LR– values for these studies (>10 and >0.1, respectively) fall within the upper right quadrant of the graph (



). This indicates the utility of RP-NMRC as a good confirmatory test for severe NPDR or worse. The HSROC curve (Figure 12) shows an excellent level of detection of severe NPDR or

worse by RP-NMRC (AUC = 0.96 [95%CI 0.94, 0.98]). In contrast to the detection of any DR, there was no threshold effect for the detection of advanced DR based on the number of fields photographed (Figure 12A). The interpretation of these results can be found in the 'Discussion' section, 'Detection of severe NPDR or worse including UIs requiring non-urgent referral'.

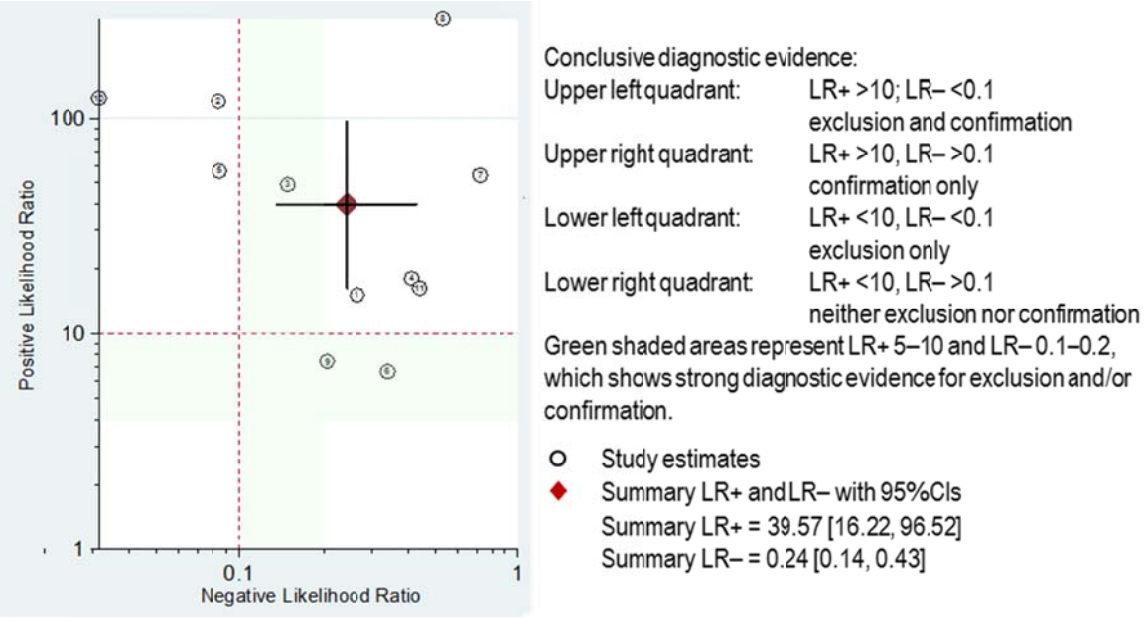


Figure 11 Likelihood ratio scattergram for detection of severe NPDR or worse by RP-NMRC compared with SLBM and/or CEE

CI = confidence interval; LR+ = positive likelihood ratio; LR– = negative likelihood ratio

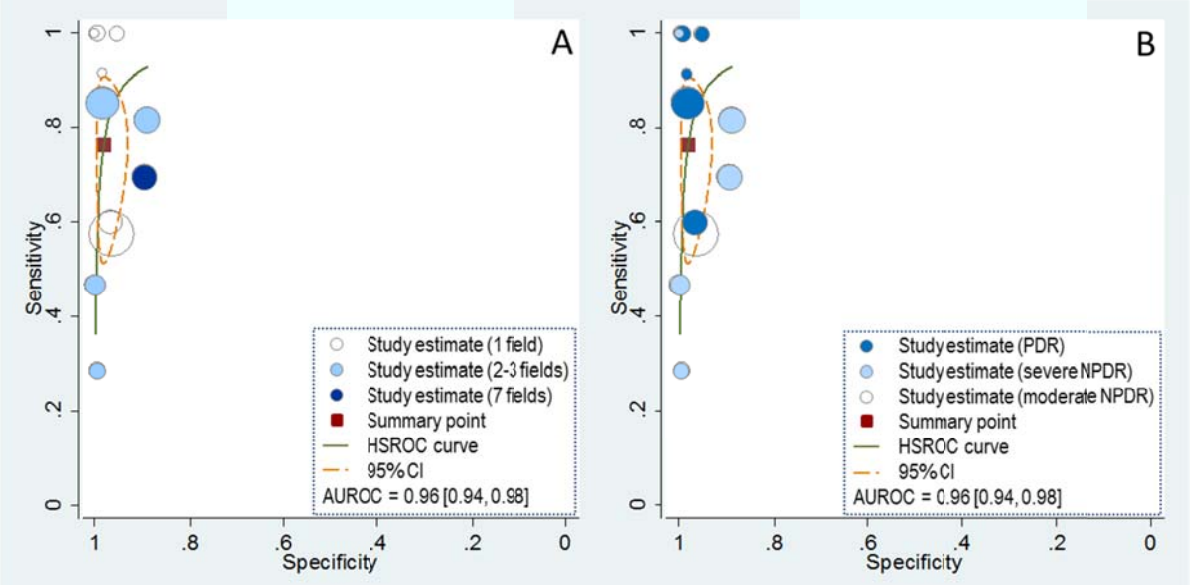
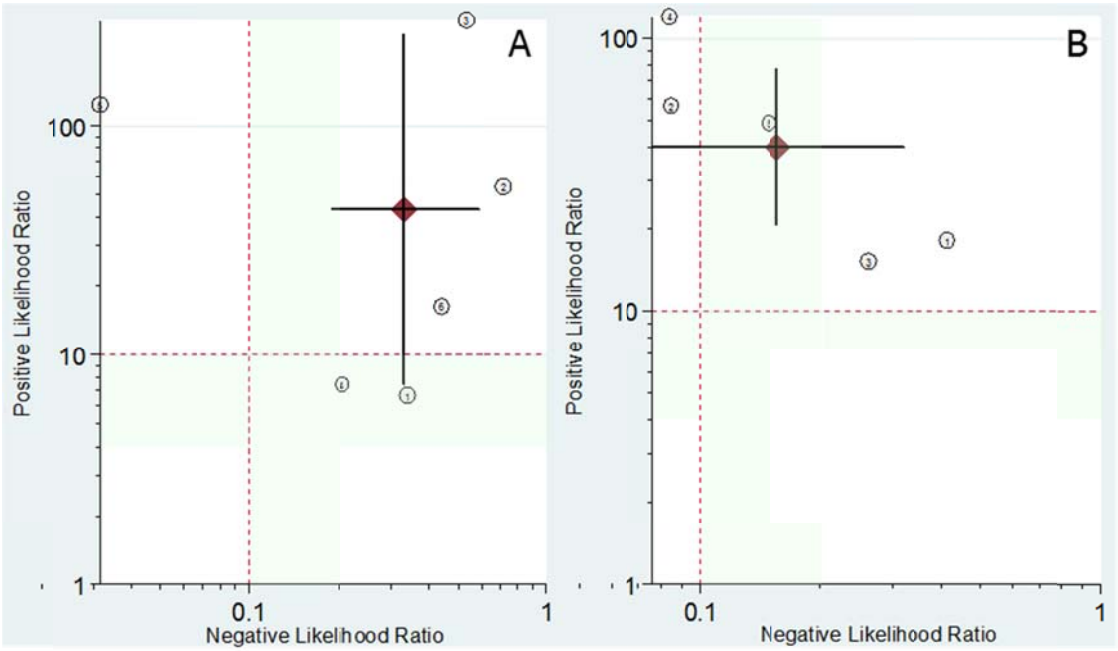


Figure 12 HSROC curve of all studies investigating sensitivity and specificity of RP-NMRC compared with SLBM and/or CEE in detection of severe NPDR or worse according to the number of fields photographed (A) and the cut-off point used (B)

AUROC = area under ROC curve; CI = confidence interval; HSROC = hierarchical summary receiver–operator characteristic curve

Improvements in sensitivity and LR– were seen when the cut-off for the level of disease deemed to be urgent increased from moderate or severe NPDR to PDR (Table 20). In the LR scattergrams shown in Figure 13, the LR– summary point for studies with PDR as the cut-off point moved towards the left compared with studies with moderate or severe NPDR as the cut-off point, indicating that the ability of the test to correctly identify patients increased as the cut-off point increased in disease severity.



Conclusive diagnostic evidence:

Upper left quadrant:	LR+ >10; LR– <0.1	exclusion and confirmation
Upper right quadrant:	LR+ >10, LR– >0.1	confirmation only
Lower left quadrant:	LR+ <10, LR– <0.1	exclusion only
Lower right quadrant:	LR+ <10, LR– >0.1	neither exclusion nor confirmation

Green shaded areas represent LR+ 5–10 and LR– 0.1–0.2, which shows strong diagnostic evidence for confirmation and/or exclusion.

◆ Summary LR+ and LR– with 95%CIs ○ Study estimates

A. Summary LR+ = 42.63 [7.57, 240.13] Summary LR– = 0.33 [0.19, 0.58]

B. Summary LR+ = 39.91 [20.76, 76.72] Summary LR– = 0.16 [0.08, 0.32]

Figure 13 Likelihood ratio scattergrams for detection of severe NPDR or worse by RP-NMRC compared with SLBM and/or CEE according to cut-off point; (A) moderate/severe NPDR or (B) PDR

CI = confidence interval; LR+ = positive likelihood ratio; LR– = negative likelihood ratio

Analysis of studies that either did not provide 2x2 data or did not include UIs

There were 18 included studies that did not provide sufficient data to be included in the meta-analyses above (Table 19, Table 20). Seventeen studies reported on the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE, and 1 on the diagnostic accuracy of RP-NMRC versus ophthalmoscopy by a GP. Fifteen of the 18 studies reported the sensitivity and specificity of detecting any DR by RP-NMRC compared with SLBM and/or CEE, and 10

for advanced DR requiring an urgent referral. Of these 10 studies, only 1 had a lower cut-off point (including moderate NPDR) than that recommended by the NHMRC guidelines of severe NPDR or worse (NHMRC 2008). Only 3 studies were published prior to 2000, all of which used 1-field RP-NMRC, either with (O'Hare et al. 1996) or without (Peters, Davidson & Ziel 1993; Williams, R et al. 1986) the use of chemical mydriasis. This is consistent with the trend towards multiple-field RP-NMRC in more recent publications that was observed for the studies included in the meta-analysis above. Of the 9 studies that did not provide 2x2 data, 3 included UIs in their analysis (Ding et al. 2012; Lawrence 2004; Murgatroyd et al. 2004) and 3 did not clarify if UIs were included or excluded (Aptel et al. 2008; Mizrachi et al. 2013; O'Hare et al. 1996). Two of the 18 studies did not report the proportion of UIs obtained (O'Hare et al. 1996; Tu et al. 2004). The proportion of UIs in the 16 studies reporting this outcome ranged from 0% to 36% (median 14.4%), of which 6 had a greater proportion (23.5–36%) than for any study included in the meta-analysis above (see Table 92 in Appendix C). These results may be a reflection of publication bias in the meta-analysis above—see 'Analysis of studies not included for meta-analysis' in the 'Discussion' section.

Nine studies provided 2x2 data that did not include the UIs and, therefore, were not suitable for inclusion in the meta-analyses above. Where there were sufficient studies providing outcomes for subgroups of interest, meta-analysis was performed using these studies to determine what effect the inclusion or exclusion of UIs had on the sensitivity and specificity of RP-NMRC compared with SLBM and/or CEE. Median sensitivity and specificity values for all studies for each subgroup were also calculated when more than 2 studies were included. The median and pooled sensitivity and specificity for detection of any DR were almost identical in all subgroups investigated (Table 21), suggesting that there was little difference between studies providing 2x2 data and those that did not.

Table 21 Sensitivity and specificity of RP-NMRC compared with SLBM and/or CEE for detection of any DR or advanced DR in studies that excluded UIs

Subgroup			Sensitivity	Specificity
Any DR excluding UIs				
All studies:	median	k = 10	85.4% (range 38.2–100)	92.7% (range 61.2–100)
	meta-analysis	k = 7	86.4% [95%CI 59.5, 96.5]	92.4% [95%CI 79.9, 97.4]
No chemical mydriasis:	median	k = 7	85.7% (range 65.6–100)	93.0% (range 84.9–100)
	meta-analysis	k = 5	89.8% [95%CI 51.6, 98.6]	95.5% [95%CI 84.1, 98.8]
Number of fields photographed:	1 field (median)	k = 6	67.1% (range 38.2–95.8)	92.7% (range 75.3–97.6)
	1 field (meta-analysis)	k = 4	67.5% [95%CI 34.7, 89.1]	91.4% [95%CI 78.1, 96.9]
	2–4 fields (median)	k = 4	92.5% (range 85.7–100)	91.3% (range 61.2–100)

Subgroup			Sensitivity	Specificity
Advanced DR excluding UIs				
All studies excluding UIs	median	k = 7	100% (range 76.9–100)	98.7% (range 87.3–100)
	meta-analysis	k = 6	81.9% [95%CI 75.6, 86.9]	98.3% [95%CI 91.8, 99.7]

CI = confidence interval; DR = diabetic retinopathy; k = number of studies; UIs = unreadable images

Included studies: Ahmed et al. (2006); Conlin et al. (2006); Gomez-Ulla et al. (2002); Herbert, Jordan & Flanagan (2003); Kuo, Hsieh & Liu (2005); Lopez-Bastida, Cabrera-Lopez & Serrano-Aguilar (2007); Peters, Davidson & Ziel (1993); Scanlon et al. (2003a); Suansilpong & Rawdaree (2008); Tanterdtham et al. (2007); Tu et al. (2004); Williams, R et al. (1986)

The median and pooled sensitivity of RP-NMRC compared with SLBM and/or CEE to detect advanced DR (severe NPDR or worse) differed markedly (Table 21). Subgroup analysis was not performed for advanced DR due to the low number of included studies. These results are interpreted in the 'Discussion' section, 'Analysis of studies not included for meta-analysis'.

The specificity for detection of any DR in the studies that excluded UIs was much higher (92.4% [95%CI 79.9, 97.4]) than the pooled specificity derived from studies that included UIs (76.5% [95%CI 67.4, 83.6]). This is not surprising, as the false positive rate would be expected to be much lower when the UIs (of which only a proportion have DR) are removed from the analysis. Conversely, the pooled sensitivity of studies excluding UIs (86.4% [95%CI 59.5, 96.5]) was a little lower than that obtained from the meta-analysis of studies that included UIs (91.2% [95%CI 81.7, 96.1]). This is likely due to the increased proportion of false negatives when the UIs are removed from the total population.

The sensitivity and specificity for detection of any DR without the use of chemical mydriasis did not differ from the overall result, which is consistent with the result from meta-analysis of this subgroup, as discussed above. The sensitivity for detection of any DR by 1-field versus multiple-field RP-NMRC, compared with SLBM and/or CEE, for studies that excluded UIs from the analysis showed a similar increase when more than 1 field was photographed to that seen for meta-analysis of these subgroups when UIs were included (Table 19, Table 20). However, there was no decrease in specificity.

The sensitivity and specificity for detecting advanced DR by RP-NMRC compared with SLBM and/or CEE were similar for studies that included UIs (80.0% [95%CI 63.7, 90.2] and 97.4% [95%CI 94.7, 98.8]) and those that did not (76.3% [95%CI 60.2, 87.3] and 98.1% [95%CI 95.4, 99.2]).

Direct comparison of RP-NMRC with and without the use of chemical mydriasis

Four studies reported on the diagnostic accuracy of RP-NMRC with and without the use of chemical mydriasis compared with SLBM and/or CEE (Table 22). All 4 studies reported the

sensitivity and specificity of detecting any DR by RP-NMRC compared with SLBM and/or CEE, and 3 for advanced DR requiring an urgent referral. Three studies included UIs in their analysis and 1 did not clarify if UIs were included or excluded.

There was a marked difference in the proportion of UIs obtained with and without the use of chemical mydriasis. When RP-NMRC was performed in the absence of chemical mydriasis, a median of 19.3% (range 11–36%) of patients had UIs. The addition of chemical mydriasis reduced the proportion of UIs to a median of 5.3% (range 2.5–8.3).

Table 22 Diagnostic accuracy for either referral of any detectable DR or urgent referral for advanced DR by RP-NMRC with and without chemical mydriasis compared with SLMB and/or CEE

Study % UIs	Sensitivity [95%CI] without mydriasis	Sensitivity [95%CI] with mydriasis	Difference	Specificity [95%CI] without mydriasis	Specificity [95%CI] with mydriasis	Difference
Aptel et al. (2008) 1-field: – mydriasis 11.4% + mydriasis 2.5% 2-field: – mydriasis 13.3% + mydriasis 3.8%	Any DR (UIs?) 1-field 76.9% 3-field 92.3%	Any DR (UIs?) 1-field 89.7% 3-field 97.4%	 +12.8% +5.1%	Any DR (UIs?) 1-field 99.2% 3-field 97.5%	Any DR (UIs?) 1-field 98.3% 3-field 98.3%	 –0.9% +0.8%
Ding et al. (2012) 1-field: – mydriasis 27.1% + mydriasis 8.3% 2-field: – mydriasis 28.2% + mydriasis 8.9%	Any DR + UIs 1-field 82.4% [74, 89] 2-field 93.3% [87, 97] Any DR – UIs 1-field 66.7% [47, 83] 2-field 85.7% [70, 95] Sev NPDR+ Ma 1-field 75.6% [60, 88] 2-field 87.8% [74, 96]	Any DR + UIs 1-field 79.0% [71, 86] 2-field 86.6% [79, 92] Any DR – UIs 1-field 71.8% [55, 85] 2-field 89.5% [75, 97] Sev NPDR+ Ma 1-field 73.2% [57, 86] 2-field 90.2% [77, 97]	 –3.4% +6.7% –5.1% +3.8% –2.4% +2.4%	Any DR + UIs 1-field 58.3% [53, 63] 2-field 56.8% [52, 62] Any DR – UIs 1-field 94.4% [92, 97] 2-field 91.6% [88, 94] Sev NPDR+ Ma 1-field 68.8% [65, 73] 2-field 64.7% [60, 69]	Any DR + UIs 1-field 69.7% [65, 74] 2-field 68.4% [64, 73] Any DR – UIs 1-field 92.2% [90, 95] 2-field 89.7% [87, 92] Sev NPDR+ Ma 1-field 84.3% [81, 87] 2-field 81.6% [78, 85]	 +11.4% +11.6% –2.2% –1.9% +15.5% +16.9%
Mollentze, Stulting & Steyn (1990) 1-field: – mydriasis 11% + mydriasis 3.5%	Any DR + UIs 54.0% [40.9, 66.6] PDR 100% [16.6, 100.0]	Any DR + UIs 46.3% [35.3, 57.7] PDR 100% [19.3, 100.0]	–8% No change	Any DR + UIs 75.2% [66.0, 83.0] PDR 95.3% [91.0, 98.0]	Any DR + UIs 78.9% [69.0, 86.8] PDR 89.4% [83.8, 93.6]	+3.7% –5.9%
Murgatroyd et al. (2004) 1-field: – mydriasis 36% + mydriasis 7%	Any DR + UIs 83% [78, 88] Sev NPDR+ 77% [71, 84]	Any DR + UIs 85% [82, 90] Sev NPDR+ 81% [76, 87]	+2% +4%	Any DR + UIs 91% [88, 94] Sev NPDR+ 95% [93, 97]	Any DR + UIs 91% [89, 94] Sev NPDR+ 92% [90, 94]	No change –3%

CI = confidence interval; DR = diabetic retinopathy; Ma = maculopathy; PDR = proliferative diabetic retinopathy; Sev NPDR+ = severe non-proliferative diabetic retinopathy or worse; UIs = unreadable images

Differences seen with and without the use of chemical mydriasis were highly variable both among and within studies (Table 22).

Direct comparison of 1-field and multiple-field RP-NMRC

Three studies reported on the diagnostic accuracy of 1-field versus multiple-field RP-NMRC compared with SLBM and/or CEE (Table 23). All 3 studies reported the sensitivity and specificity of detecting any DR by RP-NMRC compared with SLBM and/or CEE, and 2 for advanced DR requiring urgent referral. There was no difference in the proportion of UIs obtained when photographing 1 field (range 7–27.1%) compared with multiple fields (range 6.5–28.2%). Two studies included UIs in their analysis and 1 did not clarify if UIs were included or excluded. Two studies used chemical mydriasis and 1 study did not (Table 23).

Table 23 Diagnostic accuracy for either referral of any detectable DR or urgent referral for advanced DR by 1-field versus multiple-field RP-NMRC compared with SLMB and/or CEE

Study +/– mydriasis % UIs	Sensitivity [95%CI] for 1-field RP-NMRC	Sensitivity [95%CI] for multiple-field RP-NMRC	Difference	Specificity [95%CI] for 1-field RP-NMRC	Specificity [95%CI] for multiple-field RP-NMRC	Difference
Aptel et al. (2008) – mydriasis 1-field 11.4% 2-field 13.3%	Any DR (UIs?) 1-field 76.9%	Any DR (UIs?) 3-field 97.4%	+20.5%	Any DR (UIs?) 1-field 99.2%	Any DR (UIs?) 3-field 98.3%	↓0.9%
Ding et al. (2012) – mydriasis 1-field 27.1% 2-field 28.2%	Any DR + UIs 1-field: 82.4% [74, 89] Sev NPDR+ Ma 1-field: 75.6% [60, 88]]	Any DR + UIs 2-field: 93.3% [87, 97] Sev NPDR+ Ma 2-field: 87.8% [74, 96]	+10.9% +12.2%	Any DR + UIs 1-field: 58.3% [53, 63] Sev NPDR+ Ma 1-field: 68.8% [65, 73]	Any DR + UIs 2-field: 68.4% [64, 73] Sev NPDR+ Ma 2-field: 81.6% [78, 85]	↑10.1% ↑12.8%
Murgatroyd et al. (2004) + mydriasis 1-field 7% 3-field 6.5%	Any DR + UIs 1-field: 85% [82, 90] Sev NPDR+ 1-field: 81% [76, 87]	Any DR + UIs 3-field: 90% [86, 93] Sev NPDR+ 3-field: 83% [78, 88]	+5% +2%	Any DR + UIs 1-field: 91% [89, 94] Sev NPDR+ 1-field: 92% [90, 94]	Any DR + UIs 3-field: 90% [88, 93] Sev NPDR+ 3-field: 93% [91, 96]	↓1% ↑1%

CI = confidence interval; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; Sev NPDR+ = severe non-proliferative diabetic retinopathy or worse; Ma = maculopathy; UIs = unreadable images

All 3 studies showed an increase in sensitivity for multiple-field versus 1-field RP-NMRC compared with SLBM and/or CEE for detection of either any DR (range 5–20.5%) or severe NPDR or worse (range 2–12.2%). This is consistent with the previous findings for detection of any DR using 1-field versus multiple-field RP-NMRC, using SLBM and/or CEE as the reference standard (Table 19). Although subgroup meta-analysis of studies that included UIs found that 1-field RP-NMRC had a lower false negative rate than multiple-field RP-NMRC when compared with SLBM and/or CEE, this result was unreliable due to the very large CIs.

The effect of photographing more than 1 field on specificity of RP-NMRC compared with SLBM and/or CEE was variable among the 3 studies included (Table 23).

Agreement among readers

There were 7 studies that compared the interpretation of retinal photographs among different readers. None of these studies included a reference standard; all were studies using a case series of patients who had undergone RP-NMRC and whose images were graded by two or more different health providers. Two of the studies were exactly the same design in the same setting but with different patients (Andonegui et al. 2010, 2012); these, along with 1 further study, were conducted in Spain, whereas the other studies were conducted in UK, USA and Singapore. The studies were all in general practice settings, and probably generalisable and applicable to the population of interest in this assessment.

Table 24 Results for included studies on agreement among readers

Study and location / quality	Comparison	Results
Andonegui et al. (2010) Spain 3/5 (medium)	Four GPs compared with ophthalmologist	Kappa between 0.80 (95%CI [0.72–0.88]) and 0.95 (95%CI [90–99])
Andonegui et al. (2012) Spain 3/5 (medium)	Four GPs compared with ophthalmologists	Patients with suspected DR or UIs: 392/714 had no DR (55% false positives) Random sample of non-referred: 16/240 (7%) had some degree of DR, 2/240 had treatable DR
Bhargava et al. (2012) Singapore 1.5/5 (low)	Non-physician grader compared with retinal specialist Family physician compared with retinal specialist	Kappa 0.656 ± 0.038 Sensitivity 69.8% (95%CI [61.3–77.2]) Specificity 94.4% (95%CI [92.3–96.1]) AUC 0.822 (95%CI [0.78–0.863]) Kappa 0.400 ± 0.036 Sensitivity 44.7% (95%CI [36.5–53.2]) Specificity 92.4 (95%CI [90.1–94.2]) AUC 0.686 (95%CI [0.642–0.729])
Castro, Silva-Turnes & Gonzalez (2007) Spain 3/5 (medium)	Family physician compared with ophthalmologist	Lesion vs no lesion, patients with diabetes only, kappa=0.80; patients with diabetes and hypertension, kappa=0.79
Cavallerano, JD et al. (2012) USA 2/5 (medium)	Certified imagers compared with certified readers (optometrists) Primary care clinicians compared with retinal specialists	Sight threatening DR: 6/316 eyes discordant Kappa 0.95 (95%CI [0.9–-0.99]) Any DR: Sensitivity 85%, Specificity 94%, PPV 62%, NPV 98% Any referral: Sensitivity 90%, Specificity 93%, PPV 87%, NPV 95%
Owens et al. (1998)	GPs compared with expert at Diabetic Retinopathy	Any DR: Sensitivity 79.2% (95%CI [73.6–84.9])

Study and location / quality	Comparison	Results
UK 3/5 (medium)	Reading Centre	Specificity 73.5% (95%CI [68.0–79.1]) PPV 71.0% (95%CI [65.2–77.0]) Sight threatening DR: Sensitivity 87.3% (95%CI [79.4–95.2]) Specificity 84.8 (95%CI [81.2–88.5]) PPV 51.2% (95%CI [42.1–60.3])

AUC = area under curve; CI = confidence interval; DR = diabetic retinopathy; GP = general practitioner; NPV = negative predictive value; PPV = positive predictive value

There were two main comparisons among readers in these studies: the first between general practitioner (GP) or family physician and a retinal specialist, and the other between non-physician graders and retinal specialists. The photographers were either trained nurses, trained imagers or optometrists. Overall, agreement (measured by kappa statistic) between GP readers and retinal specialists ranged from 0.40 to 0.95 (the majority of measures being toward the higher limit), between non-physician readers and retinal specialist 0.66, and between trained imager and trained reader 0.95. The results are shown in Table 24.

Does RP-NMRC change patient management?

Summary—How does RP-NMRC change clinical management?

Four comparative studies found that patients were much more likely to undergo RP-NMRC in a primary care setting than make and attend an appointment with an eye care specialist (1 randomised controlled trial (RCT) and 2 level III-3 studies), and more likely to undergo screening by RP-NMRC than CEE when invited to attend (1 level III-2 study).

Two non-comparative studies reported that a high proportion of diabetes patients attended RP-NMRC when invited for either initial screening or subsequent biannual screening.

Three studies (1 level III-2 and 2 level III-3) indicated that patients were more likely to comply with annual specialist eye examinations if they had undergone RP-NMRC than if they had undergone traditional surveillance. It is likely that identification of disease, education regarding DR and facilitation with making follow-up appointments contributed to the increase in compliance.

Comparative studies indicated that compliance with management referrals to eye-care specialists was not significantly different for patients who underwent RP-NMRC compared with those who underwent traditional surveillance (1 level III-3 study), and the number of referrals made for patients who underwent RP-NMRC was not different from that for patients who underwent traditional surveillance (1 level II and 1 level III-2 studies).

A survey of GPs found that less than 60% were compliant with all patient referral recommendations from a screening program, but additional patients complied with recommendations without going through their GPs.

Studies were included to assess change in management following RP-NMRC according to criteria outlined *a priori* in Box 4.

Box 4 PICO criteria to determine whether RP-NMRC changes the clinical management / compliance of patients with diabetes

Selection criteria	Inclusion criteria
Population	Patients with a diagnosis of diabetes and no visual impairment
Intervention	RP-NMRC
Comparators	Standard medical assessment, including: a) CEE by an ophthalmologist or optometrist (includes ophthalmoscopy or SLBM of the fundus with mydriasis b) ophthalmoscopy by a GP, with mydriasis No eye examination
Outcomes	- Change in rate of appropriate referral for CEE—for DR and non-DR ocular disorders and vision impairment/loss, separately and combined - Reduction in unnecessary referral - Compliance with referral to CEE
Study design	Randomised or non-randomised controlled trials and cohort studies, case control studies, case series, or systematic reviews of these study designs
Search period	1985 – February 2014
Language	Studies in languages other than English or German were only translated if they represent a higher level of evidence than that available in the English or German language evidence-base
Systematic review question	Does the availability of RP-NMRC result in a change in the number of patients with diabetes undergoing a CEE?

RP-NMRC has the potential to change the clinical management and compliance with eye screening recommendations in patients with diabetes in a variety of ways. Due to being more accessible, or being able to combine RP-NMRC with patients' regular diabetes check-ups at their primary healthcare appointments, a greater proportion of patients may have their eyes screened on a regular basis. They may be more likely to undergo screening with RP-NMRC than dilated eye examination with an optometrist or ophthalmologist, due to the greater convenience and comfort of examination without dilation. Following RP-NMRC, patients may be more likely to go to an eye specialist once aware that they have signs of DR. It is also possible that the management strategies recommended after RP-NMRC would differ from those based on traditional surveillance. Evidence was sought on these different ways in which RP-NMRC may impact the compliance and management of patients.

The literature search identified 11 studies with outcomes relevant to change in patient management. Profiles of these studies can be found in Table 98 in Appendix D. Of these 11 studies, 2 were RCTs (level II evidence) of moderate quality in which participants were randomised to either RP-NMRC screening or traditional surveillance / usual care (Conlin et al. 2006; Mansberger et al. 2013). A third level II study (Williams, R et al. 1986) of moderate quality used a cross-over design in which patients underwent both RP-NMRC and clinical eye examination by an ophthalmologist. Two level III-2 cohort studies (Creuzot-Garcher et al. 2010; Tu et al. 2004) of moderate quality compared the patient management outcomes of a retinal screening program with a concurrent control, and 2 level III-3 studies (Leiner et al. 2009; Spurling et al. 2010) of moderate–poor quality reported on clinical management outcomes before and after the introduction of an RP-NMRC screening program. The remaining 4 studies (level IV evidence) were of moderate quality; 2 examined the impact of a retinal photography screening program in an Australian setting (Lee, SJ et al. 1999, 2000), 1 reported referral rates of different readers in patients who all underwent RP-NMRC (Romero-Aroca et al. 2010), and 1 assessed patient compliance in two RP-NMRC programs (Leese et al. 2005). Authors of the studies included for change in management all indicated that increased patient attendance at ophthalmological appointments was essential to improving eye health. Objectives across the studies were consistent, as all sought to assess the impact of RP-NMRC screening on patients' compliance with eye care recommendations. These study profiles are provided in Table 98 in Appendix E.

The outcomes for studies reporting change in management are reported below in the following sequence:

1. Patient compliance with attendance at RP-NMRC screening in primary care versus traditional surveillance (self-organised CEE with ophthalmologist or optometrist)

2. Patient compliance with invitations to attend RP-NMRC screening versus CEE (with optometrist)
3. Patient compliance with invitations to attend RP-NMRC screening (non-comparative)
4. Patient compliance with annual ophthalmological examinations following RP-NMRC versus traditional surveillance
5. Patient compliance with ophthalmological or optometrist referrals following RP-NMRC versus traditional surveillance
6. Management referrals following RP-NMRC versus CEE and RP-NMRC alone
7. GP compliance with RP-NMRC screening recommendations

1. <u>Patient compliance with attendance at RP-NMRC screening in primary care versus traditional surveillance (self-organised CEE with ophthalmologist or optometrist)</u>

Three studies (Table 25) compared a traditional surveillance model in which patients self-organised appointments with an optometrist or ophthalmologist against RP-NMRC in primary care (Leiner et al. 2009; Mansberger et al. 2013; Spurling et al. 2010). One of these studies (level II intervention evidence) randomised individuals to the two conditions (Mansberger et al. 2013), and the other 2 were historical control studies that monitored the change in behaviour before and after the introduction of RP-NMRC (Leiner et al. 2009; Spurling et al. 2010).

Table 25 Screening attendance rates for RP-NMRC versus traditional surveillance (self-organised CEE)

Study	Study design Quality appraisal	Outcome	RP-NMRC N patients (%)	Traditional surveillance N patients (%)	Comparison OR [95%CI]
Leiner et al. (2009) USA	Level III-3 Quality: 12/26 (moderate–poor)	Underwent retinal screening	1,079 / 2,436 (44.3%)	968 / 2,438 (39.7%)	(Comparing years 2005 and 2007) 1.21 [1.08, 1.35] p=0.001
Mansberger et al. (2013) USA	Level II: RCT Quality: 19/26 (moderate)	Attended retinal screening within 12 months of enrolment / patients enrolled	278 / 296 (94%)	151 / 271 (56%)	12.3 [7.20, 20.9] p<0.001
Spurling et al. (2010) Australia	Level III-3 Quality: 14/26 (moderate–poor)	Received DR screening	124 / 132 (94%)	20 / 132 (15%)	86.8 [36.8, 204.9] p<0.001

CEE = comprehensive eye examination; DR = diabetic retinopathy; OR = odds ratio; RCT = randomised controlled trial; RP-NMRC = retinal photography with a non-mydriatic retinal camera

The RCT by Mansberger et al. (2013) was conducted within two US health clinics where half of the patients reported some Native American / Alaska Native heritage, and 72% of patients reported non-white heritage. The study by Leiner et al. (2009) predominantly included patients who were of lower socioeconomic status in Virginia, USA. The Australian

study by Spurling et al. (2010) was performed in an urban Indigenous healthcare clinic. All three studies were assessed as highly applicable to the target population.

In all 3 studies, patients were much more likely to undergo RP-NMRC in the primary care setting than to make and attend appointments with an eye care specialist (Table 25; p<0.01). In 2 of the studies (Mansberger et al. 2013; Spurling et al. 2010) RP-NMRC was provided opportunistically—before, during or after their regular annual health check. This may have therefore allowed a greater attendance rate than requiring patients to make and attend a separate appointment.

2. Patient compliance with invitations to attend RP-NMRC screening versus CEE (with optometrist)

A retrospective cohort analysis (Tu et al. 2004; level III-2 interventional evidence) reported on patient compliance with retinal screening when they were invited to attend. Tu and colleagues (2004) compared two screening models, both conducted at hospital-based eye clinics, that ran concurrently in adjacent areas with a total of 3,456 invitees. The comparator arm (CEE) was considered different to the traditional surveillance conditions discussed in the previous section, as patients were actively invited to attend for a CEE, which is not considered usual care. The proportion of attendees who underwent CEE (consisting of SLBM performed by optometrists) was compared with those who took part in RP-NMRC screening (using 1% tropicamide). The proportion of patients who attended screening was statistically significantly higher in the RP-NMRC group (OR 1.22; 95%CI 1.07, 1.40). However, compliance with both screening models was poor. The results are shown in (Table 26).

Table 26 Screening attendance rates for RP-NMRC versus CEE

Study	Study design Quality appraisal	Outcome	RP-NMRC N patients (%)	CEE N patients (%)	Comparison OR [95%CI]
Tu et al. (2004) UK	Level III-2 Quality: 15/26 (moderate)	Attended screening / patients invited	874 / 1,748 (50%)	769 / 1,708 (45%)	1.22 [1.07, 1.40] p=0.003

CEE = comprehensive eye examination; OR = odds ratio; RP-NMRC = retinal photography with a non-mydriatic retinal camera

3. Patient compliance with invitations to attend RP-NMRC screening (non-comparative)

Two case series (level IV evidence; Lee, SJ et al. 2000; Leese et al. 2005) reported on the level of patient compliance with attending retinal screening (no comparator). Leese et al. (2005) assessed the impact of a new Scottish DR screening program that differed from a previous one in administration, frequency of screening (annual screening was offered in the new program), grading of digital photographs and use of staged mydriasis. Patients in both

the old and new programs underwent RP-NMRC. It was found that the proportion of patients with diabetes who underwent screening following an invitation to attend the new RP-NMRC program was larger than that who attended the old RP-NMRC program (89% vs 82%) (Table 27).

Table 27 Screening attendance rates for RP-NMRC

Study	Study design Quality appraisal	Outcome	RP-NMRC N patients (%)
Leese et al. (2005) Scotland	Level IV Quality: 4/6 (moderate)	Patients attended screening / all patients (new screening program) Patients attended screening / all patients (old screening program)	4,574 / 5,150 (89%) 5,208 / 6,335 (82%)

A second level IV study discussed in two publications (Lee, SJ et al. 1999, 2000) reported on the impact of a screening program in an Australian setting. The study examined the results of a 4-year pilot RP-NMRC screening project implemented in urban and rural areas of Victoria in 1996. The project used a mobile unit and occurred at local venues with a local phone number made available to contact for day or evening appointments. Lee, SJ et al. (2000) assessed the eye care practices of patients with diabetes who had not previously accessed regular eye care services. Patients who attended screening were given referrals for further assessment if required or, if no abnormality was detected, were advised to come back for further screening within 2 years. Information about the screening outcomes was communicated to the patients' GPs. The authors reported that, of both those who had normal and abnormal screening results, 87% of patients returned for further screening within 2 years (Table 28).

Table 28 Patients who had a follow-up eye examination within 2 years of initial screening

Study Study design Quality appraisal	Patient compliance with recommendation within 2 years of initial screening	No abnormality at initial screening N (%)	Referred for further examination at initial screening, N (%)
Lee, SJ et al. (1999) Lee, SJ et al. (2000) Australia Level IV Quality: 4/6 (moderate)	All patients examined within 2 years / those with normal screening result Examined at biennial screening Eyes examined elsewhere Eyes examined within years / those examined with abnormal screening result	321 / 370 (87%) 191 (60%) 130 (40%) 150 / 173 (87%)	150 (87%) 23 (13%)

4. Patient compliance with annual ophthalmological examinations following RP-NMRC versus traditional surveillance

Three studies comparing RP-NMRC and traditional surveillance reported on the percentage of patients who attended appointments with an ophthalmologist (recommending that everyone saw an eye specialist annually, regardless of the outcome of RP-NMRC) (Conlin et al. 2006; Creuzot-Garcher et al. 2010; Leiner et al. 2009). The results are summarised in Table 29. Conlin et al. (2006) randomised patients to either receive RP-NMRC at their regular primary care appointment or to a control group that received 'usual care' (level II interventional evidence). The digital RP-NMRC images were triaged by trained imagers, then assessed remotely for quality and level of DR.

One level III-2 study (Creuzot-Garcher et al. 2010) compared the number of ophthalmological visits between areas with and without a mobile RP-NMRC screening program in Burgundy, France. Campaigns promoting the screening program ran over three 12-month time periods (September to August in each of 2004–2005, 2005–2006 and 2006–2007), with the purpose of improving uptake of annual ophthalmological eye examinations in diabetes patients. Following RP-NMRC, patients received a letter encouraging them to attend recommended 12-monthly ophthalmological appointments, and patients' GPs were informed of outcomes. It is unknown whether any letter was sent for those in the comparative regions, where there were no RP-NMRC mobile screening units.

A further historical cohort study (level III-3 evidence; Leiner et al. 2009) compared rates of compliance with eye examination recommendations before and after the implementation of an RP-NMRC screening program. In this study, compliance was reported as 'no-show' rates for those referred for ophthalmological appointments (described as 'actual' appointments, i.e. not just referrals as a result of screening). These rates were compared before and after the implementation of the screening program (2005 and 2007).

All 3 studies reported that a greater percentage of patients attended an ophthalmologist or had a comprehensive dilated eye examination if they first received RP-NMRC than if they were in the 'usual care' or the historical setting prior to implementation of RP-NMRC (Table 29). Conlin et al. (2006) hypothesised that the increased uptake of dilated retinal examinations in the RP-NMRC group may have resulted from the identification of new cases of DR through non-mydriatic screening, the educational component of the intervention, and the facilitation of the imager who managed and contacted participants for follow-up visits.

Creuzot-Garcher et al. (2010) reported that the difference among groups was less significant in the second complete year of the RP-NMRC program (OR 1.09, 95%CI 1.00, 1.17). It is

possible that a comparison between the number of eye examinations carried out in areas covered by the campaigns and those not covered may have been more informative than a comparison between screened and non-screened areas, which were both covered by campaigns promoting attendance to an ophthalmologist.

Table 29 Compliance with annual ophthalmological visits among diabetes patients for RP-NMRC versus no eye examination

Study	Study design Quality appraisal	Diabetics who visited an ophthalmologist within 1 year	RP-NMRC N patients (%)	Traditional surveillance N patients (%)	Comparison OR [95%CI]
Conlin et al. (2006) USA	Level II Quality: 19/27 (moderate)	Follow-up comprehensive dilated eye examination within 12 months / diabetics recruited	194 / 223 (87%)	173 / 225 (77%)	2.01 [1.22, 3.31] p<0.01
Creuzot-Garcher et al. (2010) France	Level III-2 Quality: 17/26 (moderate–poor)	Ophthalmology visits in 2005 / number of diabetics Ophthalmology visits in 2006 / number of diabetics	1,499 / 3,407 (44%) 1,817 / 4,226 (43%)	2,154 / 5,254 (41%) 2,602 / 6,346 (41%)	1.13 [1.04, 1.23] p=0.006 1.09 [1.00, 1.17] p=0.04
Leiner et al. (2009) USA	Level III-3 Quality: 12/26 (moderate–poor)	Attendance at ophthalmological appointment / appointments made	3,143 / 3,807 (82.6%)	2,486 / 3,256 (76.4%)	1.47 [1.31, 1.65] p<0.001

CI = confidence interval; OR = odds ratio; RP-NMRC = retinal photography with a non-mydriatic retinal camera.

5. Patient compliance with ophthalmological or optometrist referrals following RP-NMRC vs traditional surveillance

One Australian study (level III-3 evidence), set in an Indigenous healthcare clinic in Brisbane, reported on the rate of compliance with referrals made by GPs, under a traditional surveillance model (referrals likely made without any eye examination at the primary healthcare level), and after the introduction of RP-NMRC (Spurling et al. 2010). Unlike the scenario 4 above, only those with signs of DR were referred to ophthalmologist, rather than universally recommending annual ophthalmologist appointments for everyone.

Results obtained through correspondence with the authors indicated that the proportions of patients who complied with referrals to optometrists/ophthalmologists increased slightly, although the difference was not statistically significant (Table 30). It should be noted that patients were able to attend an optometrist without a referral in both the historical setting and the RP-NMRC setting, and these attendance data are not systematically collected. Furthermore, patients waiting to see an ophthalmologist in the public sector could be required to wait a long time, so it is possible that their scheduled appointments for the public ophthalmologist did not occur within 1 year of screening with RP-NMRC. This is due to health system delays rather than patient compliance (Spurling et al. 2010).

Table 30 Patient compliance with referrals based on RP-NMRC or traditional surveillance

Study Study design Quality appraisal	Patient recommendation [a]	RP-NMRC N eyes (%)	Traditional surveillance N eyes (%)	Comparison OR [95%CI]
Spurling et al. (2010)	Optometry appointment attended / those referred	No optometry referrals made 1 seen without referral	13 / 19 (64%)	-
Australia Level III-3	Private ophthalmology appointment attended / those referred	1 / 1 (100%) due to missing/inadequate photos 6 / 6 (100%) due to confirmed referrable disease	6 / 8 (75%)	1.15 [0.03, 38.9] p=0.94
Quality: 14/26 (moderate–poor)	Public ophthalmology appointment attended / those referred	1/ 3 (33%) due to missing/inadequate photos 6/9 (67%) due to confirmed referrable disease	1 / 8 (13%)	3.5 [0.14, 8] p=0.44
	Total attended screening and appropriate follow-up	119 / 132 (90%)	20 / 132 (15%)	51.3 [24.31, 107.9] p<0.001

CI = confidence interval; OR = odds ratio; RP-NMRC = retinal photography with a non-mydriatic retinal camera

When the proportions of those who underwent screening and appropriate follow-up were analysed, patients were far more likely to have had appropriate retinal screening and management after the implementation of RP-NMRC (OR 51.3, 95%CI 24.31, 107.9).

6. Management referrals following RP-NMRC versus CEE or RP-NMRC alone

Two comparative studies reported on the treatment recommendations in groups who underwent DR screening either by RP-NMRC or CEE (Tu et al. 2004; Williams, R et al. 1986), and two case series reported referral rates after RP-NMRC (Leese et al. 2005; Romero et al. 2010). A cross-over study by Williams, R et al. (1986; level II evidence) was conducted in a group of 62 patients who were selected at random from attendees at a general diabetes clinic and a diabetic eye disease clinic. The participants underwent both RP-NMRC and CEE that consisted of direct clinical assessment by an ophthalmologist. The proportion of patients recommended for 'follow-up', 'investigate' and 'treatment' were almost identical for both groups. An analysis by Tu et al. (2004; level III-2 evidence) compared two screening models that ran in parallel in adjacent areas. The proportion of referrals made for those who underwent CEE (consisting of SLBM performed by optometrists) was compared with those who took part in an RP-NMRC screening program using 1% tropicamide. The proportion of patients who were referred for ophthalmological follow-up was higher in the RP-NMRC group but the difference was not significant. Results are shown in Table 31.

Two case series (Leese et al. 2005; Romero-Aroca et al. 2010; level IV evidence) reported the proportion of patients referred to ophthalmology services following RP-NMRC screening (Table 32). Taken together the results suggest that retinal photographs assessed by GPs for DR are more likely to have a false positive result than those assessed by an ophthalmologist.

However, the number of false positives may be reduced when technical issues are addressed within the screening program, as was the case in the new Scottish RP-NMRC screening program discussed by Leese et al. (2005). Leese and colleagues reported on the proportion of patients referred for a full ophthalmological examination following screening by the new and old programs. The new program resulted in a smaller proportion of patients being referred to the ophthalmology clinic for further examination, and a smaller proportion being immediately discharged from the clinic—an indication of fewer false positive results.

Table 31 Management referrals after RP-NMRC compared with ophthalmologist clinical examination

Study	Study design Quality appraisal	Patient recommendation	RP-NMRC N eyes (%)	Ophthalmic exam N eyes (%)	Comparison OR [95%CI]
Tu et al. (2004) UK	Level III-2 Quality: 15/26 (moderate)	Hospital referrals / patients invited	37 / 1,748 (4.2%)	29 / 1,748 (3.8%)	1.28 [0.78, 2.09] p=0.32
Williams, R et al. (1986) UK	Level III-2 Quality: 15/26 (moderate)	Follow-up Investigate Treatment	67 / 113 (59.3%) 13 / 113 (11.5%) 33 / 113 (29.2%)	6 / 113 (59.3%) 14 / 113 (12.4%) 32 / 113 (28.3%)	1.0 [0.59, 1.70] p=1.00 0.92 [0.41, 2.06] p=0.84 1.04 [0.59, 1.86] p=0.88

CI = confidence interval; OR = odds ratio; RP-NMRC = retinal photography with a non-mydriatic retinal camera

A Spanish study (Romero-Aroca et al. 2010) reported referral rates in two groups from a 2-year prospective trial using RP-NMRC screening. Whereas all participants underwent screening, images in Group 1 were assessed by a GP and in Group 2 by an ophthalmologist, with patients being referred on for further ophthalmological examination depending on the result. The study found that there were more referrals in Group 1, but that this group had a significant number of false positive readings (images of 'doubtful interpretation').

Table 32 Management referrals after NMRC

Study	Study design Quality appraisal	Management outcome	RP-NMRC N patients (%)
Leese et al. (2005) Scotland	Level IV Quality: 4/6 (moderate)	Patients referred to ophthalmology clinic / number screened (new screening program)	137 / 4,574 (3.0%)
		Patients referred to ophthalmology clinic / number screened (old screening program)	307 / 5,208 (5.9%)
		Patients immediately discharged from the ophthalmology clinic / number screened (new screening program)	572 / 4,574 (12.5%)
		Patients immediately discharged from the ophthalmology clinic / number screened (old screening program)	1,026 / 5,208 (19.7%)
Romero-Aroca et al. (2010) Spain	Level IV Quality: 5/6 (high)	Referred to ophthalmologist / patients screened by GP	387 / 4,551 (8.5%)
		Referred to ophthalmologist / patients screened by ophthalmologist	77 / 884 (8.7%)

GP = general practitioner; RP-NMRC = retinal photography with a non-mydriatic retinal camera

7. GP compliance with RP-NMRC screening recommendations

One case series (Lee, SJ et al. 1999; level IV evidence) examined the compliance of GPs with screening referral recommendations for patients who participated in a Victorian pilot study. GPs were sent a questionnaire to determine the reasons for their compliance/non-compliance with screening referral recommendation information they received regarding their patients who had undergone RP-NMRC. Of 208 patients for whom responses were received from GPs, it was found that 59% had been referred by their GP, as recommended. The reasons GPs gave for not complying with recommended referrals are provided in Table 33.

Table 33 GP and patient compliance with referral recommendations

Study	Study design Quality appraisal	Outcome	N patients (%)
Lee, SJ et al. (1999) Australia	Level IV Quality: 4/6 (moderate)	Referred by GP (% recommendations by screening program)	123 (59%)
		Not referred by GP with reasons:	
		under regular review by ophthalmologist	31 (15%)
		under regular review by optometrist	2 (1%)
		have not seen patient since screening	18 (8.7%)
		other medical problems take precedence	12 (5.8%)
		non-compliant patient	5 (2.4%)
		oversight by GP	4 (1.9%)
		other	13 (6.3%)
		Total	85 (41%)

GP = general practitioner

Other relevant considerations

Summary—Other considerations relevant to the provision of RP-NMRC for detection of DR

Healthcare provision and capital equipment may be funded in a variety of ways that can influence healthcare provider behaviour and have an impact on patient health outcomes and the efficiency of the healthcare system. Due to the nature of the population targeted for RP-NMRC, consideration should be given to whether it would be appropriate to fund this service under the Quality Assurance for Aboriginal and Torres Strait Islander Medical Services (QAAMS) program or under a separate grant program. Any prospective reimbursement scheme would need to be carefully administered so that non-mydriatic retinal cameras are placed in areas where they can be used efficiently, i.e. where this technology is likely to be used with reasonable frequency and where it is unlikely to replace the 'gold standard' treatment of a CEE by an optometrist or ophthalmologist.

In addition, initial and ongoing training and accreditation will be important determinants of the success and cost-effectiveness of any RP-NMRC service. It should be possible to effectively implement and update training and quality assurance with ongoing involvement and collaboration among key stakeholders including government, relevant clinical craft groups (e.g. RANZCO, OAA, RACGP, ACO) and educational institutions.

The provision of RP-NMRC services within rural and remote communities is not only likely to increase compliance with recommended screening for DR, but would also reduce unnecessary travel for those patients in whom no signs of DR are detected.

Methods of healthcare funding

As part of the assessment of RP-NMRC, the assessment group was requested to provide a separate consideration of an alternative funding model, other than MBS funding. It was stated that this could include a model such as grant funding for machines or direct funding to medical practices to provide this service.

A rapid review of Scopus, PubMed, EconLit, NHS EED, the CEA Registry and Google scholar was performed to determine if there was any literature available on alternative methods for funding for RP-NMRC. Likewise, a rapid review was performed to determine if there was any evidence on alternative models of funding capital equipment, other than healthcare institutions being reimbursed for a component of capital costs through a portion of service provider MBS fees (i.e. the MBS fees would cover the costs of the professional service but not the capital equipment).

No literature was found discussing the merits of different models of funding RP-NMRC. Although literature was found discussing different methods of funding health care in general (i.e. retrospective reimbursement versus prospective funding, or activity-based

funding versus per-case payment), it appears that no research has been performed on the merits of different methods of funding for capital equipment components.

Below we describe the current MBS funding system, discuss why alternative funding models could be considered for RP-NMRC, describe different funding models, and consider the implications of different funding models.

The current system (retrospective and fee-for-service)

The current method of funding through the MBS is a retrospective payment system. Services are reimbursed after they are provided, based on the number of claims made to the MBS. This fee-for-service system does not put a cap on the number of claims made across the country. Reimbursement through MBS item numbers covers professional services as well as capital equipment components. In the case of RP-NMRC, this would be likely to be based on the expected number of cameras to be used, the expected utilisation of each camera, the cost of consumables and maintenance, and the expected life of the machine. If providers invest in a non-mydriatic retinal camera, it is in their interest to seek reimbursement for the investment. In order to limit inappropriate claiming, claims on the MBS may only be made when patients meet eligibility criteria specified within the item descriptor.

This system is very similar to out-patient settings in many European countries, including Germany, Austria and Switzerland.

RP-NMRC has two key components: a) the taking of retinal photographs and b) the interpretation of these photographs. It is likely that these two services will be provided by different individuals and specialties, the former being performed in the primary healthcare setting (i.e. GP office, Indigenous healthcare centre or diabetes clinic), and the latter potentially being performed remotely, via telemedicine, by a trained and accredited reader who may or may not be a medical specialist. PASC discussed how the potential MBS item numbers would be used and, while acknowledging that only medical practitioners may claim MBS item numbers (as a general rule), concluded that it made most sense to require that a medical practitioner interpreted the photograph, claimed for both the taking of the photograph and its interpretation, and then provided a portion of the reimbursement received to the actual person who took the retinal photograph.

Why current funding may not be appropriate

Overcompensation and potential for leakage

If the camera is used for longer than its predicted life, or in more patients than expected in the calculations performed to determine the MBS fee, the amount reimbursed through the current MBS system (which would include a capital-equipment component) would be in excess of what the real costs are. The same would be true if the cameras can later be purchased at a cost below current pricing. The additional reimbursement would be absorbed by the medical practice. If claiming these item numbers is profitable, physicians may be more likely to try and claim the item number for a spectrum of patients broader than what is intended, i.e. for all diabetes patients without visual impairment, rather than just those who are unlikely to undergo a CEE with an optometrist or ophthalmologist. If patients are likely to comply with referrals to an optometrist or ophthalmologist for a CEE, this should be considered the 'gold standard' method of screening for DR. However, if healthcare institutions have invested in a non-mydriatic retinal camera, it may be in the interests of GPs and diabetes clinics to use the camera to screen all patients with diabetes, in order to seek a return on their investment. Thus, there is the risk that RP-NMRC may replace a CEE in some patients who would otherwise attend an optometrist or ophthalmologist; this is outside the scope of the target population.

Undercompensation

If new technology becomes available that supersedes RP-NMRC with the camera purchased, such that RP-NMRC is no longer considered to be best practice in the target population, the amount reimbursed during the period of use of the camera may fall short of the real costs that the health practice has incurred. Likewise, if the number of patients with diabetes meeting the criteria for RP-NMRC is smaller than the base-case proposed for the calculations, the healthcare practice may be required to effectively subsidise the costs of the capital equipment from other more-profitable services. For this reason, careful placement of technology is required.

Fee-for-service health care in Indigenous populations may restrict access if a medical practice does not bulk-bill (Scrimgeour & Scrimgeour 2007). However, bulk-billing in Indigenous communities is not a sustainable practice for healthcare institutions. An analysis performed on the financial effects of GPs servicing marginalised communities (Rogers et al. 2005) identified problems with the level of MBS compensation. This analysis focused on homosexually active men with HIV infection, who have a pattern of health disadvantage including high rates of depression or anxiety, substance use problems and

complex needs. The findings are considered to be potentially applicable to the target population, that is, those who do not follow the NHMRC recommendations regarding retinal screening on a regular basis. Rogers et al. reported that providing care to a population with complex needs, where MBS reimbursement is the only source of revenue, was not sustainable due to the requirement for longer consultations per patient and higher rates of bulk-billing. The total revenue, GP income and practice income would be lower on an hourly basis than servicing less-needy patients.

If best practice is not observed, patient health outcomes will be lowered. It is estimated that Indigenous communities receive fewer healthcare resources than other Australians, when controlling for the needs of the patients (Councillor 2003–2004).

Alternative models of healthcare funding

Alternative models of healthcare funding exist that may be considered for the funding of RP-NMRC.

Commonwealth grants

One possibility for funding of RP-NMRC (either for the whole service or the capital equipment) is by grants from the Commonwealth Government, similar to the Aboriginal and Torres Strait Islander Chronic Disease Fund. This fund was established to improve the prevention, detection and management of chronic diseases in Aboriginal and Torres Strait Islander (ATSI) peoples in order to increase life expectancy and contribute to closing the gap in life expectancy within a generation (Department of Health 2014a). RP-NMRC is one factor that may contribute to improved chronic disease management of diabetes by primary care providers. Grants can contribute to salaries, such as in Aboriginal Community Controlled Health Services (ACCHSs) (see 'Salary system' section below), with funds coming from either the Department of Health or the Department of the Prime Minister and Cabinet, which oversee Indigenous Affairs.

When the QAAMS pathology program was initially set up, grants were provided for some ACCHSs to assist with the purchase of the capital equipment required to participate in the program[14]. Further ongoing grants were provided to assist with training and quality assurance within the QAAMS program. This may be seen as a precedent, as RP-NMRC will have similar set-up requirements to the pathology components of the QAAMS program.

[14] Personal communication, Anne Shepherd, Assisting Director for QAAMS; phone call, 28 May 2014

Specifically, there will be need for capital equipment, training and ongoing quality assurance processes, as well as additional resources related to high internet data requirements if the photographs are to be interpreted remotely using telemedicine.

Salary system

In a salary system, physicians are in most instances retrospectively paid a fixed amount of money for the hours they are contracted to work (Rosen 1989). Salary payment has some advantages: it is administratively simple, offers the doctor a fixed income and does not contain incentives for deliberate cost-generating behaviour. On the other hand, because the physicians have no financial risk associated with the service, there is less motivation to contain costs or attract patients. Given that the income is generally fixed, the physicians have an incentive to minimise personal costs (Gosden et al. 2001; Rosen 1989) by selecting low-risk patients who do not have a high need of health services ('cream skimming'), shortening consultation times (e.g. by prescribing pharmaceuticals immediately) or limiting the number of consultations that can occur. In addition, physicians can reduce their effort by slowing down the pace of work (productivity). Thus, diminished quality of care and long waiting lists may result (Gosden et al. 2001; Nederlandse Zorgautoriteit 2007; Rosen 1989).

In ACCHSs, healthcare workers receive a salary that is not based on the number of consultations they perform per day (Scrimgeour & Scrimgeour 2007). This model appears to be more suitable for Indigenous populations than fee-for-service payments (Scrimgeour & Scrimgeour 2007). The majority of funding for ACCHSs comes from the Commonwealth Government (72% in 2007–08), with most of the remainder from state/territory governments (27% in 2007–08) (Martini et al. 2011).

Many ACCHSs are also part of the QAAMS pathology program, which is dedicated to providing 'point of care' (PoC) testing for Indigenous patients with diabetes, using glycosylated haemoglobin (HbA1c) to show how well glucose is being managed, and microalbumin or the albumin:creatinine ratio (ACR) to detect early stage renal disease, a common outcome of poorly managed diabetes. Given that this program has been set up to target Indigenous patients with diabetes, funding of RP-NMRC within the QAAMS program could enhance the management of diabetes in ATSI communities.

Under this model Aboriginal health workers could be trained and accredited to undertake RP-NMRC in a manner similar to how the current quality assurance system for pathology works, and the photographs would be interpreted remotely by an ophthalmologist or trained reader by telemedicine. Using RP-NMRC as a PoC system would likely result in

better health outcomes for patients who are nomadic, or who have to travel a long distance to attend appointments, as only one appointment would be required, rather than two or more, to have the tests performed and receive the results. The management of their DR could therefore be discussed at the same appointment at which they underwent retinal photography.

As discussed earlier, under standard MBS rules only medical practitioners may claim MBS items. However, there are a range of MBS items that may be claimed by eligible nurse practitioners and registered Aboriginal health workers on behalf of a GP. It is likely that, in primary care settings where there is a high rate of patients eligible for RP-NMRC, nurse practitioners or Aboriginal health workers would be trained and accredited to use the non-mydriatic retinal cameras and screen patients for DR. If separate MBS items are considered for the taking of retinal photographs, versus the interpretation of photographs, then consideration of allowing nurse practitioners or Aboriginal health workers to claim items for the taking of retinal photographs with a non-mydriatic camera could be considered.

Prospective funding

Public hospitals funded through the states and territories in Australia have a fixed budget that is *prospectively* funded. The hospitals then must work within the fixed budget to provide care. This is very similar to the in-patient sectors in several European countries (e.g. Germany, Austria and Switzerland), which are funded prospectively and are independent of any kind of reimbursement through MBS item numbers.

An Italian study examined the uptake rate of new technology, based on reimbursement mechanisms over the period 1997–2007 (Finocchiaro Castro et al. 2014). Under retrospective cost reimbursement systems, hospitals are able to invest in technology without financial risk, and therefore the uptake of new medical technologies is high. In a prospective payment system, where the amount reimbursed is fixed, hospitals are encouraged to keep costs below the rate of reimbursement to avoid making a loss. This limits the adoption of new technologies unless these innovative technologies can reduce the costs of health care. Regions that used *activity-based funding* (similar to the MBS) had a higher amount of capital equipment than those where there was *a per-case* payment, such as through diagnosis-related group (DRG) funding. These data suggest that a per-case payment system constrains technology adoption. However, it is not known whether the additional investments made in the hospitals funded through retrospective activity-based funding are appropriate or overinvesting.

In Germany, hospital funding (hospitals are mainly non-profit) works through a dual-financing model: costs for the services are covered by a system of DRG per admission and are paid by social services institutions, and investments (including capital equipment) are annually and prospectively financed by the federal government, according to the Federal German Law of Hospital Financing. Thus, treatment costs are indirectly covered by fees of insured people, and investment costs are indirectly covered by taxes (Döbereiner 2010).

Funding of capital equipment in Austria follows nearly the same scheme as in Germany. There exists a strict division between the in-patient and out-patient sectors, and reimbursement of equipment in the in-patient sector underlies a type of dual-financing model (Schützinger, Theurl & Winner 2007). Payment for capital equipment used in the out-patient sector is covered through a retrospective per treatment reimbursement system by the public health insurance companies. In the in-patient sector, treatment and investment financing are covered by federal healthcare funds, which are mainly paid through the social health insurances, taxes and fees of the federal states or communes (Bartosik et al. 2012; Schützinger, Theurl & Winner 2007). Whereas the costs for treatment are covered by an adapted system of DRGs per admission, the costs for investments (including capital equipment) are directly and prospectively paid by the federal healthcare funds (Bartosik et al. 2012; Czasný et al. 2012). The federal healthcare funds approve grants for investments, and the planning of the hospital landscape is manifested in a structural plan. This plan is revised every 2–3 years and additionally defines the arrangement of large medical equipment (e.g. MRIs) (Czasný et al. 2012; Schützinger, Theurl & Winner 2007).

This contrasts with the situation in Switzerland where a new finance system of the in-patient sector was implemented in 2012 (Atupri Krankenkasse 2012; Christen et al. 2013). DRG-based lump sums, paid at a minimum of 55% by the cantons and at a maximum of 45% by health insurances, are now covering costs for both treatment and investments. Formerly, the cantons were exclusively responsible for investments in hospitals, which were financed by taxes. However, hospitals must now gain their own capital for investments (Atupri Krankenkasse 2012; Christen et al. 2013). The aim of this new way of investment financing in the in-patient sector is to improve the level of competition among hospitals. However, the investments have to be approved by the states' councils in advance, which is a restriction on competition (Christen et al. 2013).

Finally, the reimbursement of capital equipment such as non-mydriatic retinal cameras in Switzerland and the out-patient sectors in Germany and Austria is very similar to the

Australian system. This is because the costs of capital equipment are covered by lump sums per treatment or per patient. In contrast, capital funding in the in-patient sectors in Germany and Austria is different to the Australian private hospital system: the reimbursement of capital equipment is covered by prospectively paid grants for investment, and is independent of any performance characteristics.

One possible alternative model of funding of RP-NMRC (other than MBS funding) could be a mix of the current retrospective MBS system for professional services, with a prospective component, funded separately to the MBS through grants, covering capital equipment costs.

Capitation

Capitation comprises a prospectively fixed payment amount per patient (e.g. annual or quarterly), and requires a system of listing patients or responsibility of one physician for a defined population of citizens (Gosden et al. 2001). The physician receives a fixed income that is based on the number of patients they treat and is independent of any performance benchmarks. There is an incentive to minimise costs per patient rather than per episode or appointment. Capitation also encourages physicians to provide the best possible preventive and long-term care, and in that way future costs can be reduced (Gosden et al. 2001; Nederlandse Zorgautoriteit 2007).

Healthcare providers working under a capitation system would likely be attracted to RP-NMRC, as it has the potential to identify early stages of DR that, left untreated, would result in blindness and subsequent high medical costs and lowered quality of life. Capitation gives an incentive to expand the patient list because every new patient brings in extra income. This can be positive if it leads to competition among physicians concerning the quality of care offered.

However, capitation can also lead to less-desirable outcomes: first, the physician's cost-containing function might go too far if valuable care is withheld from patients and under-treatment is the result. Moreover, because payment occurs irrespective of the quantity of care provided, doctors have an incentive to reduce efforts and costs, for example by seeing the patients as little as possible, and minimising the intensity of consultations and visits (Gosden et al. 2001; Nederlandse Zorgautoriteit 2007). Another negative incentive associated with capitation is 'cream skimming': because physicians receive a fixed amount per patient, they have an incentive to avoid high-usage (labour/time) groups (e.g. the elderly or the chronically ill) (Nederlandse Zorgautoriteit 2007). Given that the target

population comprises those with diabetes who do not comply with current NHMRC recommendations, it is likely that they come from disadvantaged backgrounds, are more likely to be Indigenous, and have multiple health conditions that require addressing. This population may therefore be unattractive to physicians wanting to minimise their costs.

Equally, capitation could be considered a positive model for this population, given that the salary is not tied to the number of consultations per day. Healthcare practitioners may therefore be able to consult patients with complex needs for longer.

In the Netherlands, GPs are renumerated through a system that is a mix of capitation and fee-for-service. Dutch publicly insured citizens are allocated to one GP (who is the 'gatekeeper'), such that one GP is responsible for approximately 2,200 patients. The capitation is a fixed amount, paid quarterly per patient that the GP is responsible for. Thus, GPs receive a fixed income, given their number of patients, that is independent from the treatment provided. To compensate for patient-related differences in the workload of the doctors, the paid capitation is higher for older patients and those living in deprived districts (Groenewegen & Greß 2013; Nederlandse Zorgautoriteit 2007). In addition to the capitation fees, three modules that take care of extra compensation can be charged if there is an agreement with the relevant insurer. The modules are called 'Population background related compensation', 'Practice support GPs' and 'Modernisation and innovation' (Nederlandse Zorgautoriteit 2007). Moreover, Dutch primary care is well regulated by guidelines for diagnosis (especially ophthalmologic diagnosis) and treatment of common diseases. The wide use of established guidelines and the use of capitation per patient makes GPs responsible for the financial cost of their healthcare decisions, specifically those that support low rates of diagnostic procedures (or drug prescriptions etc.), compared with other countries (Groenewegen & Greß 2013; Nederlandse Zorgautoriteit 2007).

Target payment

Under a target payment system, the physician's compensation is linked to targets that are set (e.g. by insurers, government) as being desirable. For example, the physician is retrospectively paid an amount of money when a certain percentage of the population has been scanned or diagnosed for a certain disease. Target payments are often used as supplements to a capitation or fee-for-service system. Because the target payment is fixed, the doctors have an incentive to minimise costs and maximise income. However, because the physicians are paid as soon as the target is reached, the incentive to provide more than the target level of care decreases. Furthermore, target payments are disadvantageous

when it becomes likely that the target will be not be reached. The incentive of the target will then disappear as it is no longer valuable for the physicians to put in the effort to meet the target. In the case of RP-NMRC, it would be possible to link compensation with a certain percentage of diabetes patients being on a retinal screening register. However, the risk would be that this would encourage the use of RP-NMRC in all patients with diabetes, instead of being restricted to those who would not otherwise see an optometrist or ophthalmologist (Nederlandse Zorgautoriteit 2007).

Budget system

Financial incentives are not only embedded in the remuneration system but also arise when physicians are given budgets (mostly prospectively) with which they have to purchase healthcare services (e.g. diagnostic tests). If physicians are allowed to retain any budget surpluses, they will search for the most cost-effective care (Dusheiko et al. 2004). Additional incentives result if there is a restriction on overspending the budget. Physicians will then try even harder to contain costs. There is also an incentive to maximise the provision of care. On the one hand this is desirable, as it keeps patients at the lowest level of care possible; on the other hand, because budget holding encourages the physician to contain costs, it raises the risk of 'cream skimming' (Dusheiko et al. 2004; Nederlandse Zorgautoriteit 2007). Although budgets can be adjusted according to age, sex and mortality to capture the health status of the physician's patient population, risk adjustment will never be perfect (Nederlandse Zorgautoriteit 2007).

There are also some incentives associated with setting the budget and with the beginning and ending of a budget scheme. If the size of the budget is based on historical activity and this is known to those physicians who will become fund holders, these doctors will have an incentive to raise their activity (e.g. referrals and medicine prescriptions) in the preparatory year. Moreover, when physicians are free to enter the scheme, historical budget setting will encourage those doctors who expect an exogenous decline in their activity in future years to join because they would be expected to save on the budget. Such selection bias should be taken into account when studying the effects of a budget scheme (Nederlandse Zorgautoriteit 2007).

Training issues

In addition to the funding model adopted, the cost-effectiveness of RP-NMRC will be underpinned by the quality of training and accreditation that photographers receive (HESP advice, personal correspondence 17 June 2014). As previously discussed in the background to this assessment, cameras that are adequate for use in primary care may be purchased

for under $10,000 (Leferink 2011). However, the performance of any camera critically depends on adequate training of prospective operators. Failure to ensure adequate training and quality assurance is likely to result in poor technical performance of RP-NMRC, and may adversely impact patient health outcomes and any potential cost savings.

The Centre for Eye Research Australia (CERA) has communicated that several programs are currently available for accreditation in the use of RP-NMRC, including programs from UK (NHS 2013), USA, and one developed through the University of Queensland and the Royal Australian College of General Practitioners as part of an NHMRC Partnership Grant. The Diabetic Retinopathy Grading Centre at CERA has also been providing this type of training for about 10 years, and these programs may provide suitable templates to design an Australian-based program. Engagement with bodies, including the Royal Australian and New Zealand College of Ophthalmologists (RANZCO), OAA and the Australian College of Optometrists (ACO), to oversee the curriculum development, training and accreditation in each state of Australia could be another approach.

From an Indigenous health perspective, it may be possible to integrate training and education within the QAAMS program (QAAMS 2009), which already has a strong emphasis on diabetes care. It would appear logical to develop training that can be used within the existing framework and infrastructure to further augment diabetes care for Indigenous Australians.

One member of HESP (optometrist) advised that training in the use of RP-NMRC has been piloted in an Australian pathology service. The study reported that 'two pathology collectors completed a 21-hour onsite training course in non-mydriatic retinal photography, image management system operation and visual acuity assessment. Pathology personnel conducted all screening tests and were certified in retinal photography before data collection'. The authors found that gradable images were obtained in 74.2% of eyes photographed (Larizza et al. 2013). HESP also advised that suppliers of the retinal cameras provide installation and initial instruction regarding usage of the instrumentation and software. Once the initial set-up is complete, it should be possible to develop both a methodology for credentialling both those taking the photographs and those reading the images, and a system that will assist those reading the images to transmit their findings to the relevant healthcare practitioners.

Consumer impact statement

During the public consultation period the consumer interest group Vision 2020 Australia responded in favour of listing RP-NMRC on the MBS for the proposed population. They provided the following reasons in support of the service:

Improved access

For patients who have limited ability or are unable to access local services for monitoring eye health, the intervention is expected to result in improved access to diagnostic services and subsequent referral, and improved management of diabetic eye disease.

Cost savings

Vision impairment and/or blindness from DR results in substantial costs to individuals, including lost productivity and learning capacity for patients and carers, reduced quality of life and independence, and increased likelihood of acquiring co-morbidities.

Reduction in adverse events

The proposed intervention will improve detection of disease and thereby decrease adverse events associated with vision impairment and blindness through the treatment of patients who would have developed diabetic retinopathy in the absence of RP-NMRC.

Potential to address service gaps other than those relating to retinopathy

While at this stage RP-NMRC imaging should not replace CEE by an optometrist or ophthalmologist, if there is sufficient evidence on the accuracy and predictive capacity of RP-NMRC for other eye diseases, this technology could have wider application as a screening or triage mechanism for other at-risk groups, or for the population more broadly.

Quality assurance for training and accreditation

Quality assurance mechanisms for the accreditation and training of photographers and readers need to be in place, and the reader must have the appropriate experience to diagnose all ophthalmological diseases, not just DR, in order to achieve the full benefit of the screening. Hence, it should only be possible for medical practitioners to claim the interpretation portion of the service.

Improved rural/remote access to DR screening

One of the key points raised in the consumer impact statement in support of the provision of RP-NMRC for testing for DR was improved access to eye health services for patients who

currently have limited ability or are unable to access local services. Non-mydriatic retinal cameras are portable and easily transported to rural or remote settings for use by non-medical staff who have been accredited via appropriate technical training (Heaven, Cansfield & Shaw 1993). In addition, photographs can be interpreted remotely, via electronic link/telemedicine, by an optometrist, ophthalmologist or specifically trained reader. A number of studies have demonstrated that retinal photography is a viable option for screening for DR in rural and remote communities (Ku et al. 2013; Lee, SJ et al. 2001; Murray et al. 2005). In addition, access to eye-care services for Indigenous people is likely to be improved if these services can be delivered within culturally appropriate facilities (Turner et al. 2011). The provision of RP-NMRC within these communities is not only likely to increase compliance with recommended screening for DR, but would also reduce unnecessary travel for those patients in whom no signs of DR are detected.

What are the economic considerations?

Economic evaluation

Summary—What are the economic implications of RP-NMRC for detection of DR?

RP-NMRC is likely to be a cost-effective option for diagnosing DR in patients with diabetes who would not otherwise receive regular eye examinations. The estimated incremental cost per quality-adjusted life-year (QALY) is $14,870 in the broader Australian population and $12,380 in the Indigenous population, and the cost per blindness prevented is approximately $51,600 and $46,600, respectively. The model is most sensitive to the cost of treatment and the quality-of-life weight applied to the advanced sight-threatening DR (STDR) health state, but the ICER remains below $45,000/QALY in all modelled scenarios.

The comparison of RP-NMRC and standard medical assessment indicates that it would be inappropriate for RP-NMRC to replace the use of CEE in patients who are currently compliant with testing recommendations, as CEE is the more effective testing strategy. While RP-NMRC is more effective than dilated ophthalmoscopy performed by a GP, it is also more expensive.

The introduction of RP-NMRC will only be effective if provisions are made to ensure compliance with regular testing, appropriate follow-up of results, and prompt treatment of STDR when indicated.

The NHMRC guidelines (NHMRC 2008) recommend that all people with diabetes have a dilated fundus examination by a trained examiner (equivalent to a CEE) at the time diabetes is diagnosed and at least every 2 years thereafter. Where this practice is not available or not adhered to, retinal photographic screening with adequate sensitivity should be performed. Annual screening is recommended for ATSI groups.

The nominated comparators for the assessment of RP-NMRC are:

1. No eye examination
2. Standard medical assessment, including
   a) ophthalmoscopy with mydriasis by a GP; and/or
   b) CEE by an optometrist or ophthalmologist, with or without mydriasis.

1. No eye examination

No eye examination is the primary comparator for RP-NMRC. The availability of RP-NMRC in the primary care setting will identify additional cases of DR in patients who would previously not have received any eye examination, thus enabling the initiation of treatment in patients who, in the absence of RP-NMRC, would either not have been treated or would have received delayed treatment. In this scenario RP-NMRC

would be used as a triage test; patients with evidence of DR would be referred for a CEE by either an ophthalmologist or an optometrist, whereas patients without evidence of DR would return for another screening eye examination (RP-NMRC) in 1 or 2 years.

2. Standard medical assessment

a) Ophthalmoscopy with mydriasis by a GP

In a national survey of Australian GPs (Ting et al. 2011), only 13% of respondents indicated that they would usually or always perform dilated fundoscopy to detect signs of DR in diabetic patients, and 91% reported referring patients to ophthalmologists every 1–2 years. These data suggest that the proportion of clinicians using ophthalmoscopy as a triage test (i.e. only referring patients for a CEE if abnormalities are detected) is low. Therefore, the relevance of dilated ophthalmoscopy, performed by a GP, as a comparator for RP-NMRC is limited. In addition, there is limited evidence comparing dilated ophthalmoscopy by a GP with a CEE performed by an ophthalmologist. Despite these reservations, on the basis that RP-NMRC is superior to dilated ophthalmoscopy by a GP, a cost-utility analysis has been performed. Given the poor level of evidence forming the basis of this comparison, the results of the economic evaluation should be interpreted with caution.

b) CEE by an optometrist or ophthalmologist

Given that a CEE performed by either an optometrist or an ophthalmologist is more accurate than RP-NMRC and more likely to detect other non-DR related lesions, it would be inappropriate for RP-NMRC to substitute for a CEE in patients currently receiving this service. However, for completeness, a cost-utility analysis has been performed for this comparison.

The type of modelled evaluation, for all comparators, is a cost-utility analysis similar to previously published Markov models (see below), incorporating seven main health states: no diabetic retinopathy, non-sight threatening DR (non-STDR), early sight-threatening DR (STDR), advanced STDR (AdvSTDR), treated DR, blind and dead. Due to variations in testing frequencies and timing of treatment between diagnosed and undiagnosed patients, an additional four health states, relating specifically to patients diagnosed with DR, were required: non-STDR (diagnosed), early STDR (diagnosed), treated DR (early) and post-treatment (advanced) (see Figure 14). Outcomes are measured in quality-adjusted life-

years (QALYs). For the primary comparison of RP-NMRC versus no testing, the incremental cost per blindness prevented is also reported.

Population and setting for the economic evaluation

RP-NMRC is intended to be used in the primary care setting, including general practices, Indigenous health centres and diabetes clinics. Under the proposed listing, acquisition of images may be conducted by appropriately trained technicians and health workers, or GPs. However, if the taking of photographs is conducted by non-medical staff, reading of the image by an optometrist, ophthalmologist or possibly a trained GP would then be required.

The main role of RP-NMRC would be to identify additional cases of DR in patients who would previously not have received any eye examination. This will enable the initiation of treatment in patients who, in the absence of RP-NMRC, would either not have been treated or would have received delayed treatment. In this scenario RP-NMRC would be used to triage patients with diabetes. For those in whom any signs of DR are detected, a referral for a CEE must be made and, given the impending threat to sight, it is assumed that additional effort would be expended to adhere to this referral. In patients with no evidence of DR, a CEE (which is ideal, but impractical) would not be pursued. In addition, where images are of inadequate quality for detection of DR by the attending medical practitioner, referral to an ophthalmologist or optometrist for a CEE is indicated; a fee must not be charged when referral is required due to inability to obtain adequate images for grading.

It is not intended that RP-NMRC should replace CEE in those patients who are already receiving regular eye examinations performed by either an ophthalmologist or an optometrist. RP-NMRC would be an alternative to testing by ophthalmoscopy (with mydriasis) performed by a GP.

Under the proposed listing for the RP-NMRC service, a fee may not be charged for an assessment of a patient where a previous medical diagnosis of DR applies at the time of presentation, or for patients with visual impairment (distance vision of less than 6/12 in either eye or of more than two lines of vision between the two eyes). In addition, a fee may only be charged for repeat assessment on the condition that 2 calendar years have elapsed since the previous presentation for RP-NMRC, except for Indigenous Australians, where a restriction of 1 calendar year applies.

In the economic evaluation the population modelled is consistent with the target population, namely patients with diagnosed diabetes who meet the requirements for

eligibility for RP-NMRC in regard to previous diagnosis of DR, visual acuity and time since previous presentation for RP-NMRC.

Two populations have been assessed: the broad Australian diabetic population and the Indigenous Australian diabetic population, in which the frequency of testing, epidemiological characteristics of DR and mortality rates are altered accordingly. The broad Australian population enters the model at age 55 years (Larizza et al. 2013), and Indigenous Australians enter at age 50 years (Ku et al. 2013; Xie et al. 2011). At entry a proportion of patients are assumed to have undiagnosed DR, based on the estimated prevalence of previously undiagnosed DR in Australian diabetic patients who had not been examined in the previous 2 years. The remaining patients are assumed to have no DR but they subsequently have a yearly probability of developing NPDR, as determined by the estimated incidence of DR in Australia.

Clinical basis of the economic evaluation

No direct evidence was identified for the effectiveness of RP-NMRC. Therefore, the economic evaluation is based on the linked evidence presented in the 'effectiveness' section of this report (Table 34).

Table 34 Linked evidence forming the basis of the economic evaluation

Diagnostic accuracy	Source	Sensitivity % [95%CI]	Specificity % [95%CI]
RP-NMRC vs CEE			
Any detectable DR plus UIs	Meta-analysis, k=13 Table 19 of report	91.2% [81.7, 96.1]	76.5% [67.4, 83.6]
Severe NPDR and worse plus UIs	Meta-analysis, k=11 Table 20 of report	76.3% [60.2, 87.3]	98.1% [95.4, 99.2]
RP-NMRC vs ophthalmoscopy by GP [a]			
Severe NPDR and worse RP-NMRC Ophthalmoscopy by GP	O'Hare et al. (1996)	- 68% 56%	- 97% 98%

CEE = comprehensive eye examination; CI = confidence interval; DR = diabetic retinopathy; GP = general practitioner; k = number of studies; NPDR = non-proliferative diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera; UIs = unreadable images

[a] The evidentiary standard in this study was CEE performed by an ophthalmologist.

Selection of the most appropriate economic evaluation to use

1. No eye examination

A modelled economic evaluation is presented to compare the costs and outcomes of RP-NMRC testing with those for the situation in which no testing is performed. The model is a

cost-utility analysis that captures the health outcomes associated with prompt diagnosis and treatment, as opposed to either delayed diagnosis and treatment, or failure to diagnose.

The economic evaluation models the impact of subsequent referral for a CEE as a result of increased testing for DR, and the resulting changes in patient management and outcomes.

2. Standard medical assessment

a) Ophthalmoscopy with mydriasis by a GP

As discussed above, in a national survey of Australian GPs (Ting et al. 2011) only 13% of respondents indicated that they would usually or always perform dilated fundoscopy to detect signs of DR in diabetic patients, with 86% reporting that lack of confidence in detecting DR was a moderate or major barrier[15]. The majority (91%) reported referring patients to ophthalmologists every 1–2 years. This suggests that the proportion of clinicians using ophthalmoscopy as a triage test (i.e. only referring patients for a CEE if abnormalities are detected) is low. Therefore, the relevance of dilated ophthalmoscopy performed by a GP as a comparator for RP-NMRC, when used as a triage test, is limited.

The only publication located during the systematic review that compared both RP-NMRC and dilated ophthalmoscopy with a CEE performed by an ophthalmologist was O'Hare et al. (1996). The applicability of retinal photography, as used in this study, was limited by the fact that it was performed after mydriasis, and the number of UIs was not reported; however, RP-NMRC was still found to be more sensitive than dilated ophthalmoscopy in detecting referrable retinopathy (68% vs 56%), and the specificity was similar for both techniques (98% and 97%, respectively).

There is insufficient evidence to define the comparative safety of RP-NMRC and dilated ophthalmoscopy. The main safety concern with ophthalmoscopy performed with mydriasis is the potential to induce acute angle-closure glaucoma due to the use of pharmacological pupil dilation; however, this is rare, with an incidence of 1–6 per 20,000 people (NHMRC 2008). Therefore, for the purposes of the economic analysis, RP-NMRC is assumed to be no less safe than ophthalmoscopy with mydriasis. Despite the poor quality of the evidence, a cost-utility analysis has been performed, similar to that for the comparison with CEE.

[15] Note: Only 429 of 2,000 (21%) GPs approached responded.

b) CEE by an optometrist or ophthalmologist

The indirect evidence presented in the 'effectiveness' section of this report indicates that RP-NMRC is less sensitive and less specific than CEE performed by either an optometrist or ophthalmologist. As for dilated ophthalmoscopy, the main safety concern with CEE is the potential for glaucoma resulting from the use of pharmacological mydriatic agents. Therefore, similarly, RP-NMRC is assumed to be no less safe than CEE.

Given that a CEE by either an optometrist or ophthalmologist is more accurate than RP-NMRC, and is more likely to detect other non-DR related lesions, it would be inappropriate for RP-NMRC to substitute for CEE in patients currently receiving this service. However, for completeness, a cost-utility analysis has been conducted comparing the cost and outcomes of RP-NMRC testing with that of a CEE performed by an ophthalmologist or optometrist.

Economic literature review

A literature search was conducted to identify cost-effectiveness analyses of RP-NMRC compared with comparator testing strategies for the diagnosis of diabetic retinopathy in patients with diagnosed diabetes, to inform the structure of the model and provide appropriate inputs for the economic evaluation. Six studies were identified, as summarised in Table 35.

Table 35 Economic evaluations identified that evaluate the cost-effectiveness of RP-NMRC with alternative testing strategies

Study	Setting	Model and results
Kirkizlar et al. (2013)	Cost-utility analysis comparing retinal photography (as part of a telemedicine program) with CEE by an ophthalmologist in a US setting in people with type 1 or type 2 diabetes	Markov model with 7 health states (no retinopathy, NPDR, PDR, MO, PDR+MO, legal blindness and death), using a lifetime time horizon. Outcomes were measured in QALYs. Retinal photography was cost-effective (cost per additional QALY gained <$50,000) under most conditions, except in patient numbers <3,500 and people aged 80 years or older. In people aged 50 years or younger, retinal photography was dominant.
Rein et al. (2011)	Cost-utility analysis comparing retinal photography (as part of a telemedicine program) with CEE by an ophthalmologist in a US setting in people with diabetes, with no or early DR Four scenarios were analysed: patient self-referral to CEE, annual CEE, biannual CEE and annual retinal photography	Monte-Carlo simulation incorporating transitions among several normal, NPDR, PDR and CSMO disease stages. Outcomes were measured in QALYs. Annual retinal photography was observed to be less costly and less effective than biannual CEE in the base-case scenario, which assumed that retinal photography could not detect other eye conditions. When it was assumed that 25–75% of other eye conditions could be detected, retinal photography was dominant.
Whited et al.	Cost-effectiveness analysis of retinal	Decision tree analysis with the following outcomes:

Study	Setting	Model and results
(2005)	photography (as part of a telemedicine program) compared with current practice in three US healthcare agency settings in people with type 1 or type 2 diabetes	cost per true cases of PDR detected, cost per patient treated and cost per case of severe vision loss averted. A 12-month time horizon was used. Retinal photography was dominant for the outcome of cost per true cases of PDR detected in all three settings, and in two of the three settings for cost per patient treated (ICER of $1,618 in other setting) and severe vision loss averted (ICER of $13,748 in other setting).
Aoki et al. (2004)	Cost-utility analysis of retinal photography (as part of a telemedicine program) compared with CEE by an ophthalmologist in a US prison setting in people with type 2 diabetes	A Markov model with 6 health states (no retinopathy, NPDR, PDR, CSMO, legal blindness and death). A lifetime time horizon was modelled. Outcomes were measured in QALYs. Retinal photography was dominant to the ophthalmologist CEE strategy, with retinal photography continuing to dominate in 68% of probabilistic sensitivity analyses.
Maberley et al. (2003)	Cost-effectiveness analysis of screening using a portable retinal camera compared with screening by retinal specialists in an isolated population in Canada. Predominantly people with type 2 diabetes.	Decision tree analysis with outcomes measured by cost per year of vision saved and QALYs. A 10-year time horizon was applied. Retinal photography was dominant for both outcomes compared with screening by a retinal specialist.
Davies et al. (2002)	Cost-effectiveness analysis of different screening strategies for DR, including fundoscopy by an optometrist, ophthalmoscopy by a diabetologist or GP, mobile retinal camera or 'gold standard' (CEE by ophthalmologist)	A lifetime diabetes progression simulation model, measuring outcomes in cost per year of sight saved. Retinal photography was the least costly and least effective screening strategy.

CEE = comprehensive eye examination; CSMO = clinically significant macular oedema; DR = diabetic retinopathy; GP = general practitioner; ICER = incremental cost-effectiveness ratio; MO = macular oedema; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; QALY = quality-adjusted life-year

It was considered that there were insufficient data to inform the more complex models presented in Rein et al. (2011) and Davis et al. (2002), and that, given the chronicity of the disease and the repetitive nature of testing for disease, a Markov model would be most appropriate for the current assessment.

The Markov models presented in Aoki et al. (2004) and Kirkizlar et al. (2013) were similar; both included the same seven health states (no retinopathy, NPDR, PDR, MO, PDR+MO, legal blindness and death) and had similar inputs. In contrast to the proposed use of RP-NMRC in the current application, RP-NMRC testing was not limited to patients with no prior diagnosis of DR. Testing continued until progressed disease was diagnosed, at which stage patients received treatment with either panretinal laser photocoagulation (PRP) or focal laser photocoagulation. Both models were consistent in that DR was considered to be a progressive, non-reversible process; patients progressed through each stage of severity and could not return to a state of lower severity disease. In the economic evaluation presented by Aoki et al. (2004), RP-NMRC was dominant to CEE performed by an

ophthalmologist in the majority of scenarios, whereas Kirkizlar et al. (2013) found RP-NMRC to be a cost-effective alternative to CEE (cost per additional QALY gained <$US50,000) under most conditions.

In addition, Vijan, Hofer & Hayward (2000) presented a Markov model in which the marginal cost-effectiveness of various screening intervals for DR was examined. This model incorporated seven health states (no retinopathy, retinopathy 1, retinopathy 2, retinopathy 3, PDR, MO, blindness and death). It did not specifically assess the cost-effectiveness of RP-NMRC, but it was used as a source of inputs for the rate of progression of DR and its effect on the rate of mortality.

Structure of the economic evaluation

For the main comparator, no testing, the economic evaluation is based on the linked-evidence presented in this report, and models the impact of subsequent referral for a CEE as a result of increased testing for DR and the resulting changes in patient management and outcomes. For comparison with standard medical assessment, the evaluation models the costs and outcomes of each testing strategy, based on differences in patient management, as determined by the accuracy of each test.

The critical points that determine patient management are:

- the detection of any DR, at which stage patients are no longer eligible for biennial RP-NMRC testing and receive closer management by an ophthalmologist
- the detection of DR of a severity requiring urgent referral for a CEE and treatment (severe NPDR, PDR or clinically significant macular oedema (CSMO)), referred to as STDR for the purposes of the model.

The structure of the economic evaluation is adapted from the Markov models presented in Aoki et al. (2004), Kirkizlar et al. (2013), and Vijan, Hofer & Hayward (2000). The health states included in the model were adapted to reflect the critical decision-making points for patient management. The use of these critical points connects the model directly to the main linked evidence for RP-NMRC presented above, namely the sensitivity and specificity of RP-NMRC for, first, the detection of any DR and, second, DR requiring urgent referral (severe NPDR or worse). One limitation of this approach is that, as the diagnostic accuracy of RP-NMRC for CSMO was incorporated in that for the detection of DR of a severity requiring urgent referral, it was not possible to include a separate health state for CSMO.

Due to the criterion that limits eligibility for RP-NMRC testing to patients with no diagnosis of DR, it was necessary to incorporate additional health states specific to patients who had a confirmed diagnosis of DR, effectively resulting in two pathways dependent on status of diagnosis, as presented in Figure 14. Subsequently, the model includes a total of 11 health states: 6 main health states representing the natural progression of DR (no DR, non-STDR, early STDR, AdvSTDR, blind and dead), 4 parallel health states specific to patients who have a confirmed diagnosis of DR resulting from regular eye examinations (non-STDR diagnosed, early STDR diagnosed, treated DR early, and advanced DR post-treatment), and a final health state allowing for diagnosis and treatment of advanced STDR in patients not undergoing regular eye examinations (treated DR, late).

In the model the benefits of testing include:

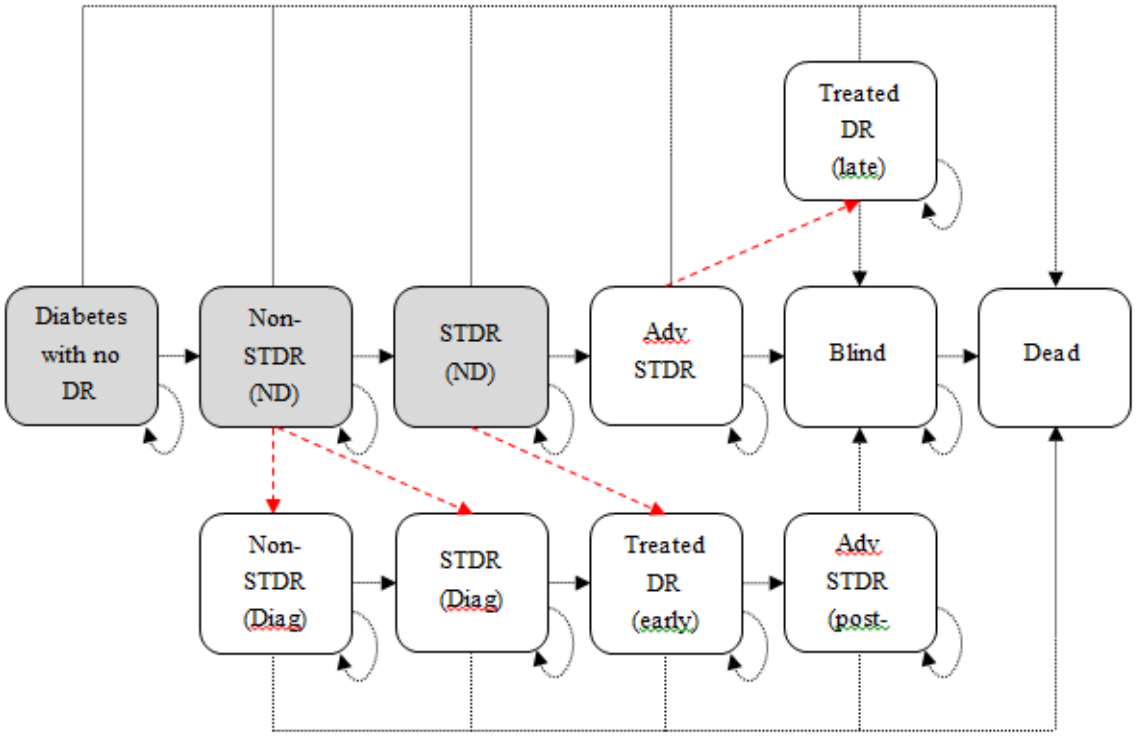
- early diagnosis of DR, with increased frequency of testing once diagnosed
- early treatment when the patient progresses to early STDR.

In comparison, in the 'no testing' arm of the model, patients are presumed to progress to the advanced STDR health state before undergoing eye testing due to deteriorating vision. Treatment at this later stage is assumed to be less effective in terms of preventing progression to blindness than early treatment (Javitt & Aiello 1996).

For the broad Australian population with diabetes, patients enter the model at age 55 years (Larizza et al. 2013) whereas Indigenous patients enter at age 50 years (Ku et al. 2013; Xie et al. 2011). The model has a 40-year time horizon, capturing lifetime costs and outcomes. The cycle length is 1 year.

The proposed health state diagram for the economic models is presented in Figure 14.

Figure 14 Health state diagram for the economic model



Adv = advanced; Diag = diagnosed DR; DR = diabetic retinopathy; ND = non-diagnosed; STDR = sight-threatening diabetic retinopathy; Tx = treatment

Note: Shaded health states indicate starting health states and are those in which screening for DR may be performed; dashed lines represent progressions resulting from confirmed positive test results.

For the purposes of the model, STDR is defined as severe NPDR or worse, consistent with a level of DR requiring urgent referral recommended by the NHMRC (2008) and with the linked evidence presented in the 'effectiveness' section of this report. Early STDR includes severe NPDR and low-grade PDR with only mild vision loss, whereas advanced STDR is assumed to be of a severity to result in moderate visual impairment. As adverse events directly associated with each testing option are rare, they have not been included in the model.

The economic evaluation is conducted from the perspective of the Australian healthcare system. A summary of the structure of the mechanics of the economic model is presented in Table 36.

Table 36 Summary of the economic model

Time horizon	40 years
Outcomes	Cases of blindness prevented (1° analysis only), quality-adjusted life-years
Methods used to generate results	Markov model (with half-cycle correction)
Cycle length	1 year
Discount rate	5% for both costs and outcomes
Software packages used	TreeAge Pro 2014

Patient flow through the model

Patients enter the model in one of the following three undiagnosed health states: diabetes with no DR, non-STDR and early STDR. Patients with advanced STDR are assumed to have visual impairment (distance vision of less than 6/12 in either eye) and are, therefore, not eligible for RP-NMRC testing. As in the Markov models presented in Aoki et al. (2004), Kirkizlar et al. (2013), and Vijan, Hofer & Hayward (2000), retinopathy is considered to be a progressive, non-reversible process; patients progress through each stage of severity and cannot return to a state of lower severity. Treatment reduces the probability of progression but does not reverse any vision loss already present.

In the intervention arm (RP-NMRC testing), patients from the broader Australian population undergo RP-NMRC every 2 years and may enter in either a testing or non-testing year. Patients alternate between testing and non-testing years until they are either diagnosed with DR, progress to advanced STDR or die. Transitioning from undiagnosed to diagnosed non-STDR and STDR health states is dependent on the accuracy of the testing strategy. All patients with evidence of DR, and those with UIs, are referred for a CEE by an ophthalmologist for confirmation of diagnosis. Falsely identified cases of DR return to the no DR health state (non-testing year) and are still eligible for biennial testing with RP-NMRC. Those in whom DR is confirmed transition to the appropriate diagnosed state; they are no longer eligible for testing by RP-NMRC and are presumed to undergo more-frequent eye examinations by CEE. Unless they die, patients with negative test results (either true or false) either remain stable or progress through the undiagnosed health states until the next testing occasion. If patients enter the advanced STDR health state without being diagnosed, they are assumed to be referred for a CEE due to the development of visual impairment. Indigenous patients are assumed to be tested on a yearly basis.

In the base-case all patients are assumed to be compliant with regular testing for DR and with referral for a CEE. The impact of this assumption on the outcome of the model is assessed in sensitivity analyses.

1. Primary comparison: no testing

For the primary comparator, no testing, transitions to the diagnosed DR health states are not allowed until patients develop advanced STDR. At this stage, on the presumption that they have deteriorating vision, they have a yearly probability of being referred for a CEE (probability of 1 in the base-case).

The primary economic evaluation for RP-NMRC is based on the assumption that, in the majority of patients, regular testing will result in DR being diagnosed and treated at a less advanced stage compared with those not receiving eye examinations. Treatment is initiated on diagnosis of STDR, either early or late, with immediate transition to the corresponding treated retinopathy health state; that is, diagnosis of STDR and subsequent treatment occur within the same cycle.

2. Secondary comparison: standard medical assessment

For the secondary comparators, CEE performed by an ophthalmologist/optometrist or ophthalmoscopy with mydriasis performed by a GP, the comparator arm of the model is similar in structure to that for RP-NMRC. The incremental effectiveness of the alternative strategies is entirely dependent on the relative accuracy of the respective testing methods. The clinical pathway for patients undergoing CEE by an optometrist or ophthalmologist differs from that for RP-NMRC and ophthalmology by a GP in that, as CEE is considered the 'gold standard' method of testing for DR, there are no false test results (i.e. it is assumed to be 100% accurate).

The possible transitions among health states, categorised by testing/non-testing year where appropriate, are summarised in Table 37.

Table 37 Possible transitions among health states in the economic model

Initial health state	Possible transitions		Testing frequency
	Non-testing year	Testing year	
Diabetes – no DR	Diabetes – no DR Non-STDR (non-diagnosed) Dead	Diabetes – no DR Non-STDR (non-diagnosed) Dead	Every 2 years ATSI: yearly
Non-STDR (non-diagnosed)	Non-STDR (non-diagnosed) Early STDR (non-diagnosed) Dead	Non-STDR (non-diagnosed) Early STDR (non-diagnosed) Non-STDR (diagnosed) STDR (diagnosed) Dead	Every 2 years ATSI: yearly
Early STDR (non-diagnosed)	Early STDR (non-diagnosed) Advanced STDR Dead	Early STDR (non-diagnosed) Advanced STDR Treated DR (early) [a] Dead	Every 2 years ATSI: yearly
Advanced STDR	Advanced STDR	Advanced STDR	Chance of undergoing

Initial health state	Possible transitions		Testing frequency
	Non-testing year	Testing year	
	Blind Dead	Treated DR (late) Blind Dead	CEE due to deteriorating vision
Non-STDR (diagnosed DR)	NA	Non–STDR (diagnosed) Early STDR (diagnosed) Dead	Yearly CEE ATSI: 2 CEEs per year
Early STDR (diagnosed DR)	NA	Treated DR (early) [a] Dead	2 CEEs per year ATSI: 3 CEEs per year
Treated DR (early)	NA	Treated DR (early) Blind Dead	3 CEEs per year ATSI: 4 CEEs per year
Advanced STDR (post-treatment)	NA	Advanced STDR (post-treatment) Blind Dead	3 CEEs per year ATSI: 4 CEEs per year
Treated DR (late)	NA	Treated DR (late) Blind Dead	3 CEEs per year ATSI: 4 CEEs per year
Blind	NA	Blind Dead	-

ATSI = Aboriginal and Torres Strait Islander (people); CEE = comprehensive eye examination; DR = diabetic retinopathy; NA = not applicable; RP-NMRC = retinal photography with a non-mydriatic retinal camera; STDR = sight-threatening diabetic retinopathy

[a] All patients with STDR who are diagnosed during screening are assumed to undergo CEE and receive treatment, progressing directly to the treated DR health state.

As outlined in the protocol, as non-DR outcomes are not the primary interest for this assessment, the consequences of incidental findings resulting from the provision of an RP-NMRC service in the primary care setting have not been included in the economic evaluation.

The Markov structures of the economic model are shown in Figure 15 and Figure 16 for RP-NMRC screening and no eye examination, respectively. The structure for screening by both CEE and ophthalmoscopy is similar to that for RP-NMRC.

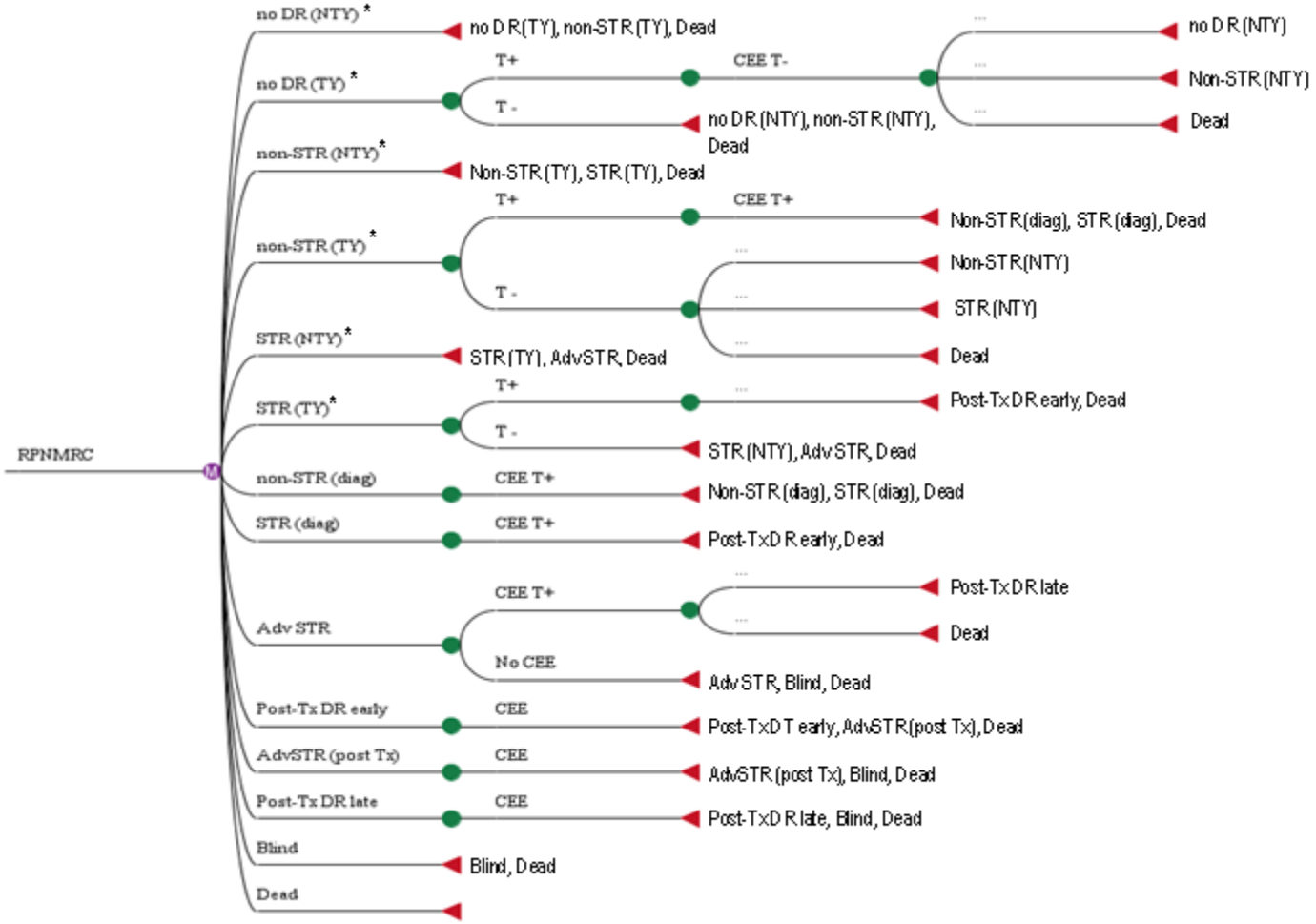


Figure 15 Markov structure of the economic evaluation; RP-NMRC screening arm [a]

AdvSTR = advanced sight-threatening retinopathy; CEE = comprehensive eye examination; diag = diagnosed; DR = diabetic retinopathy; NTY = non-testing year; STR = sight-threatening retinopathy; Tx = treatment; TY = testing year

[a] Patients may enter the model in the health states marked with an asterisk.

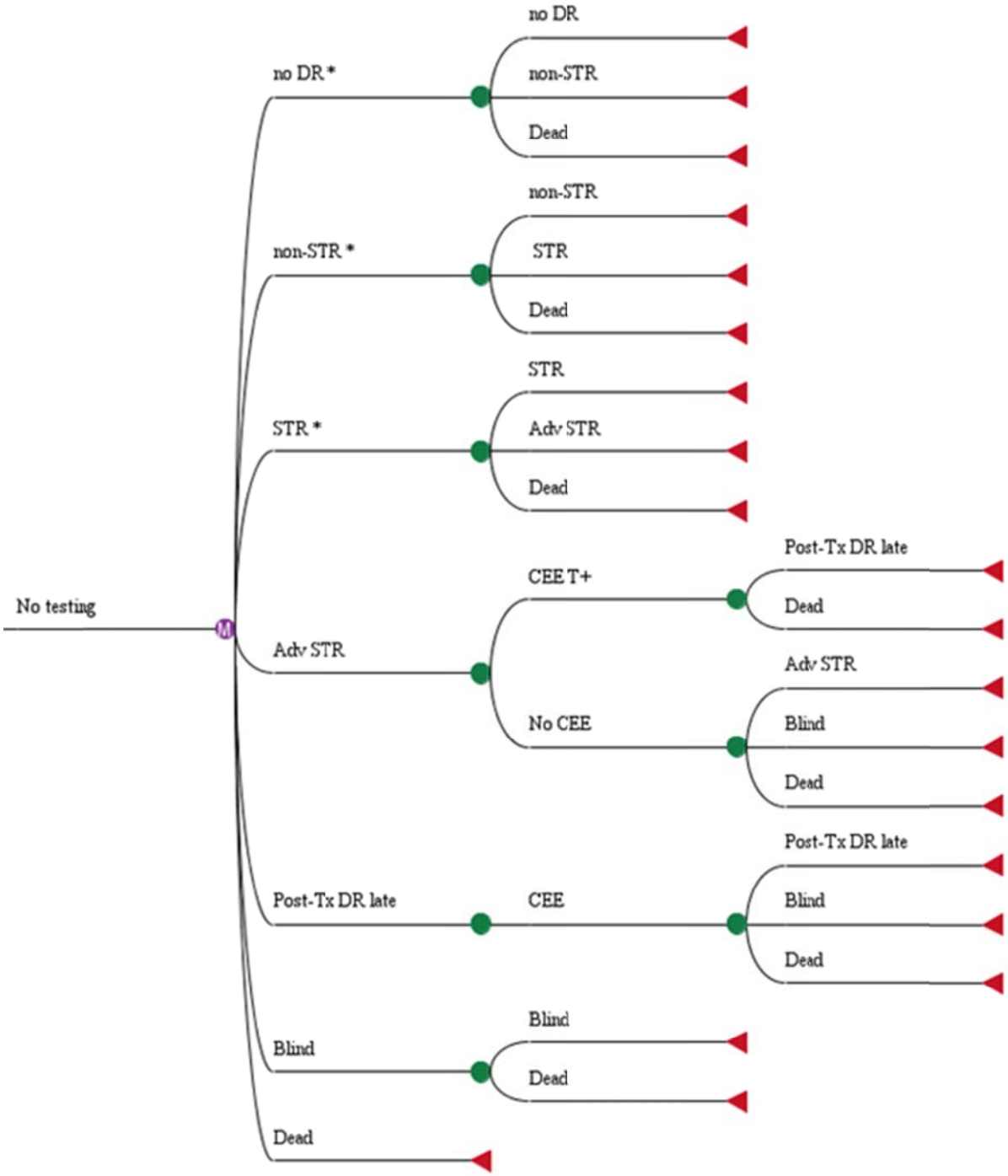


Figure 16 Markov structure of the economic evaluation; no eye examination [a]

AdvSTR = advanced sight-threatening retinopathy; CEE = comprehensive eye examination; DR = diabetic retinopathy; STR = sight-threatening retinopathy; Tx = treatment

[a] Patients may enter the model in the health states marked with an asterisk.

A number of additional assumptions have been incorporated into the model structure:

- As patients diagnosed with DR are assumed to undergo a CEE on a yearly basis, it is assumed that STDR will be diagnosed and treated prior to progression to advanced STDR.

- Patients are assumed to receive only one course of treatment; all treatment costs are accrued on transition to the post-treatment health state.
- Immediately after treatment, patients are assumed to have the same severity of DR as that at which they were diagnosed (early STDR or advanced STDR) until they either develop blindness or die.

Alternative scenarios

There is considerable uncertainty for many of the inputs in the economic model. In the base-case for each comparison, a conservative approach has been taken, with the use of inputs that tend to favour the comparator over RP-NMRC screening.

For this reason, two scenarios are presented:

- Scenario 1: low DR incidence and slow progression of DR
- Scenario 2: higher DR incidence and faster rate of progression.

Scenario 1 is used as the primary analysis for comparison with no testing. It assumes that a slow progression of disease favours the no testing strategy, minimising the benefits of early diagnosis resulting from regular testing. In contrast, Scenario 2 is used as the primary analysis for the secondary comparison with standard medical assessment. It assumes that a slow progression of disease minimises the observed incremental effectiveness between testing strategies, greatly favouring the less expensive option.

For each comparator the economic evaluation has been performed for two populations:

- Population 1: the broad Australian population with diabetes
- Population 2: Indigenous Australians with diabetes.

These populations differ in terms of prevalence, incidence and rate of progression of DR; mortality rates; and recommended frequency of testing for DR.

Inputs to the economic evaluation

Test parameters

The test accuracy parameters used in the economic model include sensitivity and specificity of RP-NMRC for detection of any grade of DR, and for DR requiring urgent referral (severe NPDR or worse), as determined by the meta-analysis of systematic review evidence presented in the 'Effectiveness' section of this report. As all patients for whom gradable images could not be obtained should be referred to an ophthalmologist for a CEE, UIs were

treated as a positive result in the meta-analysis. As discussed, there was a high level of heterogeneity among studies (I^2 >95%). In addition, the photographs in these studies were read by ophthalmologists or retinal specialists, as opposed to GPs or other professionals with minimal training in a community or rural primary care setting.

The only publication located during the systematic review that compared both RP-NMRC and dilated ophthalmoscopy with CEE performed by an ophthalmologist was O'Hare et al. (1996). As discussed above, the applicability of this study was limited by the fact that retinal photography was performed after mydriasis, and the number of UIs was not reported. RP-NMRC was found to be more sensitive than dilated ophthalmoscopy in detecting referrable retinopathy (68% vs 56%), and the specificity was similar for both techniques (98% and 97%, respectively). The sensitivity and specificity for any DR was not reported.

Only 1 other study was located that reported the accuracy of dilated ophthalmoscopy performed by a GP, compared with the evidentiary standard of CEE performed by an ophthalmologist (Lienert 1989). In this study the estimated sensitivity of dilated ophthalmoscopy was 45% for any DR and 50% for PDR. The specificity was reported to be 100% for both categories.

The accuracy data from O'Hare et al. (1996) have been used in the model, as these are more conservative and favour the comparator over RP-NMRC. The sensitivity and specificity for any DR were assumed to be the same as those for referrable DR. Due to the poor quality of data available, the results of the economic analysis for this comparison should be interpreted with caution.

As a CEE performed by an ophthalmologist or optometrist is the 'gold standard' for testing and was the evidentiary standard in the systematic review, it is assumed to have a sensitivity and specificity of 1.0.

The test parameters and the frequency of testing used in the model are summarised in Table 38 and Table 39, respectively.

Table 38 Test characteristics used in the economic evaluation

Test accuracy	Value (95%CI)	Source
RP-NMRC		
Any DR:		
sensitivity	91.2% [81.7, 96.1]	Meta-analysis, Table 19 of report
specificity	76.5% [67.4, 83.6]	
STDR:		
sensitivity	76.3% [60.2, 87.3]	Meta-analysis, Table 19 of report

Test accuracy	Value (95%CI)	Source
Ophthalmoscopy by GP		
Any DR:		
sensitivity	56%	O'Hare et al. (1996)
specificity	98%	
STDR:		
sensitivity	56%	O'Hare et al. (1996)
CEE by ophthalmologist/optometrist		
Any DR:		
sensitivity	100%	NHMRC (2008)
specificity	100%	
STDR:		
sensitivity	100%	NHMRC (2008)

DR = diabetic retinopathy; GP = general practitioner; RP-NMRC = retinal photography with a non-mydriatic retinal camera; STDR = sight-threatening diabetic retinopathy

Note: The specificity of RP-NMRC for STDR was not used in the model. For patients with STDR, the sensitivity for either any DR or for STDR was used, whichever was higher.

Table 39 Frequency of testing for DR in the model, for the broad Australian population and Indigenous Australians [a]

Health state	Broad Australian population	Indigenous
No DR	Every 2 years	1 per year
Diagnosed non-STDR	1 per year	2 per year
Diagnosed STDR	2 per year	3 per year
Treated DR	3 per year	4 per year

DR = diabetic retinopathy; STDR = sight-threatening diabetic retinopathy

[a] Based on recommendations in the NHMRC Guidelines (NHMRC 2008)

In the model the proportion of patients who are correctly identified as not having DR is determined by the specificity of the test for any DR, and the sensitivity for any DR is used to determine the proportion of patients with non-STDR who are diagnosed correctly. As all patients with evidence of DR of any severity are referred for a CEE for confirmation of diagnosis, whichever is the higher of the sensitivity for any DR or for STDR is used to determine the proportion of patients with STDR that are appropriately referred for further examination.

Transition probabilities

The rate of progression of diabetic retinopathy must be considered one of the main sources of uncertainty in the economic evaluation. Many of the studies from which estimates for the progression of DR were derived, such as the Diabetic Retinopathy Study (DRS) and the Early Treatment of Diabetic Retinopathy Study (ETDRS) (DRS 1981; ETDRS 1991a), were performed in the 1970s and 1980s. As the management of diabetes has improved considerably since these studies were performed, estimates of prevalence, incidence and progression derived from these sources are likely to be considerably higher than would be

observed in the current clinical setting. Where possible, more recent sources have been used; otherwise, the most conservative estimate has been used.

Prevalence

The distribution of the population across health states on entry to the model is based on reported prevalence rates in Australian diabetes patients.

Two Australian studies, one conducted in rural Victoria (Harper et al. 1998) and the other in urban Victoria (Larizza et al. 2013), reported the prevalence of DR as 22.4% (125/559) and 17.2% (16/93), respectively, in patients with no previous diagnosis of DR and who had not been tested for DR in the previous 2 years; neither provided details on the severity of disease. While not restricted to patients with no prior diagnosis of DR, baseline estimates of the prevalence of NPDR and PDR from the Australian Diabetes Obesity and Lifestyle (AusDiab) study were 19.8% and 2.1%, respectively (Tapp et al. 2003).

In the National Indigenous Eye Health Survey, conducted in 2008, 29.7% of those with self-reported diabetes had retinopathy (Xie et al. 2011). The prevalence of mild/moderate NPDR was 17.8% (70/394), 3.1% had severe NPDR or PDR, and 8.9% had CSMO. Only 39% of those with mild/moderate NPDR, 50% with severe NPDR/PDR, and 54% with CSMO had consulted an appropriate healthcare service regarding their eye problem within the previous year. Similarly, in a study conducted in Aboriginal health clinics in the Kimberly region, only 48% of regular Aboriginal clients with diabetes had a record of retinal screening within the previous 18 months (Murray et al. 2005). In this study the prevalence of DR in Aboriginal clients with type 2 diabetes was 20.5% (254/1,240), of whom 3.5% were classified as having STDR. Two further studies conducted in Indigenous Australian populations reported similar results. In the Katherine Region Diabetic Retinopathy Study (KRDRS), conducted in 1996, the prevalence of retinopathy in the Aboriginal population with diabetes was estimated at 21%, 1.3% had PDR and 6.7% had STDR (Jaross, Ryan & Newland 2003); and in the Central Australian Ocular Health Study (CAOHS), conducted from 2005 to 2008, the prevalence of any DR was estimated to be 23%, 7% of which was classified as STDR (Ku et al. 2013).

As there are limited data for the specific population of interest, the prevalences of NPDR and PDR reported in the AusDiab study were used for the broader Australian population. Conservatively, the lower prevalence estimates from Murray et al. (2005) were used in the primary scenario for the Indigenous Australian population, and the higher estimates from Xie et al. (2001) were used in the secondary scenario.

Incidence and rate of progression

Reliable data for the incidence of DR in the Australian diabetic population are also limited. In the prospective longitudinal AusDiab study, completed in 2004–05, the overall 5-year incidence of retinopathy in those with known diabetes at baseline was 13.9% (20/144), and in those aged 45–64 years was 15.2% (Tapp et al. 2008). Of patients with mild NPDR at baseline, 17.6% had progressed at the 5-year follow-up, predominantly to more-advanced NPDR (14.7%), with only 2.9% progressing to PDR.

The incidence and progression of DR was considerably higher in the older Blue Mountains Eye Study, completed in 1997–99 (Cikamatana et al. 2007). The 5-year incidence of DR was 22.2% (95%CI 14.1, 32.2); retinopathy progression was documented in 25.9% (95%CI 18.8, 34.0) of participants, with retinopathy and gradable images at both baseline and 5-year follow-up, and progression to PDR in 4.1% of participants. The NHMRC guidelines report the following 1-year rates of progression: mild NPDR to PDR 5%, moderate NPDR 12–26%, severe NPDR to PDR 52%, severe NPDR to high-risk stage 15%, and PDR to high-risk stage 46%; and in those with high-risk PDR, severe vision loss develops in 25–40% within 2 years (NHMRC 2008).

Based on the 5-year incidence reported in the AusDiab study, the yearly probability of developing DR is estimated to be 0.02–0.324, and the yearly probability of progressing from mild NPDR is 0.038. One limitation of the available data is that conversion of the 5-yearly incidence to yearly probabilities assumes a fixed rate with respect to time, whereas in reality the rate is likely to increase with time. These estimated probabilities are low compared with the transition probabilities used in both Aoki et al. (2004) and Kirkizlar et al. (2013), in which the assumed annual progression rate was 0.065 for no DR to NPDR, and 0.116 for NPDR to PDR.

For the primary comparison of RP-NMRC testing versus no eye examination, the annual probabilities derived from the AusDiab study are used for the yearly incidence of DR (no DR to non-STDR) and for the progression from non-STDR to early STDR. As discussed above, assuming a slow progression of disease favours the no testing scenario, minimising the benefits of early diagnosis resulting from regular testing. Therefore, for the primary comparison, the use of low-transition probabilities is a conservative approach. The transition probabilities reported in Vijan, Hofer & Hayward (2000) are used for the remaining transitions (early STDR to AdvSTDR and AdvSTDR to blind), as these are conservative compared with other published models (Scenario 1, Table 40).

For the secondary comparison with standard medical assessment, assuming a slow progression of disease minimises the observed incremental effectiveness between testing strategies. Therefore, the transition probabilities are based on the incidence reported in the Blue Mountains Eye study and the yearly rates of progression documented in the NHMRC guidelines (Scenario 2, Table 41).

The only study located that estimated the annual incidence and rates of progression of DR in the Indigenous Australian population was the KRDRS (Jaross, Ryan & Newland 2005). Based on a 3-year follow-up of subjects, the annual incidence was estimated as 5.6%. The annual rates of progression from mild NPDR to severe NPDR, and from mild NPDR to STDR, were 12.1% and 4.2%, respectively. For transitions where Indigenous-specific probabilities could not be located, they are assumed to be the same as those for the broader Australian population.

Unless they die, all patients who progress to the early STDR (diagnosed) health state are assumed to be regularly tested by CEE and treated immediately. Therefore, the probability of transitioning from this health state to treated DR (early) is '1 – probability of death'. Similarly, in the base-case, all patients in the AdvSTDR health state who remain alive are assumed to be referred for a CEE due to visual impairment, with subsequent diagnosis and treatment.

The prevalence, incidence and transition probabilities used in the model are presented in Table 40 and Table 41 for Scenario 1 and Scenario 2, respectively.

Table 40 Estimates of prevalence, incidence and rates of progression used in Scenario 1 of the modelled economic evaluation [a]

Variable	Value	Source
Broad Australian population		
Prevalence:		
non-STDR	19.8%	AusDiab Study (Tapp et al. 2003)
STDR	2.1%	AusDiab Study (Tapp et al. 2003)
Incidence non-STDR (yearly)	3%	AusDiab Study (Tapp et al. 2008)
Transition probabilities:		
non-STDR to early STDR	0.04	AusDiab Study (Tapp et al. 2008)
early STDR to AdvSTDR	0.08	Vijan, Hofer & Hayward (2000)
AdvSTDR to blind (no treatment)	0.09	Vijan, Hofer & Hayward (2000)
treated DR (early) to AdvSTDR (post-treatment)	0.016	Transition probability STDR to AdvSTDR x treatment effect (early)
treated DR (late) to blind	0.036	Transition probability AdvSTDR to blind x treatment effect (late)
Indigenous Australians		
Prevalence:		

Variable	Value	Source
non-STDR	16.9%	Murray et al. (2005)
STDR	3.5%	Murray et al. (2005)
Incidence non-STDR (yearly)	5.6%	Jaross et al. (2005)
Transition probabilities:		
non-STDR to early STDR	0.121	Jaross et al. (2005)
early STDR to AdvSTDR	0.08	Vijan, Hofer & Hayward (2000)
AdvSTDR to blind (no treatment)	0.09	Vijan, Hofer & Hayward (2000)
treated DR (early) to AdvSTDR (post-treatment)	0.016	Transition probability STDR to AdvSTDR x treatment effect (early)
treated DR (late) to blind	0.036	Transition probability AdvSTDR to blind x treatment effect (late)
Treatment effect (both populations)		
Early treatment	0.22	Vijan, Hofer & Hayward (2000), Kirkizlar et al. (2013)
Late treatment	0.42	DRS (1981)

AdvSTDR = advanced sight-threatening diabetic retinopathy; DR = diabetic retinopathy; STDR = sight-threatening diabetic retinopathy

[a] Used for the primary analysis for comparator 1, no testing

Table 41 Estimates of prevalence, incidence and rates of progression used in Scenario 2 of the modelled economic evaluation [a]

Variable	Value	Source
Broad Australian population		
Prevalence:		
non-STDR	19.8%	AusDiab Study (Tapp et al. 2003)
STDR	2.1%	AusDiab Study (Tapp et al. 2003)
Incidence non-STDR (yearly)	4.9%	BMES (Cikamatana et al. 2007)
Transition probabilities:		
non-STDR to early STDR	0.05	NHMRC (2008)
early STDR to AdvSTDR	0.24[b]	NHMRC (2008)
AdvSTDR to blind (no treatment)	0.13	NHMRC (2008)
treated DR (early) to AdvSTDR (post-treatment)	0.048	Transition probability STDR to AdvSTDR x treatment effect (early)
treated DR (late) to blind	0.052	Transition probability AdvSTDR to blind x treatment effect (late)
Indigenous Australians		
Prevalence:		
non-STDR	17.8%	Xie et al. (2011)
STDR	11.9%	Xie et al. (2011)
Incidence non-STDR (yearly)	5.6%	Jaross et al. (2005)
Transition probabilities:		
non-STDR to early STDR	0.121	Jaross et al. (2005)
early STDR to AdvSTDR	0.24[b]	NHMRC (2008)
AdvSTDR to blind (no treatment)	0.13	NHMRC (2008)
treated DR (early) to AdvSTDR (post-treatment)	0.048	Transition probability STDR to AdvSTDR x

Variable	Value	Source
treated DR (late) to blind	0.052	treatment effect (early) Transition probability AdvSTDR to blind x treatment effect (late)
Treatment effect (comparators 1 and 2)		
Early treatment	0.2	Vijan, Hofer & Hayward (2000), Kirkizlar et al. (2013)
Late treatment	0.4	DRS (1981)

AdvSTDR = advanced sight-threatening diabetic retinopathy; AusDiab study = Australian Diabetes, Obesity and Lifestyle study; BMES = Blue Mountains Eye Study; DR = diabetic retinopathy; DRS = Diabetic Retinopathy Study; NHMRC = National Health and Medical Research Council; STDR sight-threatening diabetic retinopathy

[a] Used in the primary analysis for comparator 2, standard medical assessment

[b] Calculated from product of rate of progression severe NPDR to PDR (0.52) x rate of progression PDR to high-risk PDR (0.46) (NHMRC 2008)

Treatment effect

The NHMRC guidelines state that laser photocoagulation remains the 'gold standard' therapy for STDR (NHMRC 2008). The treatment for PDR is generally PRP, which has been shown to significantly reduce severe vision loss (NHMRC 2008). Focal/grid laser photocoagulation is an established treatment for patients with CSMO, but intra-vitreal injection of anti-VEGF is increasingly being used as the primary treatment (Gupta et al. 2013).

Whereas the anti-VEGF agent ranibizumab is approved by the Therapeutic Goods Administration for the treatment of visual impairment due to diabetic MO, no anti-VEGF agents are listed on the PBS for this indication.

As previously discussed, there was insufficient evidence located in the systematic review performed for this report to support the inclusion of a separate CSMO health state. Therefore, in the base-case scenario it is assumed that all patients with STDR are treated with laser photocoagulation. The effect of the cost of treatment (including possible treatment with anti-VEGF agents) on the outcome of the economic analysis is assessed in sensitivity analyses.

Panretinal photocoagulation (PRP)

Estimates of the effectiveness of PRP, in terms of reducing the progression to severe vision loss, are largely based on the same early studies as those from which the estimated rates of progression of DR are derived.

A review of five randomised trials of PRP for prevention of blindness in DR estimated the relative risk of blindness in eyes treated by PRP, compared with no treatment, to be 0.39

(95%CI 0.28, 0.55) (Rohan, Frost & Wald 1989). The five trials included in the review were published between 1977 and 1984, and the results were dominated by the DRS, which accounted for 78% of the patients included in the analysis. The estimate of the relative risk of blindness in the five trials ranged from 0.19 (95%CI 0.10, 0.39) to 0.67 (95%CI 0.37, 1.21).

Javitt and Aiello (1996) reported that, while the DRS reported that PRP reduced the likelihood of severe vision loss by 60%, many patients enrolled in this study had advanced disease. They argued that a comparison of the results of PRP in the ETDRS with the 'no treatment' group of the DRS resulted in an 84% reduction in progression to severe vision loss (1.48% compared with 8.7%) (Javitt & Aiello 1996). This publication is the source of the assumed treatment effect in the Markov models presented by Vijan, Hofer & Hayward (2000) and Kirkizlar et al. (2013), in which the yearly transition probability from high-risk PDR to blindness is 0.09 without PRP and 0.02 with PRP.

In the model the treatment effect derived in the DRS is used for late treatment at the advanced STDR state, whereas the estimate used in both Vijan, Hofer & Hayward (2000) and Kirkizlar et al. (2013) is used for early treatment (Table 40). The treatment effect is only applied to the first transition after treatment: treated DR (early) to AdvSTDR (post-treatment) after early treatment, and treated DR (late) to blind after late treatment.

Mortality

The likelihood of death in each health state is derived by applying a mortality multiplier to the mortality rates for the general Australian population, stratified by age, as reported by the ABS (2013a). The mortality multiplier for diabetes with no DR, 1.4, is based on the relative risk of mortality for people with diabetes reported in the AusDiab study (Tanamas et al. 2013). The mortality multipliers for all DR health states were sourced from Vijan, Hofer & Hayward (2000). These were based on mortality rates published by the US Government, modified to reflect the increased mortality rates observed in patients with diabetes in general (RR 1.8) and further adjusted for disease state based on observed mortality risks in observational studies (Vijan, Hofer & Hayward 2000). The mortality adjustments for disease state were 1.36, 1.46, 1.76 and 2.34 for diabetes patients with non-STDR, STDR, advanced STDR and blindness, respectively. These disease state adjustments are made in addition to the increased risk of mortality from diabetes; that is, the mortality rate for the general population is multiplied by the mortality multiplier for diabetes (1.4) and then by the mortality state adjustment for DR state.

People in the diagnosed DR health states are assumed to have the same mortality rate as those in the corresponding undiagnosed health states. The age-specific death rates for each disease state for the broader Australian population are summarised in Table 42.

Table 42 Mortality estimates for the broad Australian population used in the economic model, in various health states

Age (years)	General population (ABS 2013a)	Diabetes, no DR	Non-STDR	STDR	AdvSTDR	Blind
Relative risk	*1.0*	*1.4*[a]	*1.90*[b]	*2.09*[b]	*2.46*[b]	*3.28*[b]
40	0.12%	0.17%	0.23%	0.25%	0.30%	0.39%
45	0.17%	0.24%	0.32%	0.35%	0.42%	0.56%
50	0.26%	0.36%	0.50%	0.54%	0.64%	0.85%
55	0.40%	0.56%	0.76%	0.83%	0.99%	1.31%
60	0.62%	0.87%	1.18%	1.29%	1.53%	2.03%
65	0.97%	1.36%	1.85%	2.02%	2.39%	3.18%
70	1.62%	2.27%	3.08%	3.38%	3.99%	5.31%
75	2.87%	4.02%	5.46%	5.99%	7.07%	9.40%
80	5.38%	7.53%	10.24%	11.22%	13.26%	17.62%
85	13.46%	18.84%	25.63%	28.08%	33.17%	44.09%

ABS = Australian Bureau of Statistics; AdvSTDR = advanced sight-threatening diabetic retinopathy; DR = diabetic retinopathy; STDR = sight-threatening diabetic retinopathy

[a] Relative risk of mortality for people with known diabetes in AusDiab study (Tanamas et al. 2013)

[b] Calculated as RR death for diabetes x mortality multiplier for disease state, sourced from Vijan, Hofer & Hayward (2000)

Source: ABS online (http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.02012)

Table 43 Mortality estimates for Indigenous Australians used in the economic model, in various health states

Age (years)	RR death [a]	ATSI population	Diabetes, no DR	Non-STDR	STDR	AdvSTDR	Blind
40	4.9	0.59%	0.82%	1.12%	1.23%	1.45%	1.93%
45	4.0	0.68%	0.95%	1.29%	1.42%	1.68%	2.23%
50	4.0	1.04%	1.46%	1.98%	2.17%	2.56%	3.41%
55	3.2	1.28%	1.79%	2.44%	2.67%	3.15%	4.19%
60	3.2	1.98%	2.78%	3.78%	4.14%	4.89%	6.50%
65	1.3	1.26%	1.77%	2.40%	2.63%	3.11%	4.13%
70	1.3	2.11%	2.95%	4.01%	4.39%	5.19%	6.90%
75	1.3	3.73%	5.22%	7.10%	7.78%	9.19%	12.22%
80	1.3	6.99%	9.79%	13.32%	14.59%	17.23%	22.91%
85	1.3	17.50%	24.50%	33.32%	36.50%	43.12%	57.32%

ABS = Australian Bureau of Statistics; AdvSTDR = advanced sight-threatening diabetic retinopathy; DR = diabetic retinopathy; RR = relative risk; STDR = sight-threatening diabetic retinopathy

[a] Relative risk of death for Indigenous versus non-Indigenous Australians (ABS 2013c)

Source: ABS online (http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.02012)

Age-specific death rates in Indigenous Australians are considerably higher than in the non-Indigenous population. The rate ratios for mortality for Indigenous versus non-Indigenous

Australians were sourced from ABS mortality data (ABS 2013c). The relative risk of mortality was applied to the mortality estimates for the broader Australian population, as presented in Table 42, to give estimates of the mortality rate for each health state for the Indigenous population with diabetes (Table 43).

Healthcare resources

The modelled healthcare resource use and costs are presented in Table 44. These costs are based on the relevant MBS items.

The proposed MBS listing for RP-NMRC stipulates that a fee must not be charged when referral is required due to inability to obtain adequate images for grading. In the studies included in the meta-analysis of the accuracy of RP-NMRC for detecting any DR, the median proportion of UIs was 8%. Using this estimate, the average cost per patient for RP-NMRC would be $46.00 ($50.00 x 92%). As the proportion of UIs was so variable among the studies (range 0–21.5%), in the base-case of the model it is assumed that there are no UIs and the full cost of RP-NMRC is used. Inclusion of a proportion of UIs has been assessed in a sensitivity analysis.

All patients diagnosed with diabetes should be attending regular appointments with a physician for monitoring of diabetes and assessment for secondary complications. It is assumed that ophthalmoscopy, if performed, and/or referral for RP-NMRC or CEE, would be part of these regular visits and would not incur an additional charge. Therefore, the cost of these consultations has not been included in the model. Similarly, the cost of interpreting RP-NMRC images is incorporated in the cost proposed for the proposed MBS item.

For the costing of CEE, it is assumed that, for patients who have been referred for confirmation of diagnosis following a positive RP-NMRC result, 51% of CEEs are performed by an ophthalmologist and 49% by an optometrist (Lee, SJ et al. 2000). Patients with a confirmed diagnosed of DR are assumed to be under the care of an ophthalmologist.

Information regarding the average lifetime cost of treating DR could not be located. Therefore, it was necessary to make a number of assumptions in the model. As discussed above, in the base-case scenario it is assumed that all patients diagnosed as having STDR are treated with laser photocoagulation and that, on average, patients require four treatment sessions[16]. The cost of one initial consultation and four subsequent consultations with an

[16] Personal communication: HESP member (ophthalmologist); email, received 10 June 2014

ophthalmologist, and one episode of retinal angiography, are also included in the total treatment cost (Table 44).

Sensitivity analyses have been performed presuming that a proportion of patients are treated with anti-VEGF agents rather than by PRP. In a recent study assessing 3-year outcomes of ranibizumab treatment in patients with diabetic MO, each received 14 intra-vitreal injections on average over 3 years (Schmidt-Erfurth et al. 2014). While not listed for this indication, the cost of ranibizumab was assumed to be the same as the dispensed price for maximum quantity for a 1 x 2.3 mg/0.23 mL vial, as listed on the PBS (item 1382R).

Table 44 Testing and treatment-related healthcare resources used in the economic model

Type of resource item	Unit cost	Utilisation	Total cost	Source
Testing costs				
RP-NMRC	$50.00	1	$50.00	Provisional MBS item
CEE:				
optometrist	$71.00	1	$71.00	MBS item 10915
ophthalmologist	$85.55	1	$85.55	MBS item 104
Ophthalmoscopy GP [a]	$0.00	1	$0.00	-
Laser photocoagulation				
Retinal photocoagulation	$451.10	4 [b]	$1,804.40	MBS item 42809
Retinal angiography	$151.95	1	$151.95	MBS item 11218
Ophthalmologist consultations:				
initial	$85.55	1	85.55	MBS item 104
subsequent	$43.00	4	$172.00	MBS item 105
Total cost PRP			$2,213.90	
Anti-VEGF therapy				
Ranibizumab	$1,431.37	14	20,039.18	PBS item 1382R
Administration	$300.75	14	4,210.50	MBS item 42738, 42740
Total cost anti-VEGF			$24,249.68	-

CEE = comprehensive eye examination; DR = diabetic retinopathy; GP = general practitioner; PRP = panretinal photocoagulation; STDR = sight-threatening diabetic retinopathy; VEFG = vascular endothelial growth factor

[a] Ophthalmoscopy by a GP is assumed to be performed as part of a patient's regular consultation with the GP

[b] Source: Personal communication[16]

A report prepared by Access Economics (2005), 'Investing in Sight', estimated the average health costs per case of DR to be $3,745 in 2007–08. However, no data were located that estimated the healthcare costs for specific stages of DR in the Australian setting. Due to the lack of information on the specific population of interest, estimates of the healthcare costs for the broader diabetic population have been used to estimate the cost associated with each health state included in the model.

Lee, CM et al. (2013) reported the annual direct healthcare costs associated with diabetes in 2004–05 in the Australian setting, based on the participants enrolled in the population-based AusDiab study. Participants in the cost analysis attended the 5-year follow-up survey

in 2004–05, which included questions related to use of all health services and health-related expenditure in the previous 12 months, including health-resource use unrelated to diabetes. Costs of visits to GPs, hospitalisations, prescription medication and medically related consumables (blood glucose strips etc.) were included. Costs were reported by diabetes complication status: no complications, microvascular only, macrovascular only, or both micro- and macrovascular. The Diabetes Australia report 'DiabCo$t Australia: assessing the burden of type 2 diabetes in Australia' (Colagiuri et al. 2003) also reported the average cost per patient with type 2 diabetes, categorised by complication status; these values were higher than those in the AusDiab study. In the absence of any other relevant data, an annual indexation adjustment (healthcare inflation rate) has been applied to the costs from the AusDiab study, and these have been used in the base-case economic model (Table 45). The indexation calculations are presented in Table 99 in Appendix F.

Table 45 Annual Australian healthcare costs used in the economic model

Model health state	Classification by complication [a]	2004–05 yearly healthcare cost [a] (95%CI)	Modelled healthcare cost 2013–14 (95%CI)
Diabetes, no DR	DM, no complications	$2,357 ($1,850–$2,863)	$3,568 ($2,801–$4,334)
Non-STDR	DM, no complications	$2,357 ($1,850–$2,863)	$3,568 ($2,801–$4,334)
STDR	DM, microvascular complications only	$3,051 ($2,356–$3,745)	$4,619 ($3,567–$5,669)
Advanced STDR	DM, microvascular complications only	$3,051 ($2,356–$3,745)	$4,619 ($3,567–$5,669)
Post-treatment DR (early)	DM, microvascular complications only	$3,051 ($2,356–$3,745)	$4,619 ($3,567–$5,669)
Post-treatment DR (late)	DM, microvascular complications only	$3,051 ($2,356–$3,745)	$4,619 ($3,567–$5,669)
Blind	DM, both micro- and macrovascular complications	$5,935 ($4,692–$7,178)	$8,985 ($7,103–$10,866)

CI = confidence interval; DM = diabetes mellitus; DR = diabetic retinopathy; STDR = sight-threatening diabetic retinopathy
[a] Source: Table 2, Lee, CM et al. (2013)

In the base-case the cost associated with the advanced STDR state is assumed to be the same as that for less-advanced STDR. Sensitivity analyses were conducted to test the effect of health state costs on the results of the economic evaluation using the 95%CI ranges reported in Table 45 and the costs (with annual indexation adjustment) from the Diabetes Australia report (Colagiuri et al. 2003).

Utility values

Health state utilities used in the economic model are presented in Table 46. No Australian sources could be found for these inputs.

The utility values used in the base-case model were sourced from two studies. The first was a large study of patients with diabetes (n=7,327) performed in USA, which estimated

quality-of-life scores associated with type 2 diabetes using the EuroQol (EQ)-5D instrument (Zhang et al. 2012), including the different clinical states of DR (no DR, NPDR and PDR); no utilities were reported for patients with vision loss. A smaller study (n=150) performed in UK elicited preferences regarding different severities of retinopathy, based on level of visual acuity, from people with DR, using a number of different methods (Lloyd et al. 2008). The health-related quality-of-life scores derived using the EQ-5D in this latter publication were used for the health states assumed to have marked vision loss, namely advanced STDR and blind.

Table 46 Health state utilities used in the economic evaluation

Health state	Utility weight	Source
Diabetes – no DR	0.82	Zhang et al. 2012
Non-STDR	0.78	Zhang et al. 2012
Early STDR	0.76	Zhang et al. 2012
Advanced STDR	0.68	Lloyd et al. 2008 (visual acuity 6/24–6/36) [a]
Post-treatment DR (early)	0.76	Assumed to be the same as STDR
Post-treatment DR (late)	0.68	Assumed to be the same as advanced STDR
Blind	0.53	Lloyd et al. 2008 (visual acuity 6/60–6/120)

DR = diabetic retinopathy; STDR = sight-threatening diabetic retinopathy

[a] The utility for visual acuity 6/12–6/18 (0.5) was not used as it was lower than that reported for the range 6/24–6/36.

Outputs from the economic evaluation

Incremental costs and effectiveness

Primary comparison: RP-NMRC versus no testing

The overall costs and outcomes, and incremental costs and outcomes as calculated for RP-NMRC and the primary comparator (no testing), are shown in Table 47 and Table 48, for Scenario 1 (slow progression) and Scenario 2 (more rapid progression), respectively.

Table 47 Scenario 1: Primary comparison of RP-NMRC versus no testing, assuming slow progression

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Broader Australian population					
RP-NMRC	$52,381	$1,054	10.964	0.071	$14,875
No testing	$51,327		10.894		
Indigenous population					
RP-NMRC	$52,020	$2,005	9.925	0.162	$12,379
No testing	$50,015		9.763		

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 48 Scenario 2: Comparison of RP-NMRC with no testing, assuming more-rapid progression

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Broader Australian population					
RP-NMRC	$53,509	$858	10.735	0.133	$6,443
No testing	$52,651		10.602		
Indigenous population					
RP-NMRC	$54,070	$1,409	9.624	0.271	$5,204
No testing	$52,661		9.353		

ICER = incremental cost-effectiveness ratio; QALY, =quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

In the primary analysis for the broader Australian population (Scenario 1) the estimated incremental cost per additional QALY for RP-NMRC compared with no testing is $14,875. As discussed above, the assumption of a slow progression of disease favours the no testing strategy, minimising the benefits of early diagnosis resulting from regular testing. Due to this, the incremental cost per additional QALY gained improves markedly in the scenario in which a more rapid rate of progression is assumed, with an estimated incremental cost-effectiveness ration (ICER) of $6,440/QALY.

Despite an increase in costs resulting from more-frequent testing, RP-NMRC is more cost-effective in the Indigenous Australian population compared with the broader Australian population, with an estimated ICER of $12,380 per QALY gained in Scenario 1 and $5,204 in Scenario 2. This is due to the epidemiological differences of DR in this population, including earlier age at onset, higher incidence and faster rate of progression.

A Monte Carlo microsimulation was conducted for the RP-NMRC and the no testing strategies, for both the broad Australian and Indigenous Australian populations, using Scenario 1 and 100,000 iterations. Table 49 presents the mean proportion of patients progressing to advanced STDR and blindness, and the mean cost and QALYs gained in each arm of the model. These data have been used to calculate the mean incremental costs per blindness prevented and per QALY gained in the microsimulation.

The outcomes of this analysis indicate that both the proportion of patients progressing to the advanced STDR health state and the incidence of blindness are markedly reduced by regular testing for DR. Few patients in the RP-NMRC arm progress to advanced STDR without being diagnosed and treated.

The incremental cost per blindness prevented is estimated to be approximately $51,600 in the broad Australian population and $46,600 in the Indigenous Australian population.

Table 49 Results of microsimulation for the comparison of RP-NMRC versus no testing, Scenario 1

	RP-NMRC	No testing	Increment
Broader population			
Cost	$52,338	$51,340	$998
Proportion of subjects entering health state (%)			
Total AdvSTDR:	5.5%	17.8%	–12.3%
AdvSTDR	0.15%	17.8%	–17.7%
AdvSTDR (post-treatment)	5.3%	0%	5.3%
Blind	2.6%	4.5%	–1.9%
QALYs	10.952	10.888	0.064
Incremental cost/blindness prevented			$51,616
Incremental cost/QALY gained			$15,584
Indigenous population			
Cost	$52,079	$49,999	$2,080
Proportion of subjects entering health state (%)	-	-	-
Total AdvSTDR:	11.1%	35.7%	–24.5%
AdvSTDR	0.03%	35.7%	–35.7%
AdvSTDR (post-treatment)	11.1%	0%	11.1%
Blind	5.5%	10.0%	–4.45%
QALYs	9.932	9.753	0.178
Incremental cost/blindness avoided			$46,614
Incremental cost/QALY gained			$11,666

AdvSTDR = advanced STDR; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Secondary comparison: RP-NMRC versus standard medical assessment

The overall costs and outcomes, and incremental costs and outcomes, for the comparison of RP-NMRC and standard medical assessment are presented in Table 50.

Table 50 Secondary comparison, RP-NMRC versus standard medical assessment, Scenario 2

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
a) Ophthalmoscopy GP					
Broad Australian population					
RP-NMRC	$53,509	$332	10.735	0.013	$26,173
Ophthalmoscopy	$53,178		10.722		
Indigenous population					
RP-NMRC	$54,070	$510	9.624	0.019	$26,308
Ophthalmoscopy	$53,560		9.605		
b) CEE					
Broad Australian population					
RP-NMRC	$53,509	–$5.21	10.735	–0.002	*Undefined; RP-NMRC is less costly but less*

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
					effective [a]
CEE	$53,515		10.737		
Indigenous population					
RP-NMRC	$54,070	–$22.43	9.624	–0.003	*Undefined* [a]
CEE	$54,092		9.627		

GP = general practitioner; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] *Numerically calculated ICERs for RP-NMRC over CEE of $3,282 for the broad Australian population and $8,636 for the Indigenous population are in the south-west quadrant of the cost-effectiveness plane, and therefore the ICER is not interpreted in conventional terms.*

a) Dilated ophthalmoscopy by GP

RP-NMRC is more effective than dilated ophthalmoscopy performed by a GP, but it is also the more expensive strategy, resulting in an incremental cost per additional QALY gained of $26,170 in the broad Australian population and $26,310 in the Indigenous Australian population. Due to the paucity of data comparing the diagnostic accuracy of dilated ophthalmoscopy by a GP with an appropriate reference standard, the results of this analysis are highly uncertain and should be interpreted with caution.

Due to the high frequency of testing, even tests with relatively low diagnostic accuracy are reasonably effective in preventing progression to advanced stages of DR. As all patients with positive results are referred for a CEE, any patients falsely diagnosed with DR will be detected at this point and return to twice-yearly screening. Any patients with DR who have a false negative test result may progress in the intervening interval, but they are still likely to be diagnosed prior to development of any major vision impairment. This is evident from the results of a Monte Carlo microsimulation for ophthalmoscopy by a GP, in which only 2.7% of the general Australian patients and 2.8% of Indigenous patients progressed to advanced STDR without being diagnosed. While these percentages are considerably higher than those for RP-NMRC (0.5% of general patients and 0.3% of Indigenous patients in Scenario 2), they still represent a low proportion of the population.

These observations are consistent with the NHMRC guidelines (NHMRC 2008), which state that screening tests should aim for a sensitivity of at least 60%, noting that mild DR missed at one visit would likely be detected at the next.

Yearly testing reduces the delay in diagnosis resulting from the lower sensitivity of ophthalmoscopy compared with RP-NMRC, minimising the incremental effectiveness between the two testing strategies. This is demonstrated by the fact that, if the

epidemiological inputs for the broader Australian population are used in the Indigenous yearly testing model, the incremental effectiveness of RP-NMRC compared with dilated ophthalmology for this population decreases from 0.013 to 0.005. The results suggest that, if GPs were more confident and better trained at performing dilated ophthalmoscopy, this would be an acceptable alternative triage test for DR; however, further investigation of this strategy is beyond the scope of this assessment.

b) CEE performed by ophthalmologist/optometrist

Regular testing by RP-NMRC is marginally less expensive than CEE performed by either an optometrist or an ophthalmologist, but is also slightly less effective in terms of QALYs gained. The numerically calculated ICERs for RP-NMRC over CEE of $3,282 for the broad Australian population and $8,636 for the Indigenous population are in the south-west quadrant of the cost-effectiveness plane and, therefore, the ICER is not interpreted in conventional terms. As the incremental difference in both cost and effectiveness between the two strategies is very small, the ICER is very sensitive to even minor changes in inputs.

Given that CEE is the more effective strategy, it is inappropriate for RP-NMRC to replace the use of CEE in patients who are currently compliant with testing recommendations.

Scenario and sensitivity analyses—RP-NMRC versus no testing

Given the limited relevance of standard medical assessment as a comparator, sensitivity analyses are only presented for the comparison with no testing. All sensitivity analyses are based on the broad Australian population, as RP-NMRC is consistently more cost-effective in the Indigenous Australian population.

Main sources of uncertainty

In the base-case for all models, all patients who are not undergoing regular testing are assumed to be tested and treated when they progress to advanced STDR. Therefore, the main difference between the RP-NMRC testing and no testing arms is that patients who are not being tested progress to the advanced STDR state before being treated, whereas patients in the RP-NMRC arm receive treatment when they progress to early STDR, greatly reducing the rate of progression to advanced STDR. Due to this, the model is sensitive to the difference in the utility and costs between the early STR and advanced STDR health states.

Sensitivity analyses have been performed to assess the effect of the following inputs in the economic model:

1. The proportion of patients in the no testing arm who are assumed to be diagnosed and treated when they progress to advanced STDR has been varied from 1 in the base-case to 0.5 and 0.
2. The utility associated with the advanced STDR state, which in the base-case is assumed to be 0.68, is increased to that of early STDR (0.76) and decreased to that of the blind health state (0.53).
3. The cost of the advanced STDR health state, which in the base-case is assumed to be the same as that for early STDR ($4,619), is increased to $5,669 (the upper limit of the 95%CI for the early STDR state) and $7,103 (the lower limit of the 95%CI for the blind state).

The other main sources of uncertainty in the model are the effectiveness of early treatment compared with late treatment, and the cost of treatment. The impact of the assumed effectiveness of early treatment is assessed by increasing the relative risk of progression from 0.2, in the base-case, to that for late treatment (0.4). In this scenario the benefit of regular testing is that treatment is initiated at an earlier stage of progression of DR, compared with the no testing situation.

The base-case assumes that all patients are treated with laser photocoagulation but, in practice, patients with CSMO are increasingly being treated with intra-vitreal injection of anti-VEGF. It should be noted that there are no anti-VEGF agents listed on the PBS for this indication and, therefore, the use of anti-VEGF for treatment of DR may not be cost-effective in the Australian clinical setting.

These factors were assessed in the following analyses:

4. The relative risk of progression after early treatment is increased to that for late treatment (0.4).
5. The proportion of treatment with anti-VEGF is varied from 0 to 1, the remainder being PRP.

The results of these analyses are presented in Table 51.

Table 51 Sensitivity analyses for the main sources of uncertainty in the model inputs, broad Australian population, Scenario 1

	Alternative value(s) tested	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
Base-case		$52,381	10.964	$51,327	10.894	$14,875
% patients in no testing arm assumed to be diagnosed when progress to AdvSTDR Base-case: 100%	0	$52,381	10.964	$51,546	10.864	$8,286
	0.5	$52,381	10.964	$51,370	10.888	$13,314
Utility AdvSTDR Base-case 0.68	0.76 [a]	$52,381	10.974	$51,327	10.938	$29,910
	0.53 [a]	$52,381	10.947	$51,327	10.809	$7,657
Cost AdvSTDR health state Base-case $4,619	$5,669 [b]	$52,502	10.964	$51,916	10.894	$8,277
	$7,103 [b]	$52,668	10.964	$52,720	10.894	RP-NMRC dominant
Early treatment effect (RR) Base-case 0.2	0.4	$52,500	10.937	$51,327	10.894	$26,836
% treatment anti-VEGF [c] Base-case 0	0.5	$54,195	10.964	$52,162	10.894	$28,687
	1.0	$56,008	10.964	$52,997	10.894	$42,499

AdvSTDR = advanced sight-threatening diabetic retinopathy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera; RR = relative risk of progression; VEFG = vascular endothelial growth factor

[a] The utility of the AdvSTDR health state is assumed to be, first, the same as that for the early STDR state (0.76) and, second, equal to that of the blind health state (0.53).

[b] The cost of the AdvSTDR health state is increased to the upper 95%CI for the health state cost of early STDR and the lower 95%CI for the blind health state (base-case is equal to the early STDR health state).

[c] Anti-VEGF agent is assumed to be ranibizumab (see Table 47); treatment cost: anti-VEGF $24,250 per patient, PRP $2,214 per patient.

The outcome of modelled economic evaluation is moderately sensitive to the quality-of-life weight applied to the AdvSTDR health state. However, even when this is assumed to be the same as for early STDR (i.e. it is assumed that there is no deterioration in health between these two stages), the cost per additional QALY gained is still only approximately $30,000. Similarly, if it is assumed that the treatment effect remains the same, regardless of whether it is performed at the early stages of STDR or the more advanced stages, the ICER rises to $27,000/QALY.

The cost of treatment has a considerable impact on the outcome of the model, with the ICER increasing to over $40,000 per QALY gained in the extreme case where the cost of treatment is increased to $24,250 per patient.

Loss to follow-up and non-compliance

In the base-case it is assumed that all patients are compliant with both regular testing for DR and referral for a CEE when appropriate. The following sensitivity analyses were performed to assess the impact of these factors on the ICER:

- In each testing year a proportion of patients in the non-diagnosed non-DR, non-STDR and STDR health states are assumed to be lost to follow-up and are assumed to progress as in the no testing arm of the model.
- A proportion of patients who have a positive RP-NMRC result are assumed to be non-compliant with referral for a CEE and progress in the same way as those who had a negative RP-NMRC test outcome (i.e. it is assumed they are still eligible for RP-NMRC at the recommended frequency).

The outcomes of these analyses are presented in Table 52.

Table 52 Sensitivity analyses on loss to follow-up and non-compliance

	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
Loss to follow-up					
Broad Australian population					
Base-case, 0	$52,381	10.964	$51,327	10.894	$14,875
10%	$52,102	10.951	$51,327	10.894	$13,504
20%	$51,925	10.941	$51,327	10.894	$12,713
30%	$51,801	10.932	$51,327	10.894	$12,283
40%	$51,708	10.925	$51,327	10.894	$12,109
50%	$51,632	10.919	$51,327	10.894	$12,159
80%	$51,463	10.903	$51,327	10.894	$14,921
Indigenous population					
Base-case, 0	$52,020	9.925	$50,015	9.763	$12,379
10%	$51,253	9.876	$50,015	9.763	$10,955
20%	$50,901	9.848	$50,015	9.763	$10,341
30%	$50,690	9.830	$50,015	9.763	$10,050
40%	$50,544	9.816	$50,015	9.763	$9,942
50%	$50,431	9.804	$50,015	9.763	$9,980
80%	$50,188	9.777	$50,015	9.763	$11,778
Non-compliance					
Broad Australian population					
Base-case, 0	$52,381	10.964	$51,327	10.894	$14,875
10%	$52,365	10.964	$51,327	10.894	$14,814
20%	$52,346	10.962	$51,327	10.894	$14,781
30%	$52,325	10.961	$51,327	10.894	$14,789

	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
40%	$52,299	10.959	$51,327	10.894	$14,862
50%	$52,268	10.956	$51,327	10.894	$15,039
80%	$52,077	10.936	$51,327	10.894	$17,719
Indigenous population					
Base-case, 0	$52,020	9.925	$50,015	9.763	$12,379
10%	$51,997	9.924	$50,015	9.763	$12,279
20%	$51,971	9.923	$50,015	9.763	$12,185
30%	$51,941	9.922	$50,015	9.763	$12,099
40%	$51,906	9.920	$50,015	9.763	$12,030
50%	$51,861	9.917	$50,015	9.763	$11,993
80%	$51,569	9.885	$50,015	9.763	$12,713

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

With both increasing loss to follow-up and increasing non-compliance, the cost and effectiveness of RP-NMRC both decrease. When the loss to follow-up or non-compliance is reasonably low, there is a small decrease in the ICER for both the broad Australian population and the Indigenous population. However, once the proportion lost to follow-up or the rate of non-compliance reaches approximately 50%, the decrease in effectiveness predominates and the ICER starts to increase. Even at loss to follow-up or non-compliance rates up to 80%, the ICER is within a few per cent of the base-case estimate and might, therefore, be considered relatively robust despite the uncertainty in these variables.

Test accuracy

In the base-case analysis the diagnostic accuracy of RP-NMRC for any detectable DR is that derived in the meta-analysis presented in Table 19. The upper and lower limits of the 95%CIs from this analysis were used to assess the impact of the sensitivity and specificity of RP-NMRC on the outcome of the economic evaluation.

In the studies included in the meta-analysis the photographs were read by an ophthalmologist or retinal specialist. The accuracy of interpretation of the retinal images is likely to differ for GPs or other professionals in the primary care setting, who are likely to have minimal training and less experience. There were limited data available comparing the interpretation of retinal images among different readers, and those studies located reported concordance data rather than accuracy compared with a reliable reference standard (see Table 24). Given these limitations, the relative sensitivity and specificity for GPs' interpretation of photographs, compared with an ophthalmologist or other expert's interpretation as reported in Bhargava et al. (2012) and Owens et al. (1998), have been used

in sensitivity analyses, as these studies reported the poorest outcomes. The data used in the analyses are summarised in Table 53, and the results are presented in Table 54.

Table 53 Source of data for sensitivity analyses assessing the impact of test accuracy

Source	Reader	Sensitivity % [95%CI]	Specificity % [95%CI]
Meta-analysis, any DR [a] (see Table 19)	Ophthalmologist / retinal specialist	91.2% [81.7, 96.1]	76.5% [67.4, 83.6]
Bhargava et al. (2012)	Family physician	44.7%	92.4%
Owens et al. (1998)	GPs	Any DR 79.2% STDR 87.3%	Any DR 73.5%

CI = confidence interval; DR = diabetic retinopathy; GP = general practitioner; STDR = sight-threatening diabetic retinopathy

[a] Only the sensitivity of RP-NMRC for any DR was used in the base-case model as this was higher than that for STDR.

Table 54 Sensitivity analyses on accuracy of RP-NMRC, by reader

	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
Base-case	$52,381	10.964	$51,327	10.894	$14,875
Ophthalmologist					
Meta-analysis:					
lower limit 95%CI	$52,433	10.964	$51,327	10.894	$15,791
upper limit 95%CI	$52,345	10.965	$51,327	10.894	$14,296
General practitioner					
Bhargava et al. (2012)	$52,250	10.956	$51,327	10.894	$14,834
Owens et al. (1998)	$52,381	10.963	$51,327	10.894	$15,119

CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

As explained for the comparison of RP-NMRC and ophthalmoscopy by a GP, the model is relatively insensitive to changes in the diagnostic accuracy of the test. As all patients with positive results are referred for a CEE, any falsely diagnosed with DR will be detected at this point and return to twice-yearly screening. Any patients with DR who have a false negative test result may progress in the intervening interval, but they are still likely to be diagnosed prior to development of any major vision impairment, as is evident in the results of the microsimulation presented in Table 49.

Healthcare resources

The proposed fee for the new MBS item for RP-NMRC is $50.00. This was based on the following estimates for each component (per service): cost of camera $20.00, reader salary $20.00, imager salary $8.00 and consumables $2.00. As the assessment group was requested to provide an assessment of alternative models of funding capital equipment, a sensitivity analysis is presented excluding the estimated component cost for equipment (i.e.

assuming an MBS fee of $30.00). It should be noted that this cost will still be incurred by the alternative funding source and, therefore, it is only the cost-effectiveness from the perspective of the MBS that will improve with exclusion of the equipment costs from the analysis (Table 55). The effect of increasing the MBS fee to $70.00 and $100.00 has also been assessed.

In addition, the proposed listing states that a fee must not be charged when referral is required due to inability to obtain adequate images for grading. As discussed above, in the studies included in the meta-analysis of the accuracy of RP-NMRC for detecting any DR, a median of 8% reduces the average cost of RP-NMRC per patient tested to $46.00, resulting in a decrease in the ICER (Table 55).

Table 55 Sensitivity analysis for scheduled fee for RP-NMRC

	Value	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
Base-case ($50.00, no UIs)		$52,381	10.964	$51,327	10.894	$14,875
Fee RP-NMRC	$30.00	$52,286	10.964	$51,327	10.894	$13,531
	$70.00	$52,476	10.964	$51,327	10.894	$16,218
	$100.00	$52,619	10.964	$51,327	10.894	$18,233
Proportion UIs	8%	$52,362	10.964	$51,327	10.894	$14,606

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera; UIs = unreadable images

Finally, the impact of variations in the cost associated with the health states included in the model has been evaluated using the upper and lower limits of the 95%CI for each health state reported in the AusDiab study (Lee, CM et al. 2013), as presented in Table 56, and using costs sourced from the Diabetes Australia publication 'DiabCo$t Australia: assessing the burden of type 2 diabetes in Australia' (Colagiuri et al. 2003).

Table 56 Sensitivity analysis of health state costs

	RP-NMRC Cost ($)	RP-NMRC Outcomes (QALYs)	No testing Cost ($)	No testing Outcomes (QALYs)	ICER
Base-case (AusDiab)[a]	$52,381	10.964	$51,327	10.894	$14,875
AusDiab study [a]:					
lower 95%CI	$41,324	10.964	$40,267	10.894	$14,926
upper 95%CI	$63,423	10.964	$62,372	10.894	$14,821
Colaguiri et al. (2003) [b]	$106,260	10.964	$104,968	10.894	$18,232

CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Costs: no DR and non-STDR $3,568 (95%CI: $2,801, $4,334); STDR and AdvSTDR $4,619 (95%CI: $3,567, $5,669); blind $8,985 (95%CI: $7,103, $10,866)

[b] 2003 costs: no DR and non-STDR $4,025; STDR and AdvSTDR $7,025; blind $9,645. 2014 indexed costs: no DR and non-STDR $6,973; STDR and AdvSTDR $12,171; blind $16,710

These alternative health state costs have minimal impact on the outcome of the economic evaluation.

The sensitivity analyses confirm that the results of the economic model comparing RP-NMRC testing with the primary comparator, no testing, are reasonably robust. The model is most sensitive to the cost of treatment and the quality-of-life weight applied to the advanced STDR health state, but the ICER remains below $45,000/QALY in all modelled scenarios. Therefore, RP-NMRC is likely to be a cost-effective option for diagnosing DR in patients with diabetes who would not otherwise receive regular eye examinations.

It is important to note that the introduction of RP-NMRC will only be effective if provisions are made to ensure compliance with regular testing, appropriate follow-up of results, compliance with referrals for further examination by an ophthalmologist, and prompt treatment of STDR when indicated.

Financial and costing impact

Summary—What are the financial implications of RP-NMRC for detection of DR?

If the new listing for RP-NMRC testing is approved, within 3 years the cost to the MBS is likely to exceed $10 million per year. The cost attributable to CEE initially increases markedly as more patients are diagnosed with DR and require ongoing monitoring for disease progression. This rapidly becomes the major source of the cost to the MBS. The main sources of uncertainty are the proportion of patients with diabetes who are not receiving regular eye examinations, and the likely uptake of RP-NMRC testing in this population.

The total cost to the non-Indigenous patient population increases to approximately $4.5 million by 2020–21. The majority of this cost results from the out-of-pocket cost for CEE performed by an ophthalmologist to monitor patients who have been diagnosed with DR as a result of RP-NMRC testing. Due to the high rate of bulk-billing by GPs for patients with chronic diseases such as diabetes, the total cost to patients for RP-NMRC is minimal.

Depending on the uptake of RP-NMRC, the provision of alternative funding for the initial set-up costs of RP-NMRC would potentially result in cumulative savings to the MBS in the order of $5–$9 million over the first 6 years of listing. Assuming an initial RP-NMRC set-up cost of $50,000, these potential savings are sufficient to fund approximately 100–180 cameras.

RP-NMRC is primarily intended to be used to identify additional cases of DR in patients who would otherwise not have received any eye examination. RP-NMRC would be used as a triage test; patients with evidence of DR would be referred for a CEE by either an ophthalmologist or an optometrist. Patients in whom diagnosis is confirmed would then require regular eye examinations to monitor for progression of disease. The financial implications of the introduction of this proposed new service, both in terms of the direct cost of RP-NMRC and the cost associated with the consequent increase in CEE services, have been estimated using an epidemiological approach.

As for the economic evaluation, separate analyses have been performed for the non-Indigenous and Indigenous Australian populations. These have then been combined to present the financial implications for the total population.

Data sources used in the financial analysis

The data sources used in the estimated budgetary impact of listing RP-NMRC testing to diagnose DR are summarised in Table 57.

Table 57 Data sources used in financial analysis

Data source	Purpose
Epidemiological data	
ABS (2013d) 3222.0 Population Projections Australia. Table A.9	To estimate the Australian population aged 35 years or older in the period 2015–21

Data source	Purpose
ABS (2013b) Australian Health Survey: Updated results, 2011–12, Australia. Table 8.3	To estimate the proportion of people aged 35 years or older with diabetes mellitus
ABS (2013a) Deaths, Australia, 2012. Table 2.9 Death rates, summary, Australia, 2002–2012	To estimate the age-specific death rate for the Australian population
ABS (2014b) Australian Demographic Statistics, Dec 2013. Table 11	To estimate the age distribution of the Australian Indigenous population
ABS (2014a) Australian Demographic Statistics, Dec 2013. Table 10	To estimate the Indigenous Australian population aged 25 years or older in the period 2015–21
ABS (2014c) Australian ATSI Health Survey: Updated results, 2012–13, Australia. Table 6.3	To estimate the proportion of Indigenous Australian people aged 25 years or older with diabetes mellitus
ABS (2013c) Deaths, Australia, 2012. Table 19.1 Age-specific death rates, Indigenous status, 2008–2012	To estimate the relative risk of death in the Australian Indigenous population compared with the non-Indigenous population
AIHW (2005). Vision problems among older Australians.	To estimate the proportion of non-Indigenous patients with diabetes who have visual impairment
AIHW (2011a). Eye Health in Aboriginal and Torres Strait Islander people.	To estimate the proportion of Indigenous people with diabetes who have not had an eye examination within the previous year
Department of Health (2014b). Quarterly Medicare Statistics - March Quarter 2007 to March Quarter 2014.	To estimate the proportion of RP-NMRC services that are likely to be bulk-billed
AusDiab study	To estimate the prevalence of DR in non-Indigenous people with diabetes (Tapp et al. 2003) To estimate the proportion of non-Indigenous people with diabetes who have not had an eye examination within the previous 2 years (Tapp et al. 2004) Relative risk of mortality in people with diabetes compared with the general population (Tanamas et al. 2013)
Xie et al. (2011)	To estimate the prevalence of DR in Indigenous Australians with diabetes To estimate the proportion of Indigenous patients with diabetes who have visual impairment
Vijan, Hofer & Hayward (2000)	Mortality multiplier for people with non-STDR
MBS data reports for items 104, 10915 [a]	To estimate: • the proportion of services that are bulk-billed • the proportion of patients covered by the Medicare safety net • the proportion of patients covered by the Extended Medicare Safety Net (EMSN) • the average fee charged for items 104 and 10915 • the average benefit per service • the average cost to the patient per service • the average EMSN payment per service
MBS [b]	Scheduled fees and benefits for Medicare items 104 and 10915
Lee, SJ et al. (2000)	To estimate the relative proportions of CEEs performed by an ophthalmologist or an optometrist

ABS = Australian Bureau of Statistics; ATSI = Australian and Torres Strait Islander (people); CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; STDR = sight-threatening diabetic retinopathy

[a] Unpublished data requested from the Australian Government Department of Health

[b] MBS online: http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1, accessed February 2014

Table 58 lists the MBS fee and benefits for MBS items included in the financial analysis, and Table 59 and Table 60 summarise the inputs used in the financial analyses for non-Indigenous and Indigenous patients, respectively. MBS data for item 104 (Specialist, referred consultation) for the financial years 2007–08 to 2012–13 were provided, on request, by the Australian Government Department of Health, and are tabulated in Table 100 in Appendix G.

Table 58 MBS item fees and patient co-payments for items included in the financial analysis

	Item number	MBS fee	MBS benefit	Patient co-payment
CEE by ophthalmologist	104	$85.55	$72.75	$12.80
CEE by optometrist	10915	$71.00	$60.35	$10.65
RP-NMRC		$50.00 [a]	$42.50	$7.50

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Proposed fee

Table 59 Summary of data used in the financial analysis for non-Indigenous patients

Data	Value	Source
Proportion of patients with diabetes who have vision impairment	10%	AIHW (2005)
Prevalence of DR in diabetic population	21.9%	Tapp et al. (2003)
Death rate for people with diagnosed DR	0.033	ABS (2013a)
Proportion of follow-up CEE performed by ophthalmologist	51%	Lee, SJ et al. (2000)
Diagnostic accuracy of RP-NMRC: Sensitivity Specificity	 91.2% 76.5%	Meta-analysis, see Table 19 of report
Proportion of UIs with RP-NMRC	8%	'Effectiveness' section of report
% of services bulk-billed: Optometrist Ophthalmologist RP-NMRC	 100% 20.9% 97.2%	 MBS data report item 10915 MBS data report item 104 Department of Health Quarterly Medicare statistics
Proportion of patients covered by MSN	26.0%	MBS data report item 104
Proportion of patients covered by EMSN	6.4%	MBS data report item 104
Costs		
CEE ophthalmologist (Item 104): Average fee per service Average benefit paid per service Average cost to patient Average EMSN payment per service	 $151.29 $75.38 $59.49 $4.82	 MBS data report item 104, see Table 100 in Appendix G
CEE optometrist (item 10915): Average fee per service Average benefit paid per service Average cost to patient	 $60.35 $60.35 $0	 MBS item 10915 [a]

CEE = comprehensive eye examination; DR = diabetic retinopathy; EMSN = Extended Medicare Safety Net; MBS = Medicare Benefits Schedule; MSN = Medicare safety net; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] 100% bulk-billing

Table 60 Summary of data used in the financial analysis for Indigenous patients

Data	Value	Source
Proportion of patients with diabetes who have vision impairment	10%	Xie et al. (2011)
Prevalence of DR in diabetic population	29.7%	Xie et al. (2011)
Death rate for people with diagnosed DR	0.124 [a]	ABS (2013c)
Proportion of follow-up CEE performed by ophthalmologist	51%	Lee, SJ et al. (2000)
Diagnostic accuracy of RP-NMRC: Sensitivity Specificity	 91.2% 76.5%	Meta-analysis, see Table 19 of report
Proportion of UIs with RP-NMRC:	8%	'Effectiveness' section of report
% of services bulk-billed Optometrist Ophthalmologist RP-NMRC	 100% 100% 100%	 MBS data report item 10915 MBS data report item 104

ABS = Australian Bureau of Statistics; CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Relative risk of mortality of 4.0 compared with non-indigenous Australians (ABS 2013c)

Estimating the population likely to be tested by RP-NMRC

The intended population is patients with diagnosed diabetes, without marked visual impairment, who are not receiving regular eye examinations as recommended in the NHMRC guidelines, namely every 2 years for non-Indigenous patients and yearly for Indigenous Australians (NHMRC 2008).

An epidemiological approach, based on ABS age-specific population projections and the proportion of persons with diabetes categorised by age, was used to estimate the projected total non-Indigenous and Indigenous populations with diabetes (Table 61). The age range of the population was limited to persons aged 35 years or older in the non-Indigenous population and 25 years or older in the Indigenous population, as the estimated prevalence of diabetes in people below this age was low and highly uncertain.

Patients with vision impairment are not eligible for RP-NMRC. The AIHW (2005) reported that 9.4% of Australians aged 55 years or older are visually impaired; similarly, the prevalence of vision loss in Indigenous people with diabetes was 10% (Xie et al. 2011). As the prevalence reported in the AIHW was not specific to people with diabetes, a prevalence of 10% has been used for both populations.

The proportion of people with diabetes who had not had an eye examination within the previous 2 years was similar in both the AusDiab study (23%) (Tapp et al. 2004) and the Melbourne Visual Impairment Project (23.7%) (McCarty et al. 2003), whereas in the Indigenous Australian population it was estimated that only 20% of those with diabetes had undergone an eye examination in the previous 12 months (AIHW 2011b).

The estimated numbers of patients, for the non-Indigenous and Indigenous Australian populations, who meet the criteria for the population for which RP-NMRC is intended for the financial year 2015–16 are presented in Table 61 and Table 62, respectively.

Table 61 Estimated number of non-Indigenous patients for intended indication, 2015–16

	Population	2015–16	Source
A	Population projection (aged 35 years or older)	12,735,493	ABS (2013d)
B	Population with diabetes	1,067,474	ABS (2013b)
C	Proportion without visual impairment	90%	Xie et al. (2011)
D	Proportion not receiving regular CEE every 2 years	23%	Tapp et al. (2004)
E	Patients meeting criteria for intended indication	220,967	B x C x D

ABS = Australian Bureau of Statistics; CEE = comprehensive eye examination

Table 62 Estimated number of Indigenous patients for intended indication, 2015–16

	Population	2015–16	Source
A	Population projection (aged 25 years or older)	329,148	ABS (2014a)
B	Total population with diabetes	54,764	ABS (2014c)
C	Proportion without visual impairment	90%	Xie et al. (2011)
D	Proportion not receiving regular yearly CEE	80%	AIHW (2011b)
E	Patients meeting criteria for intended indication	39,430	B x C x D

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; CEE = comprehensive eye examination

The likely uptake of RP-NMRC is one of the major uncertainties in the financial analysis; there are no data on which to base this input. As the non-Indigenous population are only eligible for RP-NMRC testing every 2 years, the average maximum annual uptake is 50%, whereas in the Indigenous population, who are eligible for yearly testing, the maximum uptake can be 100%. Conservatively, a relatively high uptake has been assumed in the base-case scenario; 20% in year 1 of listing, 30% in year 2, and 40% thereafter for the non-Indigenous population. In the Indigenous population uptake is assumed to be twice as high, reflecting the higher frequency of testing recommended in this population. The impact of these assumptions on the outcome of the evaluation has been assessed in sensitivity analyses.

The prevalence of DR in the tested population is assumed to remain constant, at 21.9% in the non-Indigenous and 29.7% in the Indigenous population, over the years of the projections. Once patients with DR have been diagnosed, they are no longer eligible for RP-NMRC and, unless they die, are subtracted from the eligible population.

The resulting estimates of the number of patients likely to be tested by RP-NMRC each year are presented in Table 63, Table 64 and Table 65 for the non-Indigenous, Indigenous and total populations, respectively. At the introduction of testing there is a pool of undiagnosed patients with DR who, once diagnosed, will not be eligible for RP-NMRC. This factor, combined with the initial lower uptake of RP-NMRC and the fact that patients are only tested every 2 years, means that the first 3–4 years of the analysis are not reflective of the ongoing number of patients likely to be tested each year. After this time the majority of the initial pool of patients with DR will have been diagnosed, and the number of patients tested, as a proportion of the prevalent cases of diabetes, will remain relatively stable; the cases of DR detected will largely be newly incident cases. Due to this, the estimates have been projected over 6 years after the introduction of testing in 2015–16.

Table 63 Estimated number of patients likely to be tested by RP-NMRC each year, non-Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Projected population aged 35 years or older	12,735,493	12,990,576	13,257,250	13,538,570	13,824,845	14,119,322
Patients with DM	1,067,474	1,095,439	1,123,862	1,152,716	1,181,432	1,210,177
Patients without visual impairment	960,726	985,895	1,011,476	1,037,445	1,063,288	1,089,159
Patients not receiving regular CEE	220,967	226,756	232,639	238,612	244,556	250,507
Patients with DR	48,392	49,660	50,948	52,256	53,558	54,861
With diagnosed DR	0	8,537	19,138	29,733	36,703	41,445
With undiagnosed DR	48,392	41,123	31,810	22,523	16,854	13,416
Patients without DR	172,575	177,096	181,691	186,356	190,999	195,646
Patients without diagnosis of DR [a]	220,967	218,219	213,501	208,879	207,853	209,062
Uptake [b]	20%	30%	40%	40%	40%	40%
Total patients tested by RP-NMRC	44,193	65,466	85,400	83,552	83,141	83,625

CEE = comprehensive eye examination; DM = diabetes mellitus; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Patients with undiagnosed DR plus patients without DR

[b] Maximum uptake 50% as only eligible for testing every 2 years

Table 64 Estimated number of patients likely to be tested by RP-NMRC each year, Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Projected population aged 25 years or older	329,148	336,024	342,900	349,776	356,651	363,527
Patients with DM	54,764	55,908	57,052	58,196	59,340	60,484
Patients without visual impairment	49,288	50,317	51,347	52,376	53,406	54,435

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Patients not receiving regular CEE	39,430	40,254	41,077	41,901	42,725	43,548
Patients with DR	11,711	11,955	12,200	12,445	12,689	12,934
With diagnosed DR	0	3,712	7,144	9,412	10,099	10,416
With undiagnosed DR	11,711	8,244	5,056	3,033	2,590	2,518
Patients without DR	27,719	28,298	28,877	29,456	30,035	30,615
Patients without diagnosis of DR [a]	39,430	36,542	33,934	32,489	32,625	33,132
Uptake	40%	60%	80%	80%	80%	80%
Total patients tested by RP-NMRC	15,772	21,925	27,147	25,992	26,100	26,506

CEE = comprehensive eye examination; DM = diabetes mellitus; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Patients with undiagnosed DR plus patients without DR

Table 65 Estimated number of patients tested by RP-NMRC, total population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Non-Indigenous	44,193	65,466	85,400	83,552	83,141	83,625
Indigenous	15,772	21,925	27,147	25,992	26,100	26,506
Total patients tested by RP-NMRC	59,965	87,391	112,547	109,543	109,241	110,131

RP-NMRC = retinal photography with a non-mydriatic retinal camera

Estimated cost of RP-NMRC testing for DR—using MBS all-inclusive fee (conventional approach)

RP-NMRC is intended for use in the primary care setting. Therefore, all services are provided out-of-hospital. In the non-Indigenous population the proportion of RP-NMRC services that are bulk-billed is assumed to be the same as the proportion of non-referred attendances for chronic disease management GP services (formerly enhanced primary care services)—97.2%—as reported in the Department of Health Quarterly Medicare statistics, March quarter 2014 (Department of Health 2014b). In the Indigenous population it is assumed that all services are bulk-billed. Due to the high proportion of bulk-billed services, Medicare safety net payments for RP-NMRC are minimal; however, based on Medicare data for item 104, it is assumed that 26% of non-Indigenous patients who are not bulk-billed qualify for the safety net.

The proposed listing for RP-NMRC states that a fee must not be charged when a referral is required due to inability to obtain photographs of adequate quality for grading. The proportion of UIs in the studies located during the systematic review was highly variable. In the financial analysis 8% of images are assumed to be unreadable, which is the median percentage reported in the studies included in the meta-analysis for the accuracy of RP-NMRC for the detection of any DR (including UIs) in the 'effectiveness' section of this report.

The derivation of the costs for RP-NMRC services for non-Indigenous and Indigenous populations are presented in Table 66 and Table 67, respectively, and the projected costs for the total population are summarised in Table 68.

Table 66 Estimated cost of RP-NMRC services, non-Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total patients tested	44,193	65,466	85,400	83,552	83,141	83,625
% with gradable images:	40,658	60,228	78,568	76,868	76,490	76,935
Patients bulk-billed	39,520	58,542	76,368	74,715	74,348	74,781
Patients not bulk-billed	1,138	1,686	2,200	2,152	2,142	2,154
Cost RP-NMRC (no bulk-billing)	$2,032,897	$3,011,422	$3,928,421	$3,843,377	$3,824,493	$3,846,734
Total cost (with bulk-billing)	$1,736,500	$2,572,357	$3,355,657	$3,283,013	$3,266,882	$3,285,880
Cost to MBS						
Rebates	$1,727,962	$2,559,709	$3,339,157	$3,266,871	$3,250,819	$3,269,724
Safety net payments	$2,218	$3,286	$4,287	$4,194	$4,174	$4,198
Total (including safety net)	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922
Cost to patient						
No bulk-billing	$304,934	$451,713	$589,263	$576,507	$573,674	$577,010
With bulk-billing	$8,538	$12,648	$16,499	$16,142	$16,063	$16,156
Total including safety net	$6,320	$9,362	$12,212	$11,948	$11,889	$11,958
TOTAL	$1,736,500	$2,572,357	$3,355,657	$3,283,013	$3,266,882	$3,285,880

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 67 Estimated cost of RP-NMRC services, Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total patients tested	15,772	21,925	27,147	25,992	26,100	26,506
% with gradable images	14,510	20,171	24,975	23,912	24,012	24,385
Cost RP-NMRC (no bulk-billing)	$725,513	$1,008,562	$1,248,756	$1,195,613	$1,200,612	$1,219,270
Total cost (with bulk-billing)	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Cost to MBS	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 68 Estimated total cost of RP-NMRC services, total population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Cost to MBS						
Non-indigenous population	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922
Indigenous population	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Total	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
Cost to patient						
Non-indigenous population	$6,320	$9,362	$12,212	$11,948	$11,889	$11,958
Indigenous population	-	-	-	-	-	-
Total	$6,320	$9,362	$12,212	$11,948	$11,889	$11,958
Total cost						

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Non-indigenous population	$1,736,500	$2,572,357	$3,355,657	$3,283,013	$3,266,882	$3,285,880
Indigenous population	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Total cost	$2,353,186	$3,429,635	$4,417,099	$4,299,284	$4,287,402	$4,322,260

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

The total cost of RP-NMRC for diagnosis of DR, in the population of diabetic patients who would not otherwise receive regular eye examinations, is estimated to increase from approximately $2,353,000 to $4,322,000 over the first 6 years of listing of this item on the MBS. Due to the low compliance with regular CEE, the high prevalence of diabetes and the higher frequency of testing, the Indigenous Australian population accounts for approximately one-quarter of this cost. As a very high proportion of services are expected to be bulk-billed, the majority of the cost is accrued by the MBS. The total cost to patients for undergoing RP-NMRC testing is minimal[17].

The major uncertainties in these estimates relate to the number of people likely to be tested, namely the proportion of patients currently not receiving regular eye examinations, and the likely uptake of RP-NMRC.

Estimating the change in the utilisation and cost of CEEs

The proposed listing for RP-NMRC stipulates that all patients in whom signs of DR are detected, and all patients with UIs, should be referred to an ophthalmologist or an optometrist for a CEE. Those patients for whom the diagnosis of DR is confirmed will then require regular CEEs on an ongoing basis to monitor the progress of disease and initiate treatment as required.

RP-NMRC test-positive patients

Both patients who are correctly identified as having DR and those with false positive results are assumed to be referred for a CEE for confirmation of diagnosis. The number of patients in each of these categories is determined by the sensitivity and specificity of RP-NMRC. Patients with UIs are included as true positive results requiring referral, as in the studies in the meta-analysis for the sensitivity of RP-NMRC reported in the 'effectiveness' section of

[17] In the 2014–15 Federal Budget the introduction of a patient co-payment for previously bulk-billed patients was proposed for GP, pathology and imaging services (http://www.budget.gov.au/2014-15/content/glossy/health/download/Health.pdf). If this legislation is introduced, previously bulk-billed patients may incur a fee of $7 for RP-NMRC services.

this report. It is assumed that 51% of confirmatory CEEs are performed by an ophthalmologist (Lee, SJ et al. 2000), consistent with the economic analysis.

Ongoing confirmed cases of DR

All patients with a confirmed diagnosis of DR require ongoing monitoring by CEE and, conservatively, patients with UIs have also been assumed to require ongoing observation; both groups of patients are assumed to be under the care of an ophthalmologist. The average number of examinations that these patients are likely to have per year is highly uncertain. The NHMRC guidelines recommend that patients with any signs of NPDR should be examined annually or at 3- to 6-monthly intervals, depending on the DR level (NHMRC 2008). In the base-case non-Indigenous patients are assumed to be tested, on average, 1.5 times a year, whereas Indigenous Australians are tested twice a year. These may be underestimations, but there is also likely to be some degree of non-compliance with examinations. The impact of these factors on the financial implications has been assessed in the sensitivity analyses.

Patients diagnosed with DR are assumed to continue requiring CEEs until they die. Therefore, each year, a proportion of these patients are assumed to die. The age-specific mortality rates for non-STDR, as presented in Table 42 in the 'Economics' section, were weighted by the proportion of patients with diabetes within each age range, and this weighted average rate was applied to non-Indigenous patients with diagnosed DR. Based on the age-weighted relative risk of mortality derived from ABS data (ABS 2013c), the death rate in Indigenous patients was assumed to be four times that in the non-Indigenous population.

Estimates of the increase in numbers of CEE services likely to be performed as a result of the introduction of RP-NMRC testing in the non-Indigenous population are presented in Table 69, and those for the Indigenous population in Table 70.

Table 69 Estimated increase in the number of CEE services as a result of additional diagnoses of DR, non-Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total patients tested by RP-NMRC	44,193	65,466	85,400	83,552	83,141	83,625
With undiagnosed DR	9,678	12,337	12,724	9,009	6,742	5,366
Without DR	34,515	53,129	72,677	74,542	76,399	78,258
Test outcome						
True positive [a]	8,827	11,251	11,604	8,216	6,148	4,894
False negative	852	1,086	1,120	793	593	472
True negative	26,404	40,644	55,598	57,025	58,446	59,868

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
False positive	8,111	12,485	17,079	17,517	17,954	18,391
Diagnosed cases of DR						
Cases diagnosed that year	8,827	11,251	11,604	8,216	6,148	4,894
Ongoing diagnosed cases	0	8,537	19,138	29,733	36,703	41,445
Total	8,827	19,788	30,742	37,949	42,852	46,339
Deaths	290	650	1,009	1,246	1,407	1,521
Continuing diagnosed cases	8,537	19,138	29,733	36,703	41,445	44,818
Number of CEE services						
True positives	8,827	11,251	11,604	8,216	6,148	4,894
False positives	8,111	12,485	17,079	17,517	17,954	18,391
Ongoing diagnosed cases [a]	0	12,805	28,707	44,600	55,055	62,167
Total	16,938	36,542	57,391	70,334	79,158	85,452

CEE = comprehensive eye examination; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Includes patients with UIs

[b] Assuming that ongoing diagnosed cases have an average of 1.5 CEEs per year

Table 70 Estimated increase in the number of CEE services as a result of additional diagnoses of DR, Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total patients tested by RP-NMRC	15,772	21,925	27,147	25,992	26,100	26,506
With undiagnosed DR	4,684	4,946	4,045	2,426	2,072	2,014
Without DR	11,088	16,979	23,102	23,565	24,028	24,492
Test outcome						
True positive	4,272	4,511	3,689	2,213	1,890	1,837
False negative	412	435	356	214	182	177
True negative	8,482	12,989	17,673	18,027	18,382	18,736
False positive	2,606	3,990	5,429	5,538	5,647	5,756
Diagnosed cases of DR						
Cases diagnosed that year	4,272	4,511	3,689	2,213	1,890	1,837
Ongoing diagnosed cases	0	3,712	7,144	9,412	10,099	10,416
Total	4,272	8,223	10,833	11,624	11,989	12,253
Deaths	560	1,079	1,421	1,525	1,573	1,608
Continuing diagnosed cases	3,712	7,144	9,412	10,099	10,416	10,645
Number of CEE services						
True positives	4,272	4,511	3,689	2,213	1,890	1,837
False positives	2,606	3,990	5,429	5,538	5,647	5,756
Ongoing diagnosed cases [a]	0	7,423	14,288	18,823	20,199	20,832
Total	6,878	15,924	23,406	26,574	27,735	28,425

CEE = comprehensive eye examination; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Assuming that ongoing diagnosed cases have an average of 2 CEEs per year

The total numbers of additional CEE services resulting from the introduction of RP-NMRC are summarised in Table 71.

Table 71 Summary of the numbers of additional CEE services, total population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Non-indigenous population						
RP-NMRC test positive	16,938	23,736	28,683	25,734	24,102	23,285
Ongoing diagnosed cases DR	0	12,805	28,707	44,600	55,055	62,167
Total	16,938	36,542	57,391	70,334	79,158	85,452
Indigenous population						
RP-NMRC test positive	6,878	8,501	9,118	7,751	7,536	7,593
Ongoing diagnosed cases DR	0	7423	14288	18823	20199	20832
Total	6,878	15,924	23,406	26,574	27,735	28,425
Total population						
RP-NMRC test positive	23,815	32,238	37,801	33,485	31,639	30,877
Ongoing diagnosed cases DR	0	20,228	42,995	63,423	75,254	82,999
Total	23,815	52,466	80,796	96,907	106,892	113,877

CEE = comprehensive eye examination; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Estimated cost associated with increased CEE services

As for RP-NMRC, all services are assumed to be performed out-of-hospital, and services for Indigenous Australians are assumed to be bulk-billed. Based on 2012–13 MBS data for items 104 and 10915, in the non-Indigenous population 20.9% of CEEs performed by an ophthalmologist and 100% of those performed by an optometrist are assumed to be bulk-billed.

The cost to the MBS, excluding safety net impacts, was calculated using the current rebates of $72.75 for a CEE performed by an ophthalmologist and $60.35 for that performed by an optometrist. As 100% of optometrist services are bulk-billed, Medicare safety net considerations are not relevant. For ophthalmologist services the cost to the MBS, including safety net impacts, was derived using the 2012–13 average benefits paid per service for item 104, as provided in the MBS report for this item (see Table 100 in Appendix G).

Total patient co-payments for CEE performed by an ophthalmologist, excluding safety net impacts, were derived assuming that 20.9% of services were bulk-billed and the remaining 79.1% of services incurred a patient co-payment of $12.80. The total cost to patients was calculated by subtracting the total benefits paid by the MBS from the total fees charged. This inherently incorporates safety net impacts.

Finally, the average Extended Medicare Safety Net (EMSN) payment per service for CEE by an ophthalmologist was estimated by dividing the total EMSN payments by the number of services not bulk-billed ($4.82). This was used to estimate the increase in EMSN payments resulting from the increased CEE services performed by an ophthalmologist. As the average EMSN payment per service covered by the EMSN was $62.42 and the EMSN cap for this service is $256.65, it is not expected that many patients will exceed this cap.

The estimated costs of the likely increase in CEE services resulting from additional cases of DR being diagnosed by RP-NMRC are presented in Table 72 and Table 73, for non-Indigenous and Indigenous patients, respectively. The total costs are summarised in Table 74.

Table 72 Estimated costs resulting from increase in the number of CEE services, non-Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
CEE services						
RP-NMRC test-positives:						
Ophthalmologist	8,638	12,106	14,628	13,124	12,292	11,875
Optometrist	8,299	11,631	14,055	12,610	11,810	11,410
Total	16,938	23,736	28,683	25,734	24,102	23,285
Ongoing DR patients (ophthalmologist)	0	12,805	28,707	44,600	55,055	62,167
Total	16,938	36,542	57,391	70,334	79,158	85,452
Total costs						
RP-NMRC test-positives:						
Ophthalmologist	$1,165,041	$1,632,687	$1,972,942	$1,770,077	$1,657,853	$1,601,623
Optometrist	$500,873	$701,923	$848,205	$760,989	$712,742	$688,568
Total	$1,665,914	$2,334,609	$2,821,146	$2,531,066	$2,370,596	$2,290,191
Ongoing DR patients	$0	$1,727,052	$3,871,785	$6,015,172	$7,425,315	$8,384,544
Total	$1,665,914	$4,061,661	$6,692,931	$8,546,238	$9,795,911	$10,674,735
Cost to MBS						
Excluding safety net						
RP-NMRC test positives						
Ophthalmologist	$628,431	$880,682	$1,064,218	$954,791	$894,257	$863,926
Optometrist	$500,873	$701,923	$848,205	$760,989	$712,742	$688,568
Total	$1,129,304	$1,582,605	$1,912,422	$1,715,780	$1,606,999	$1,552,494
Ongoing DR patients	$0	$931,583	$2,088,467	$3,244,624	$4,005,264	$4,522,679
Total	$1,129,304	$2,514,188	$4,000,889	$4,960,404	$5,612,264	$6,075,173
Including safety net						
RP-NMRC test positives						
Ophthalmologist	$651,153	$912,525	$1,102,697	$989,313	$926,591	$895,163
Optometrist	$500,873	$701,923	$848,205	$760,989	$712,742	$688,568
Total	$1,152,026	$1,614,447	$1,950,901	$1,750,303	$1,639,333	$1,583,731

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Ongoing DR patients	$0	$965,267	$2,163,979	$3,361,939	$4,150,082	$4,686,205
Total	$1,152,026	$2,579,714	$4,114,880	$5,112,242	$5,789,415	$6,269,936
Safety net payments	$22,722	$65,526	$113,991	$151,838	$177,152	$194,763
Estimated EMSN	$32,960	$95,050	$165,352	$220,251	$256,970	$282,517
Cost to patient						
Excluding safety net						
RP-NMRC test positives	$536,610	$752,005	$908,724	$815,286	$763,596	$737,697
Ongoing DR patients	$0	$795,469	$1,783,319	$2,770,548	$3,420,051	$3,861,866
Total	$536,601	$1,547,473	$2,692,042	$3,585,834	$4,183,647	$4,599,563
Including safety net						
RP-NMRC test positives	$513,888	$720,162	$870,24	$780,763	$731,263	$706,460
Ongoing DR patients	$0	$761,786	$1,707,806	$2,653,233	$3,275,233	$3,698,339
Total	$513,888	$1,481,947	$2,578,051	$3,433,996	$4,006,496	$4,404,799

CEE = comprehensive eye examination; DR = diabetic retinopathy; EMSN = Extended Medicare Safety Net; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 73 Estimated cost resulting from increase in the number of CEE services, Indigenous population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
CEE services						
RP-NMRC test positives	6,878	8,501	9,118	7,751	7,536	7,593
Ophthalmologist	3,508	4,336	4,650	3,953	3,843	3,872
Optometrist	3,370	4,166	4,468	3,798	3,693	3,720
Ongoing DR patients (ophthalmologist)	0	7,423	14,288	18,823	20,199	20,832
Total	6,878	15,924	23,406	26,574	27,735	28,425
Total costs						
RP-NMRC test positives						
Ophthalmologist	$255,179	$315,410	$338,298	$287,571	$279,613	$281,703
Optometrist	$203,383	$251,389	$269,631	$229,201	$222,858	$224,523
Total	$458,563	$566,79	$607,930	$516,772	$502,471	$506,226
Ongoing DR patients	$0	$540,036	$1,039,422	$1,369,381	$1,469,458	$1,515,530
Total	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756

CEE = comprehensive eye examination; DR = diabetic retinopathy; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 74 Estimated cost of CEE services, total population

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Cost to MBS						
Non-indigenous population	$1,152,026	$2,579,714	$4,114,880	$5,112,242	$5,789,415	$6,269,936
Indigenous population	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Cost to patient						
Non-indigenous population	$513,888	$1,481,947	$2,578,051	$3,433,996	$4,006,496	$4,404,799

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Indigenous population	-	-	-	-	-	-
Total	$513,888	$1,481,947	$2,578,051	$3,433,996	$4,006,496	$4,404,799
Total cost						
Non-indigenous population	$1,665,914	$4,061,661	$6,692,931	$8,546,238	$9,795,911	$10,674,735
Indigenous population	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total cost	$2,124,477	$5,168,496	$8,340,283	$10,432,390	$11,767,840	$12,696,491

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule

The introduction of RP-NMRC testing for DR has the potential to greatly increase the utilisation and costs associated with CEEs for ongoing monitoring of the additional cases of DR identified, with potential costs for additional CEE services likely to exceed $10 million per year.

Financial implications to the MBS

The financial implications to the MBS resulting from the proposed listing of RP-NMRC by Indigenous status are summarised in Table 75.

Table 75 Total costs to the MBS associated with RP-NMRC testing for DR and associated CEE services

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Excluding safety net impacts						
RP-NMRC						
Number of services	59,965	87,391	112,547	109,543	109,241	110,131
Non-indigenous population	$1,727,962	$2,559,709	$3,339,157	$3,266,871	$3,250,819	$3,269,724
Indigenous population	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Total	$2,344,648	$3,416,987	$4,400,600	$4,283,142	$4,271,340	$4,306,104
CEE						
Number of services	16,938	36,542	57,391	70,334	79,158	85,452
Non-indigenous population	$1,129,304	$2,514,188	$4,000,889	$4,960,404	$5,612,264	$6,075,173
Indigenous population	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total	$1,587,867	$3,621,023	$5,648,240	$6,846,556	$7,584,193	$8,096,92
Total cost						
Non-indigenous population	$1,129,304	$2,514,188	$4,000,889	$4,960,404	$5,612,264	$6,075,173
Indigenous population	$1,075,249	$1,964,113	$2,708,794	$2,902,423	$2,992,449	$3,058,136
Total	$3,932,515	$7,038,010	$10,048,840	$11,129,698	$11,855,532	$12,403,033
Including safety net impacts						
RP-NMRC						
Number of services	59,965	87,391	112,547	109,543	109,241	110,131
Non-indigenous population	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922
Indigenous population	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
Total	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE						

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Number of services	16,938	36,542	57,391	70,334	79,158	85,452
Non-indigenous population	$1,152,026	$2,579,714	$4,114,880	$5,112,242	$5,789,415	$6,269,936
Indigenous population	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total cost						
Non-indigenous population	$2,882,207	$5,142,709	$7,458,325	$8,383,307	$9,044,408	$9,543,858
Indigenous population	$1,075,249	$1,964,113	$2,708,794	$2,902,423	$2,992,449	$3,058,136
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994

CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

If the new listing for RP-NMRC testing is approved, within 3 years the cost to the MBS is likely to exceed $10 million per year, assuming a relatively high uptake of the new service. Table 76 presents the cost to the MBS for CEE services, categorised by whether the CEE was performed after a positive RP-NMRC test result or for ongoing monitoring of diagnosed DR.

Table 76 Cost to the MBS for CEE services, by reason for examination (including safety net implications)

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Non-indigenous population						
Number of services:						
RP-NMRC test positive	16,938	23,736	28,683	25,734	24,102	23,285
Ongoing DR	0	12,805	28,707	44,600	55,055	62,167
Cost:						
RP-NMRC test positive	$1,152,026	$1,614,447	$1,950,901	$1,750,303	$1,639,333	$1,583,731
Ongoing DR	$0	$965,267	$2,163,979	$3,361,939	$4,150,082	$4,686,205
Total cost	$1,152,026	$2,579,714	$4,114,880	$5,112,242	$5,789,415	$6,269,936
Indigenous population						
Number of services:						
RP-NMRC test positive	6,878	8,501	9,118	7,751	7,536	7,593
Ongoing DR	0	7,423	14,288	18,823	20,199	20,832
Cost:						
RP-NMRC test positive	$458,563	$566,79	$607,930	$516,772	$502,471	$506,226
Ongoing DR	$0	$540,036	$1,039,422	$1,369,381	$1,469,458	$1,515,530
Total cost	$458,563	$1,106,835	$1,647,351	$1,886,153	$1,971,929	$2,021,756
Total population						
RP-NMRC test positive	$1,610,589	$2,181,247	$2,558,831	$2,267,074	$2,141,804	$2,089,956
Ongoing DR	$0	$1,505,302	$3,203,401	$4,731,320	$5,619,540	$6,201,735
Total	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692

CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

The cost attributable to CEEs performed to confirm diagnosis after a positive RP-NMRC test result peaks at around $2.5 million per year, then gradually declines as the prevalent pool of

patients with undiagnosed DR decreases. In contrast, the cost for CEE services to monitor disease progression in patients with a confirmed diagnosis increases markedly as more patients are diagnosed with DR, rapidly becoming the major source of the cost to the MBS.

Uncertainty scenarios

Main sources of uncertainty

There are two major sources of uncertainty that affect the number of patients likely to be tested by RP-NMRC and the consequent increase in the number of CEEs likely to be performed, namely the proportion of patients who are not receiving regular eye examinations and the likely uptake of RP-NMRC testing in this population. Additional uncertainties that will influence the number of patients tested are the prevalence of DR in the population and the average number of CEEs performed in patients diagnosed with DR.

The impact of these factors has been assessed in the following sensitivity analyses:

- The proportion of non-Indigenous patients currently not receiving regular eye assessments is increased from 23% to 40%, as estimated in the application.
- The assumed uptake of RP-NMRC is both increased and decreased, as indicated in Table 77.
- The prevalence of DR in both the non-Indigenous and Indigenous populations is increased to 44%, in line with the upper estimate of the prevalence of DR reported in the NHMRC guidelines (NHMRC 2008).
- The average frequency of CEE tests in patients diagnosed with DR is increased from 1.5 per year to 2 per year in the non-Indigenous population, and from 2 per year to 3 per year in the Indigenous population.

The results of sensitivity analyses assessing the cost to the MBS with various levels of uptake are presented in Table 77, and the outcomes for the remaining sensitivity analyses are summarised in Table 78.

Table 77 Sensitivity analyses assessing impact of level of uptake of RP-NMRC on the cost to the MBS (including safety net implications)

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case						
Non-Indigenous uptake	20%	30%	40%	40%	40%	40%
Indigenous uptake:	40%	60%	80%	80%	80%	80%
RP-NMRC	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
High uptake						
Non-Indigenous uptake:	30%	40%	50%	50%	50%	50%
RP-NMRC	$2,595,271	$3,350,483	$4,056,970	$3,969,542	$3,967,089	$4,009,818
CEE	$1,728,039	$3,494,588	$5,115,414	$6,049,857	$6,625,354	$7,012,047
Total	$4,323,310	$6,845,071	$9,172,385	$10,019,399	$10,592,444	$11,021,866
Indigenous uptake:	50%	70%	90%	90%	90%	90%
RP-NMRC	$770,857	$974,761	$1,160,878	$1,124,031	$1,136,628	$1,156,922
CEE	$573,204	$1,296,815	$1,809,097	$2,000,466	$2,064,293	$2,108,263
Total	$1,344,061	$2,271,576	$2,969,975	$3,124,498	$3,200,921	$3,265,185
Total	**$5,667,371**	**$9,116,647**	**$12,142,360**	**$13,143,897**	**$13,793,365**	**$14,287,051**
Low uptake						
Non-Indigenous uptake:	5%	10%	20%	20%	25%	25%
RP-NMRC	$432,545	$879,398	$1,772,590	$1,759,233	$2,195,531	$2,188,358
CEE	$288,007	$819,181	$1,842,652	$2,646,769	$3,568,208	$4,259,008
Total	$720,552	$1,698,580	$3,615,242	$4,406,002	$5,763,739	$6,447,366
Indigenous uptake:	10%	20%	40%	40%	50%	50%
RP-NMRC	$154,171	$307,528	$602,511	$572,817	$701,237	$689,743
CEE	$114,641	$357,795	$787,168	$1,126,623	$1,410,176	$1,584,620
Total	$268,812	$665,323	$1,389,679	$1,699,440	$2,111,413	$2,274,364
Total	**$989,364**	**$2,363,903**	**$5,004,921**	**$6,105,442**	**$7,875,152**	**$8,721,730**

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 78 Sensitivity analyses assessing impact of number of patients likely to be tested on the cost to the MBS (including safety net implications)

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base case						
RP-NMRC	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994
Patients not receiving regular CEE 40% [a]						
RP-NMRC	$3,625,695	$5,314,661	$6,876,128	$6,705,080	$6,681,377	$6,730,157
CEE	$2,462,086	$5,593,294	$8,803,665	$10,777,008	$12,040,477	$12,925,992
Total	**$6,087,782**	**$10,907,955**	**$15,679,793**	**$17,482,088**	**$18,721,855**	**$19,656,150**
Prevalence of DR 44% [b]						
RP-NMRC	$2,346,866	$3,277,167	$3,994,852	$3,675,716	$3,543,381	$3,498,471
CEE	$2,162,118	$5,543,292	$8,958,995	$11,273,099	$12,717,385	$13,713,271
Total	**$4,508,984**	**$8,820,459**	**$12,953,847**	**$14,948,815**	**$16,260,766**	**$17,211,742**
Frequency of CEE in diagnosed patients [c]						
Non-Indigenous: 2/year:						
RP-NMRC	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
CEE	$1,152,026	$2,901,469	$4,836,207	$6,232,888	$7,172,776	$7,832,004
Total	$2,882,207	$5,464,465	$8,179,651	$9,503,953	$10,427,769	$11,105,926
Indigenous: 3/year:						
RP-NMRC	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380
CEE	$458,563	$1,376,853	$2,167,062	$2,570,843	$2,706,658	$2,779,521
Total	$1,075,249	$2,234,131	$3,228,504	$3,587,114	$3,727,178	$3,815,901
Total	$3,957,455	$7,698,596	$11,408,156	$13,091,067	$14,154,947	$14,921,827

CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Base-case 23%: Only the proportion of non-Indigenous patients not receiving regular CEEs has been altered; the proportion of Indigenous patients not receiving regular CEEs is assumed to remain the same at 80%.

[b] Base-case: 21.9% in the non-Indigenous population and 29.7% in the Indigenous population

[c] Base-case: non-Indigenous patients 1.5 CEEs per year, Indigenous patients 2 CEEs per year

It is evident that both the proportion of patients with diabetes who are not currently receiving regular eye examinations, and the uptake of RP-NMRC within this population, have considerable impact on the estimated cost to the MBS resulting from listing of RP-NMRC. While the prevalence of DR in people with diabetes will affect the additional number of CEE services, the prevalence used in the sensitivity analysis is the upper limit cited in the NHMRC guidelines (NHMRC 2008) and is highly likely to be an overestimate.

Increasing the frequency of CEE testing in diagnosed patients has only a relatively small effect on the annual cost to the MBS. Similarly, both the relative proportion of CEE services performed by ophthalmologists or optometrists for confirmation of diagnosis after a positive RP-NMRC result, and the proportion of CEE services performed by ophthalmologists that are bulk-billed, have minimal impact on the outcome of the financial analysis.

Test accuracy

The diagnostic accuracy of RP-NMRC will affect both the number of patients who require follow-up CEE to confirm diagnosis and the number of diagnosed patients who are no longer eligible for RP-NMRC but who will require ongoing monitoring by CEE. Table 79 presents the results of sensitivity analyses based on the upper and lower limits of the 95%CI for the sensitivity and specificity of RP-NMRC to detect any DR, as derived in the meta-analysis presented in Table 19.

Table 79 Sensitivity analyses assessing impact of diagnostic accuracy of RP-NMRC on the cost to the MBS (including safety net implications)

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case [a]						
RP-NMRC	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994
Upper limits 95%CI [a]						
RP-NMRC	$2,455,693	$3,560,667	$4,567,652	$4,440,404	$4,432,803	$4,473,535
CEE	$1,438,984	$3,471,100	$5,462,551	$6,685,437	$7,418,034	$7,918,409
Total	$3,894,677	$7,031,766	$10,030,203	$11,125,841	$11,850,836	$12,391,944
Lower limits 95%CI [a]						
RP-NMRC	$2,346,866	$3,439,788	$4,450,931	$4,339,719	$4,323,281	$4,352,584
CEE	$1,799,283	$3,878,018	$6,023,373	$7,265,712	$8,074,311	$8,654,009
Total	$4,146,149	$7,317,805	$10,474,304	$11,605,432	$12,397,592	$13,006,593

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

[a] Diagnostic accuracy of DR: sensitivity 91.2% (95%CI: 81.7–96.1), specificity 76.5% (95%CI: 67.4–83.6)

The diagnostic accuracy of RP-NMRC has minimal impact on the estimated financial implications.

MBS scheduled fee for RP-NMRC

In the justification of the proposed MBS scheduled fee for RP-NMRC ($50.00), only $28.00 is assigned to salaries, $2.00 to consumables and $20.00 for equipment costs (see Table 83). It is possible that the proposed fee may not adequately cover the costs associated with RP-NMRC in terms of staff time and ongoing maintenance and training costs. In addition, there is a requirement to provide a room that can be adequately darkened for non-mydriatic photography. Therefore, sensitivity analyses have been performed assuming an MBS scheduled fee of $75.00 and $100.00 for RP-NMRC (Table 80).

In addition, it has been proposed that an alternative funding source for the provision of retinal cameras may be considered. Therefore, the impact of removing the equipment component from the scheduled fee has also been assessed by assuming a scheduled fee of $30.00.

Table 80 Sensitivity analyses assessing impact of scheduled fee for RP-NMRC on the cost to the MBS (including safety net implications)

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case $50.00						
RP-NMRC	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994
RP-NMRC $30.00						
RP-NMRC	$1,408,120	$2,052,164	$2,642,932	2,572,402	$2,565,308	$2,586,181
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$3,018,709	$5,738,713	$8,405,164	$9,570,796	$10,326,652	$10,877,873

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
RP-NMRC $75.00						
RP-NMRC	$3,520,299	$5,130,410	$6,607,330	$6,431,004	$6,413,270	$6,465,453
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$5,130,888	$8,816,959	$12,369,562	$13,429,398	$14,174,614	$14,757,145
RP-NMRC $100.00						
RP-NMRC	$4,693,732	$6,840,547	$8,809,773	$8,574,672	$8,551,026	$8,620,604
CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$6,304,321	$10,527,096	$14,572,005	$15,573,066	$16,312,370	$16,912,296

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

If an alternative source of funding for the non-mydriatic retinal cameras is implemented, once the uptake of RP-NMRC has stabilised, the cost to the MBS for RP-NMRC is reduced by approximately $1.7 million per year. This is discussed further below.

Potential for use outside the intended population

As discussed in the 'Other relevant considerations' section of this report, there is the risk that RP-NMRC may replace a CEE in some patients who would otherwise attend an optometrist or ophthalmologist. While this would increase the number of patients tested by RP-NMRC each year and, consequently, the cost associated with this testing procedure, there would be a corresponding decrease in the utilisation of CEEs for screening for DR. The economic model indicated that, due to the high frequency of testing, any patients who have a false negative result with RP-NMRC may have disease progression in the intervening interval, but are still likely to be diagnosed prior to development of any major vision impairment; therefore, substitution of RP-NMRC for CEE for testing for DR is unlikely to have any major implications on the utilisation and cost of CEE for the ongoing monitoring of patients diagnosed with DR. Accordingly, as CEE is the more costly procedure, it is likely that the substitution of RP-NMRC for CEE for testing for DR would result in cost savings to the MBS. However, while RP-NMRC is less expensive than CEE, as demonstrated in the economic evaluation, it is also less effective, resulting in worse health outcomes for patients (e.g. vision loss).

Cost to patients

It is assumed that all services for Indigenous patients will be bulk-billed and, therefore, these patients will not accrue any costs. The costs to non-Indigenous patients are summarised in Table 81. The majority of the cost to patients results from the out-of-pocket cost for a CEE performed by an ophthalmologist to monitor patients who have been

diagnosed with DR. Due to the high-rate of bulk-billing by GPs for patients with chronic diseases such as diabetes, the total cost to patients for RP-NMRC is minimal.

Table 81 Total costs to non-Indigenous patients associated with RP-NMRC testing for DR and associated CEE services

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Excluding safety net impacts						
RP-NMRC						
Number of services	59,965	87,391	112,547	109,543	109,241	110,131
Total cost	$8,538	$12,648	$16,499	$16,142	$16,063	$16,156
CEE						
Number of services	16,938	36,542	57,391	70,334	79,158	85,452
Total cost	$536,610	$1,547,473	$2,692,042	$3,585,834	$4,183,647	$4,599,563
Total cost RP-NMRC/CEE	$545,148	$1,560,121	$2,708,542	$3,601,976	$4,199,710	$4,615,719
Including safety net impacts						
RP-NMRC						
Number of services	59,965	87,391	112,547	109,543	109,241	110,131
Total cost	$6,320	$9,362	$12,212	$11,948	$11,889	$11,958
CEE						
Number of services	16,938	36,542	57,391	70,334	79,158	85,452
Total cost	$513,888	$720,162	$870,24	$780,763	$731,263	$706,460
Total cost	$520,208	$1,491,309	$2,590,263	$3,445,944	$4,018,385	$4,416,758

CEE = comprehensive eye examination; DR = diabetic retinopathy; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Total Australian healthcare system costs

The component costs and the total cost to the Australian healthcare system are provided in Table 82. It is evident that the majority of the cost associated with the proposed new listing for RP-NMRC is due to the increase in the number of CEEs performed to monitor patients diagnosed with DR. Most of the cost will be borne by the MBS.

Table 82 Total healthcare system costs resulting from proposed listing for RP-NMRC

	2015 –16	2016–17	2017–18	2018–19	2019–20	2020–21
Cost to MBS						
Cost of RP-NMRC	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
Cost of CEE	$1,610,589	$3,686,549	$5,762,232	$6,998,394	$7,761,344	$8,291,692
Total	$3,957,455	$7,106,822	$10,167,118	$11,285,730	$12,036,857	$12,601,994
Cost to patient						
Cost of RP-NMRC	$6,320	$9,362	$12,212	$11,948	$11,889	$11,958
Cost of CEE	$513,888	$1,481,947	$2,578,051	$3,433,996	$4,006,496	$4,404,799
Total	$520,208	$1,491,309	$2,590,263	$3,445,944	$4,018,385	$4,416,758
Total cost						
Cost of RP-NMRC	$2,353,186	$3,429,635	$4,417,099	$4,299,284	$4,287,402	$4,322,260

	2015 –16	2016–17	2017–18	2018–19	2019–20	2020–21
Cost of CEE	$2,124,477	$5,168,496	$8,340,283	$10,432,390	$11,767,840	$12,696,491
Total	$4,477,663	$8,598,131	$12,757,382	$14,731,674	$16,055,242	$17,018,752

CEE = comprehensive eye examination; MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Alternative funding approach for non-mydriatic retinal cameras

The justification for the proposed MBS fee for RP-NMRC, as presented in the application, is summarised in Table 83.

Table 83 Justification of proposed MBS fee for RP-NMRC

Component	Cost	Justification
Staff component:		
Reader	$20.00	Salary of $120 per hour 10 minutes per service to read image and report on retinal status
Imager	$8.00	Salary of $30 per hour 15 minutes per procedure including: • maintenance of camera • confirming patient eligibility • taking retinal images of both eyes • sending images to reader for evaluation
Consumables	$2.00	Consumables, camera servicing and software updates
Equipment	$20.00	Based on 5-year amortisation of $50,000 camera (including set-up cost / training) and 10 services per week
Total	$50.00	

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

It has been proposed that an alternative funding mechanism for the initial set-up costs associated with RP-NMRC testing may be considered. The potential annual savings to the MBS resulting from excluding the equipment cost component from the MBS scheduled fee, for both the base-case scenario (relatively high uptake) and the low-uptake scenario (see Table 77), are presented in Table 84, and the cumulative potential savings are summarised in Table 85.

Table 84 Potential *annual* savings to the MBS for RP-NMRC testing with alternative funding of cameras

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case (high uptake)						
Total patients tested:						
Non-Indigenous	44,193	65,466	85,400	83,552	83,141	83,625
Indigenous	15,772	21,925	27,147	25,992	26,100	26,506
Total	59,965	87,391	112,547	109,543	109,241	110,131
Cost to MBS—fee $50.00:						
Non-Indigenous	$1,730,181	$2,562,995	$3,343,444	$3,271,065	$3,254,993	$3,273,922
Indigenous	$616,686	$857,278	$1,061,442	$1,016,271	$1,020,520	$1,036,380

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Total	$2,346,866	$3,420,273	$4,404,887	$4,287,336	$4,275,513	$4,310,302
Cost to MBS—fee $30.00:						
Non-Indigenous	$1,038,108	$1,537,797	$2,006,067	$1,962,639	$1,952,996	$1,964,353
Indigenous	$370,011	$514,367	$636,865	$609,763	$612,312	$621,828
Total	$1,408,120	$2,052,164	$2,642,932	$2,572,402	$2,565,308	$2,586,181
Saving to MBS						
Non-Indigenous	$690,272	$1,025,198	$1,337,378	$1,308,426	$1,301,997	$1,309,569
Indigenous	$246,674	$342,911	$424,577	$406,508	$408,208	$414,552
Total	$938,746	$1,368,109	$1,761,955	$1,714,934	$1,710,205	$1,724,121
Low uptake						
Total patients tested:						
Non-Indigenous	11,048	22,462	45,277	44,935	56,080	55,896
Indigenous	3,943	7,865	15,409	14,650	17,934	17,640
Total	14,991	30,327	60,686	59,586	74,014	73,537
Cost to MBS—fee $50.00:	$432,545	$879,398	$1,772,590	$1,759,233	$2,195,531	$2,188,358
Non-Indigenous	$154,171	$307,528	$602,511	$572,817	$701,237	$689,743
Indigenous	$586,717	$1,186,926	$2,375,101	$2,332,050	$2,896,768	$2,878,101
Cost to MBS—fee $30.00:						
Non-Indigenous	$259527	$527,639	$1,063,554	$1,055,540	$1,317,318	$1,313,015
Indigenous	$92,503	$184,517	$361506	$343,690	$420,742	$413,846
Total	$352,030	$712,156	$1,425,060	$1,399,230	$1,738,061	$1,726,861
Saving to MBS						
Non-Indigenous	$173,018	$351,759	$709036	$703,693	$878,212	$875,343
Indigenous	$61,669	$123,011	$241,004	$229127	$280,495	$275,897
Total	$234,687	$474,770	$950,040	$932,820	$1,158707	$1,151,240

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 85 Potential *cumulative* savings to the MBS for RP-NMRC testing with alternative funding of cameras

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case (high uptake)						
Cumulative savings						
Non-Indigenous	$692,072	$1,717,270	$3,054,648	$4,363,074	$5,665,071	$6,974,640
Indigenous	$246,674	$589,585	$1,014,162	$1,420,671	$1,828,879	$2,243,431
Total	$938,746	$2,306,856	$4,068,810	$5,783,745	$7,493,950	$9,218,071
Low uptake						
Cumulative savings						
Non-Indigenous	$173,018	$524,777	$1,233,813	$1,937,507	$2,815,719	$3,691,062
Indigenous	$61,669	$184,680	$425,684	$654,811	$935,306	$1,211,203
Total	$234,687	$709,457	$1,659,497	$2,592,317	$3,751,024	$4,902,265

MBS = Medicare Benefits Schedule; RP-NMRC = retinal photography with a non-mydriatic retinal camera

In the base-case scenario, which assumes a relatively high uptake of RP-NMRC, provision of alternative funding for the initial set-up costs associated with RP-NMRC testing would potentially result in savings to the MBS in the order of $9 million over the first 6 years of listing of RP-NMRC on the MBS, or $1.7 million annually once the uptake of RP-NMRC has stabilised. However, if the uptake of RP-NMRC is low, the potential cumulative savings are considerably less, at approximately $5 million over 6 years.

These potential savings to the Commonwealth Government could be redirected into grant funding, similar to that provided to set up the QAAMS pathology program, in which grants were provided for some ACCHSs to assist with the purchase of capital equipment. As discussed in the 'Other relevant considerations' section of this report, suitable non-mydriatic retinal cameras can be purchased for under $10,000 (Leferink 2011); however, funding would also be required for training, ongoing quality assurance processes, and additional resources related to internet data requirements. Table 86 presents estimates of the cumulative number of cameras that could be funded, assuming total set-up costs in the range $20,000–$80,000.

Table 86 Cumulative number of non-mydriatic retinal cameras that could be funded with potential savings to the MBS

	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case scenario						
Cumulative savings	$938,746	$2,306,856	$4,068,810	$5,783,745	$7,493,950	$9,218,071
No. of cameras, by set-up cost:						
$20,000	47	115	203	289	375	461
$30,000	31	77	136	193	250	307
$40,000	23	58	102	145	187	230
$50,000	19	46	81	116	150	184
$60,000	16	38	68	96	125	154
$70,000	13	33	58	83	107	132
$80,000	12	29	51	72	94	115
Low up-take scenario						
Cumulative savings	$234,687	$709,457	$1,659,497	$2,592,317	$3,751,024	$4,902,265
No. of cameras, by set-up cost:						
$20,000	12	35	83	130	188	245
$30,000	8	24	55	86	125	163
$40,000	6	18	41	65	94	123
$50,000	5	14	33	52	75	98
$60,000	4	12	28	43	63	82
$70,000	3	10	24	37	54	70
$80,000	3	9	21	32	47	61

MBS = Medicare Benefits Schedule

Assuming an initial set-up cost of $50,000, as proposed in the application, the cumulative savings over the first 6 years of listing would be sufficient to fund approximately 180 cameras in the base-case scenario. In contrast, in the scenario in which the uptake of RP-NMRC is low, only 100 cameras could be funded with the potential 6-year cumulative savings. It would also be necessary to provide some form of ongoing financial support for replacement of outdated or defective equipment, and ongoing training and quality assurance measures.

One benefit of alternative funding for RP-NMRC is that resources can be directed to areas of most need. For instance, in the 'Other relevant considerations' section of this report, it is suggested that funding of RP-NMRC within the QAAMS program could further improve the management of diabetes in ATSI communities.

Table 87 presents the estimated number of cameras that could be purchased with the potential savings on MBS reimbursements for RP-NMRC services provided to Indigenous Australian patients.

Table 87 Cumulative number of non-mydriatic cameras that could be funded with potential savings on MBS reimbursements for services provided to Indigenous Australians

Set-up cost	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21
Base-case scenario						
Cumulative savings	$246,674	$589,585	$1,014,162	$1,420,671	$1,828,879	$2,243,431
No. of cameras, by set-up cost:						
$20,000	12	29	51	71	91	112
$30,000	8	20	34	47	61	75
$40,000	6	15	25	36	46	56
$50,000	5	12	20	28	37	45
$60,000	4	10	17	24	30	37
$70,000	4	8	14	20	26	32
$80,000	3	7	13	18	23	28
Low up-take scenario						
Cumulative savings	$61,669	$184,680	$425,684	$654,811	$935,306	$1,211,203
No. of cameras, by set-up cost:						
$20,000						
$30,000	2	6	14	22	31	40
$40,000	2	5	11	16	23	30
$50,000	1	4	9	13	19	24
$60,000	1	3	7	11	16	20
$70,000	1	3	6	9	13	17
$80,000	1	2	5	8	12	15

MBS = Medicare Benefits Schedule

As there are presently approximately 180 ACCHSs associated with the QAAMS program[18], it is evident that additional funding would be required to provide adequate services to this high-risk population, even if initial set-up costs are low. The level of funding required to provide RP-NMRC services to the clinics within the QAAMS program, for total set-up costs ranging from $20,000 to $80,000, is summarised in Table 88.

A further issue is that, under the normal MBS reimbursement arrangements, there is a critical patient caseload below which a healthcare practice may not recoup their capital investment. The equipment component of the proposed MBS fee for RP-NMRC of $20 per service was based on a 5-year amortisation of a $50,000 camera (including set-up costs and training) and an average of 10 services per week. A primary care facility servicing a predominantly Indigenous population would require a client base of at least 500 patients with diabetes to justify the initial capital outlay for RP-NMRC, and a practice covering a more general population would require 1,000 patients with diabetes. Many healthcare practices, especially those in more remote communities, may be reluctant to expend what amounts to a considerable capital outlay if they cannot guarantee recouping their investment.

Table 88 Funding required to provide RP-NMRC services to clinics within the QAAMS program

Number of cameras	% clinics in QAAMS	Set-up cost $20,000	Set-up cost $30,000	Set-up cost $40,000	Set-up cost $50,000	Set-up cost $60,000	Set-up cost $80,000
20	11%	$400,000	$600,000	$800,000	$1,000,000	$1,200,000	$1,600,000
40	22%	$800,000	$1,200,000	$1,600,000	$2,000,000	$2,400,000	$3,200,000
60	33%	$1,200,000	$1,800,000	$2,400,000	$3,000,000	$3,600,000	$4,800,000
80	44%	$1,600,000	$2,400,000	$3,200,000	$4,000,000	$4,800,000	$6,400,000
100	56%	$2,000,000	$3,000,000	$4,000,000	$5,000,000	$6,000,000	$8,000,000
120	67%	$2,400,000	$3,600,000	$4,800,000	$6,000,000	$7,200,000	$9,600,000
140	78%	$2,800,000	$4,200,000	$5,600,000	$7,000,000	$8,400,000	$11,200,000
160	89%	$3,200,000	$4,800,000	$6,400,000	$8,000,000	$9,600,000	$12,800,000
180	100%	$3,600,000	$5,400,000	$7,200,000	$9,000,000	$10,800,000	$14,400,000

MBS = Medicare Benefits Schedule; QAAMS = Quality Assurance for Aboriginal and Torres Strait Islander Medical Services; RP-NMRC = retinal photography with a non-mydriatic retinal camera

In conclusion, an alternative funding mechanism may be the only way of ensuring that access to RP-NMRC is provided to those primary care facilities where the need is greatest and where they can be used most efficiently. However, the introduction of this service also

[18] Personal communication, QAAMS Management Team; phone call on 14 July 2014

needs an investment in time and space by the healthcare provider, and provision of fully funded equipment lowers the incentive to use the technology to its full potential.

Discussion

Safety

Limited data were available on the safety of RP-NMRC. One study used mydriasis in 75 patients; 1 patient presented later with angle-closure glaucoma (Maberley et al. 2003). No other safety concerns relating to RP-NMRC were identified. An overall summary of the body of evidence regarding the safety of RP-NMRC may be seen in Table 89.

Table 89 Body of evidence matrix for safety

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base [a]				Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency [b]				Not applicable
Clinical impact				Slight or restricted
Generalisability		Population studied in the body of evidence is similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)

[b] If there is only one study, rank this component as 'not applicable'.

Source: adapted from NHMRC (2009)

One systematic review on the risk of intraocular pressure changes or acute glaucoma following mydriasis, including data from 28 original studies, found that risk from mydriasis is low (Pandit & Taylor 2000). In the general population no cases of acute glaucoma were identified after tropicamide alone (n=3,972), and for all agents combined (including tropicamide, atropine, homatropine, phenylephrine, cyclopentolate and hydroxyamphetamine), the rate of acute glaucoma was 1 in 18,020. Some participants in these studies had transient rises in intraocular pressure, but these were considered to be modest, asymptomatic and clinically inconsequential. It may therefore be concluded that the risk of acute glaucoma resulting from mydriasis is very low. Furthermore, it should be kept in mind that mydriasis may or may not be used with RP-NMRC, whereas it is always used for CEEs; therefore, any safety issues associated with mydriasis would favour the intervention rather than the comparator.

RP-NMRC was found to be highly acceptable to the majority of patients across the included studies on patient acceptability. Few patients were found to experience discomfort during RP-NMRC. Even fewer patients experienced discomfort that was described as severe, due to the high-power flash used on older Polaroid cameras, and these findings are unlikely to be applicable to current digital systems. Patient attitudes toward the use of RP-NMRC in local Indigenous health services were found to be positive overall.

Effectiveness

Direct evidence

No direct evidence was identified for the effectiveness of RP-NMRC. Results of studies that reported diagnostic accuracy outcomes and change in management outcomes were therefore included for a synthesis of indirect evidence, as discussed below.

Linked evidence

Is RP-NMRC accurate?

Thirty-one studies were included to assess the diagnostic accuracy of RP-NMRC as per criteria stated *a priori*. Twenty-three of the included studies reported 2x2 data and could be included in the meta-analyses as reported in the 'Results' section (see 'Approach to assessment' for methodology). Fourteen of the studies that could be meta-analysed included UIs and 9 did not. The implications of studies that did and did not include UIs, for the detection of *any DR* and *DR requiring urgent referral*, are considered under the relevant headings below. Twelve studies reported the results per patient, including 6 out of 8 studies that did not provide 2x2 data; the other studies reported the results per eye examined. The potential for differences across the range of studies included for meta-analysis was investigated by way of subgroup analyses, notably according to use of chemical mydriasis and in the number of fields photographed. Potential variation according to the year of publication and study sample size were also examined. Subgroup analyses based on the area of reader specialisation could not be undertaken, due to the limited number of studies that used a reader other than an ophthalmologist or retinal specialist. The overall results and those of the subgroup analyses performed are discussed below. The evidence was also summarised using the body of evidence matrix as per NHMRC standards in Table 90.

Table 90 Body of evidence matrix for diagnostic accuracy

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base [a]	One or more level I studies with a low risk of			

	bias or several level II studies with a low risk of bias			
Consistency [b]		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)

[b] If there is only one study, rank this component as 'not applicable'.

Source: adapted from NHMRC (2009)

Detection of any DR including UIs

Meta-analysis (n=13 studies) that compared RP-NMRC with SLBM and/or CEE to detect any DR was conducted provided that the UIs were included. As UIs are a clinical indication for referral to an ophthalmologist, they were treated as a positive result in the meta-analysis. Given that results *without* mydriasis are considered the most relevant outcome for the purposes of this assessment, these were preferentially used in the meta-analysis when studies provided results with and without mydriasis as the most relevant outcome in the context of this assessment. Overall pooled results showed that RP-NMRC can accurately confirm the presence of any DR (sensitivity 91.2%, 95%CI 81.7, 96.1; LR+ 3.88, 95%CI 2.79, 5.40), with a trade-off in the ability of the test to *rule out* DR (specificity 76.5%, 95%CI 67.4, 83.6; LR– 0.11, 95%CI 0.05, 0.24). However, it should be noted that in 7 of the studies included in the meta-analysis, the photographs were read by ophthalmologists or retinal specialists, as opposed to GPs or other professionals with minimal training in a community or rural primary care setting. Subgroup analyses were undertaken to investigate the effect of chemical mydriasis, publication year, sample size and the number of fields photographed on these summary measures. For detection of any DR, little or no difference among studies was observed based on whether photographs were taken with the use of chemical mydriasis (sensitivity 89.4%, 95%CI 72.2, 96.5; specificity 74.2%, 95%CI 63.5, 82.7) or without (sensitivity 91.7%, 95%CI 79.2, 97.0; specificity 74.4%, 95%CI 61.2, 84.2). Similarly, a lack of effect was observed based on the study size (refer to Table 19). An increase in sensitivity from 82.7% (95%CI 70.9, 90.3) to 96.6% (95%CI 87.0, 99.2) was observed when more than one field was photographed, and the specificity decreased from 78.5% (95%CI 68.7, 85.9) to 65.5% (95%CI 52.0, 76.0). Similar results were observed when subgroup analyses were

performed based on studies published prior to and after 2000 (see Table 19). Given that only 1 study was published before 2000, the differences in results by publication date are likely explained by the number of fields photographed, as only 1 study published before 2000 photographed more than one field. Logically, the likelihood of identifying DR increases, with a corresponding decrease in false negative results, if the examination covers larger or overlapping areas of the fundus.

The mean false negative rate of 8.3% showed that, out of every 12 patients who undergo RP-NRMC, 1 can be expected to be incorrectly diagnosed as not having DR. This is of clinical significance because patients who wrongly receive an 'all clear' diagnosis may not return for retesting for some time (at least 1 year, unless symptoms arise earlier), increasing the risk of permanent vision loss. The mean false positive rate was 25.6%. In other words, one-quarter of those who would be referred to an ophthalmologist do not actually have DR. However, as RP-NMRC is proposed to triage patients to ophthalmological management, the high false positive rate is not likely to have adverse clinical implications.

LR scattergrams that plotted LR+ against the LR– were inconclusive regarding the utility of RP-NMRC to confirm or exclude the presence of any level of DR; LR– (0.1–0.2) considered alone supports the conclusion above that RP-NMRC operates as an effective triage. When LR+ and LR– were plotted on a scattergram according to number of fields photographed, LR+ and LR– values were observed to shift from the lower right quadrant (plot of 1-field results) to the lower left quadrant (plot of multiple-field results). This suggests that the utility of RP-NMRC as a triage is increased when fundus cameras with multiple fields are used. However, it should be noted that the analysis of multiple fields included 1 study that used seven overlapping stereoscopic fields, a standard of photography currently limited to research and specialist grading settings, and certainly not applicable in rural and remote settings where such state-of-the art equipment would not be available. Whereas seven overlapping stereoscopic fields is useful for *grading* according to standards such as the Airlie House System and Early Treatment of Diabetic Retinopathy Study system (ETDRS 1991b; Wu et al. 2013), this kind of imaging is not essential to determine the absence or presence of DR (i.e. in a triaging environment).

The benefits of even a modest increase in number of fields have been documented by Vujosevic et al. (2009), who concluded that one central 45-degree image is only sufficient to determine the presence or absence of DR, and three fields may be an effective tool in a screening setting to determine *critical levels* of DR and diabetic macular oedema (DMO) for prompt referral to an ophthalmologist or retinal specialist. The benefit of multiple fields for

the detection of DR requiring urgent referral (i.e. severe NPDR or worse), as highlighted in the results of our meta-analysis, are discussed under the following heading. In contrast to these results, a recent systematic review (Raj & de Verteuil 2009) comparing single, two-field and three-field retinal photography reported that consensus is still lacking regarding the minimum/optimal number of fields for use in DR screening settings. The currently available evidence is insufficient to draw conclusions about the optimum number of fields, recognising the trade-off of reduced specificity when field number and sensitivity increase.

Detection of severe NPDR or worse including UIs requiring non-urgent referral

Meta-analysis was undertaken for 11 studies that compared RP-NMRC with SLBM and/or CEE in the detection of advanced DR that would require an urgent referral, and provided 2x2 data with UIs included. In contrast to the analysis for detection of *any* DR, the UIs were regarded as a negative result as these *would not* form a basis for *urgent* referral. As per the analyses for any DR, when a study provided data with and without the use of chemical mydriasis, the results without mydriasis were used in the meta-analysis, as this was the most relevant outcome for the purposes of this assessment.

Pooled sensitivity, specificity, LR+ and LR– for the detection of severe NPDR or worse (i.e. DR considered to require urgent referral) by RP-NMRC, compared with an SLBM and/or CEE, were calculated. The findings suggested that RP-NMRC is more likely to confirm the presence of severe NPDR or worse compared with any DR (specificity 98.1%, 95%CI 95.4, 99.2 versus 76.5%, 95%CI 67.4, 83.6), but is less sensitive (76.3%, 95%CI 60.2, 87.3 versus 91.2%, 95%CI 81.7, 96.1). The mean false negative rate was high (24%), but it would be reasonable to expect that the majority of false negative patients would be diagnosed as having less-severe disease but still be referred to an ophthalmologist. Thus, the high false negative rate would not be expected to have a large adverse impact on patient health outcomes. The rate of false positive patients was low (2%), but it is probable that these patients would have less-severe DR and still benefit from an appointment with an ophthalmologist. Subgroup analyses according to the same categories used for the analysis of any DR are discussed below.

As in the detection of any DR, detection of DR requiring urgent referral *did not* improve upon the use of chemical mydriasis. There was an apparent improvement in diagnostic accuracy for studies that assessed more than 400 eyes, but the CIs reported were exceedingly large and do not provide a reliable basis on which to draw conclusions. Similarly, it is uncertain why the CIs observed for studies that used only 1-field photography were larger than for studies using multiple fields.

An LR scattergram showed that summary LR+ and LR– values for these studies fell within the upper right quadrant of the graph. This result indicates that RP-NMRC should reliably confirm if a patient has severe NPDR or worse, but cannot eliminate the possibility that the patient has severe disease (LR+ and LR– values >10 and >0.1, respectively). The HSROC curve analysis similarly showed an excellent level of detection of severe NPDR or worse by RP-NMRC (AUC = 0.96, 95%CI 0.94, 0.98). In contrast to the detection of any DR, there was no threshold effect for the detection of advanced DR based on field number, possibly because advanced DR should be easier to detect within a single field compared with small changes associated with early stage disease that may not be present in all photographed fields.

Improvements in sensitivity and LR– were seen when the cut-off for the level of disease deemed to be urgent increased from moderate or severe NPDR to PDR. The LR scattergrams (see Figure 13) showed that the LR– summary point for studies with PDR as the cut-off point was located left of the summary point for studies where moderate or severe NPDR was the cut-off. This indicates that the ability of RP-NMRC to correctly identify patients increases when a higher cut-off point for disease severity applies. A 50% decrease in LR– from 0.33 to 0.16 effectively means that, for patients testing negative when the severity threshold is set at PDR, it is twice as likely that they are truly negative compared with patients who test negative when the lower disease severity threshold is applied. However, such a conclusion would be inadvisable due to the wide CIs observed. Furthermore, setting a threshold that would only increase the probability of correctly ruling out proliferative disease is less desirable than increasing the probability of ruling out a wider spectrum of disease, including NPDR, that would still require urgent referral. In other words, a testing scenario that applies a higher cut-off is more likely to include supposedly 'test-negative' patients that actually have severe NPDR, whereas the latter scenario is likely to include a higher proportion of patients with negative test results who are truly disease free or at a stage of onset not requiring immediate ophthalmological referral.

Analysis of studies not included for meta-analysis

A total of 18 studies that met the inclusion criteria did not provide adequate data for inclusion in meta-analyses (i.e., they either did not provide 2x2 data or did not include UIs). Of these, 15 studies reported results for any DR and 10 reported results for the detection of advanced DR requiring urgent referral, for which 1 study had a cut-off point lower than the NHMRC recommendation (severe NPDR or worse)(NHMRC 2008). As in the meta-analyses described above, studies published after 2000 typically used multiple-field photography and the 3 studies published prior to 2000 all used single-field photography. Sixteen out of the 18 included studies reported the proportion of UIs obtained, and 6 of these had a greater

proportion of UIs (23.5–36%) than any study included in the meta-analyses above. This may have implications for the specificity of RP-NMRC given that UIs are considered to be referrable and are counted as positive results for the detection of any DR. Accordingly, the results from the meta-analyses above may be subject to publication bias.

Nine studies provided 2x2 data that did not include UIs, and therefore were not included in the meta-analyses above. However, where there was an adequate number of studies with outcomes on subgroups of interest, a meta-analysis was performed to investigate whether inclusion or exclusion of UIs had any effect on the sensitivity and specificity of RP-NMRC. The median and pooled sensitivity and specificity for the detection of any DR were almost identical in all subgroups investigated, suggesting no differences of consequence between studies with and without 2x2 data.

By contrast, there were pronounced differences in median and pooled sensitivity of RP-NMRC compared with SLBM and/or CEE to detect advanced DR (severe NPDR or worse). This is due to the majority of studies reporting 100% sensitivity, resulting in a high median value; however, the remaining studies reported much lower sensitivities, and the pooled sensitivity obtained from meta-analysis of this data is likely to reflect a more appropriate measure (81.9%, 95%CI 75.6, 86.9). Specificity was not greatly affected due to the low number of false positives across all studies. Subgroup analysis was not performed for advanced DR due to the few included studies.

The specificity for the detection of any DR in the studies that excluded UIs was much higher (92.4%, 95%CI 79.9, 97.4) than the pooled specificity derived from studies that included UIs (76.5%, 95%CI 67.4, 83.6). This is most likely due to the lower false positive rate expected when the UIs are removed from the analysis. The small difference observed for the pooled sensitivity of studies excluding UIs (86.4%, 95%CI 59.5, 96.5) versus the pooled sensitivity obtained from the meta-analysis that included UIs (91.2%, 95%CI 81.7, 96.1) is explained by the increased proportion of false negatives expected when the UIs are not included.

Consistent with results from the meta-analysis performed for any DR including UIs (see Table 19), accuracy results for any DR (not including UIs) without the use of chemical mydriasis did not differ from the overall result (i.e. with *and* without mydriasis). Also, for studies that excluded UIs from the analysis, the sensitivity to detect any DR by multiple-field RP-NMRC was higher than for 1-field, similar to the increase observed for the meta-analysis of these subgroups when UIs were included (see Table 19, Table 20). However, there was no

decrease in specificity, possibly due to the low false positive rate, which would be relatively robust to the inclusion or exclusion of UIs.

The sensitivity and specificity for detecting advanced DR by RP-NMRC compared with SLBM and/or CEE were similar for studies that included UIs (80.0%, 95%CI 63.7, 90.2 and 97.4%, 95%CI 94.7, 98.8) and those that did not (81.9%, 95%CI 75.6, 86.9 and 98.3%, 95%CI 91.8, 99.7]). This suggests that there was little difference in the proportion of patients with and without UIs who had advanced DR.

Direct comparison of RP-NMRC with and without the use of chemical mydriasis

There was a marked difference in the proportion of UIs obtained with and without the use of chemical mydriasis. The addition of chemical mydriasis reduced the proportion of UIs from a median of 5.3% (range 2.5–8.3%) to 19.3% (range 11–36%), indicating that it may be warranted to chemically dilate the pupil and re-photograph the retina of patients with UIs from RP-NMRC taken without chemical mydriasis.

No conclusions about the effect of chemical mydriasis on the sensitivity and specificity of RP-NMRC compared with SLBM and/or CEE could be made, given the small number (n=4) of studies and high variability observed among and within these studies according to the use or non-use of chemical mydriasis (see Table 22).

Direct comparison of 1-field and multiple-field RP-NMRC

For the comparison of single-field versus multiple-field RP-NMRC compared with SLBM and/or CEE, no differences in the proportion of UIs were observed (see Table 23), based on 3 included studies. However, these studies did show an increase in sensitivity for multiple-field versus 1-field RP-NMRC compared with SLBM and/or CEE for the detection of either any DR or severe NPDR or worse (see Table 23). This is consistent with the findings of the meta-analysis for the detection of any DR using 1-field versus multiple-field RP-NMRC, using SLBM and/or CEE as the reference standard. These results are logical in that the likelihood of identifying advanced DR should increase, lowering the false negative rate, if a larger area of the retina is examined. Subgroup meta-analyses of studies that included UIs found that 1-field RP-NMRC had a lower false negative rate than RP-NMRC using multiple fields when compared with SLBM and/or CEE, but this result was unreliable due to the very wide CIs. No conclusions about the effect of multiple-field images on the specificity of RP-NMRC compared with SLBM and/or CEE could be drawn due to the variability among the 3 included studies.

Agreement among readers

There were 7 studies (case series; level IV diagnostic evidence) that compared the interpretation of retinal photographs among different readers. Agreement, as measured by a kappa statistic, between GP or family physician readers and a retinal specialist was variable (range 0.40–0.95, with the majority of measures being toward the higher limit). Between non-physician graders and retinal specialists, agreement was moderate (0.66); in contrast, agreement between trained imagers and trained readers was high (0.95).

These data provide low-level evidence (based on case series only) of low to moderate quality that, in RP-NMRC programs used in settings where non-specialists or non-physicians are expected to interpret photos, training and quality assurance mechanisms are likely to be critical if a benefit from RP-NMRC is to be expected. This is of much less importance in a scenario where images are sent for remote interpretation by an ophthalmologist or retinal specialist, but training and quality assurance for those taking the images will need to be ensured in either type of RP-NMRC program.

Does RP-NMRC change patient management?

RP-NMRC allows opportunistic screening in the primary healthcare setting, which can achieve much higher rates of retinal screening in diabetes patients than requiring them to make and attend separate appointments. This could greatly increase the likelihood of patients with diabetes complying with the NHMRC recommendations to have their eyes screened annually (if Indigenous) or every 2 years (if non-Indigenous).

There is a risk of false positive results from RP-NMRC; however, this may not be of particular concern in the context of RP-NMRC as a triage tool. Those who are thought to have DR based on RP-NMRC would be expected to be referred to an eye specialist for further evaluation and possible treatment of DR. Therefore, patients will not receive unnecessary treatment when they are truly negative for DR. However, in the Australian setting, it must be emphasised that, for those found to have DR, RP-NMRC will be an additional test to the CEE. Thus, the effectiveness of RP-NMRC may only be realised if this service encourages patients to comply with the recommendation to have a CEE.

The introduction of RP-NMRC would likely mean that a small proportion of patients would receive false reassurance due to false negative results. These patients would therefore not receive a referral for further eye examinations and may have delayed management of their DR, with identification likely to be delayed by 1 year (if Indigenous) or 2 years (if non-Indigenous) unless symptoms of DR occur. However, the population being targeted for RP-NMRC are those who would be unlikely to attend an optometrist or ophthalmologist in the

absence of RP-NMRC. The small proportion of patients who receive false negative results is unlikely to be negatively impacted, compared with no screening. If, however, there is a chance they would have attended an optometrist or ophthalmologist for a CEE in the absence of RP-NMRC, and having RP-NMRC results in them not making or attending an appointment to see an eye specialist, then there are clear negative implications to their clinical management. Furthermore, having a CEE is useful at detecting eye conditions other than DR, and replacing CEE with RP-NMRC is not recommended.

Eleven studies provided moderate- to low-quality evidence (Table 91) on how RP-NMRC may change patient management. Outcomes reported were rate of attendance at screening, rates of compliance with recommended screening, rates of compliance with recommended follow-up ophthalmological appointments, and referral rates for follow-up and management.

Table 91 Body of evidence matrix for change in patient management

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base [a]			One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	
Consistency [b]		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 12)

[b] If there is only one study, rank this component as 'not applicable'.

Source: adapted from NHMRC (2009)

Three studies (Leiner et al. 2009; Mansberger et al. 2013; Spurling et al. 2010) conducted in populations of patients with diabetes, typically demonstrating poor access to health care, were considered to be of particular relevance to this review. These populations are often at high risk of DR. It is within these groups that RP-NMRC could hypothetically act as an acceptable triage tool, effectively linking patients to better eye care services. Attendance rates at RP-NMRC screening were higher than attendance at an annual ophthalmological appointment in all 3 studies. An increase in attendance was to be expected where RP-NMRC

was conducted opportunistically at annual health check-ups. These studies provided evidence that, should such a service be offered as part of that check-up, a large proportion of patients are likely to undergo screening (Mansberger et al. 2013; Spurling et al. 2010). Of note for the Australian healthcare setting is the screening service conducted in an urban Indigenous health clinic, as reported by Spurling et al. (2010). The study demonstrated that 94% of patients with diabetes who attended the clinic were given a retinal health check through opportunistic RP-NMRC screening, compared with only a small percentage (15%) who had attended an annual traditional eye care appointment in the previous year.

Whereas the convenience of opportunistic screening is evident, results were varied when patients were invited to attend RP-NMRC screening rather than have opportunistic screening. In one cohort study (Tu et al. 2004) in which patients were invited to undergo screening by either RP-NMRC or CEE, more patients underwent RP-NMRC. The difference in attendance was small but statistically significant (50% vs 45%). Two non-comparative studies reported a larger response to an invitation to undergo RP-NMRC screening (Lee, SJ et al. 2000; Leese et al. 2005). Leese et al. (2005) found that a Scottish program that recommended an annual recall improved attendance rates when compared with an older RP-NMRC program offering a less frequent service (89% vs 82%). In Victoria, Australia, a high proportion of patients (87%) who had not previously accessed eye care services on a regular basis complied with further screening within the recommended 2 years (Lee, SJ et al. 2000). Although no comparator was featured in these last 2 studies, their reported screening rates could be reasonably assumed to be higher than attendance rates for CEE.

Three studies assessing patient compliance with annual eye examination recommendations (Conlin et al. 2006; Creuzot-Garcher et al. 2010; Leiner et al. 2009) indicated the importance of GPs in providing a successful RP-NMRC service. One RCT (Conlin et al. 2006) demonstrated that patients were more likely to undergo a self-organised follow-up dilated eye examination if they had undergone RP-NMRC than if they had not. As part of the RP-NMRC service from their GP, patients also received education and information about their condition and encouragement to follow-up with an ophthalmological appointment. When RP-NMRC screening programs in France and USA were assessed for their influence on the compliance of patients in attending recommended ophthalmological eye examinations, both screening programs were found to increase patient compliance. However, this increase was small in the first year after screening implementation, and for the French program less significant a year later (Creuzot-Garcher et al. 2010). The impact of such screening programs is likely to be dependent on campaigns to inform and educate GPs who recruit patients, and the patients themselves, of the program's existence and the perceived incentives for screening. Accordingly, Creuzot-Garcher et al. (2010) noted that a more revealing

comparison of patient compliance may be between campaigned areas and those not campaigned, rather than areas with access to the mobile screening unit and those without access. Leiner et al. (2009) identified the following barriers to initiating such a program: training, coordination among different specialties, operational costs and reimbursement (or lack of) for services provided.

Evidence further identifies the role that GPs play in the success of RP-NMRC screening. In a survey of Australian GPs that had received referral recommendations for their patients who had undergone RP-NMRC screening, it was found that 41% (85 patients) were not referred as recommended (Lee, SJ et al. 1999). Thirty-one of these patients were reported as being under regular review by an eye specialist (21 of whom did not recall ever having had a dilated fundus examination performed by an ophthalmologist), and the remaining 52 patients had 'fallen through the cracks'. Reasons for not referring patients may well be legitimate, but may also be influenced by GP education and emphasis on prioritising eye care for this group of patients. The results of this study are in contrast with the Australian study by Spurling et al. (2010), in which 90% of patients were reported as having undergone appropriate screening and follow-up on introduction of RP-NMRC screening in a primary care setting. This suggests that opportunistic screening by GPs who have undergone prior training and accreditation for reading retinal photographs is likely to be more effective.

Economic considerations

In the absence of any direct evidence comparing the relative effectiveness of RP-NMRC with either no testing or standard medical assessment, the economic evaluation is based on the linked evidence presented in the 'effectiveness' section of the report, namely the diagnostic accuracy of each alternative testing method.

The health states in the model were adapted to connect the model directly to the main linked evidence, namely the sensitivity and specificity of RP-NMRC for, first, the detection of any DR and, second, for DR requiring urgent referral, which in turn reflect the critical decision-making points for patient management. DR is a chronic progressive disease and testing is recommended on an ongoing basis; therefore, in order to capture the full costs and benefits of each alternative testing method, it is necessary to model the changes in patient management that occur as a result of testing over an extended period of time. This inherently increases the uncertainty of the results derived from the economic evaluation.

Given the high prevalence of diabetes in the Australian population, there is a remarkable lack of up-to-date data on the prevalence, incidence and rate of progression of DR. As the risk of DR is increased by poor glycaemic control, as well as high blood pressure and blood

lipids (NHMRC 2008), the current prevalence and incidence of DR should reflect recent medical advances in the control of these predisposing factors, which have been made since many of the studies reporting the rate of progression of DR were performed. To allow for these uncertainties, two scenarios were presented for the primary comparison with no testing, one assuming low incidence and slow progression and the other assuming high incidence and a faster rate of progression. Only the second scenario was used for the secondary comparison with standard medical care, as assuming a low incidence and slow progression minimises the observed incremental effectiveness between testing strategies, making the ICER highly sensitive to even minor changes in inputs.

For the primary comparison with no testing, the outcomes for both scenarios indicate that RP-NMRC is likely to be a cost-effective option for diagnosing DR in patients who would not otherwise receive regular eye examinations. The sensitivity analyses confirm that the results of the economic model are reasonably robust.

In the model the main difference between the RP-NMRC testing and the no testing arms is that patients who are not being tested progress to the advanced STDR (AdvSTDR) state before being treated, whereas patients in the RP-NMRC arm receive treatment when they progress to early STDR, greatly reducing the rate of progression to AdvSTDR. Due to this, the model is reasonably sensitive to the difference in the utility and costs between the early STDR and the AdvSTDR health states. In terms of the relative cost of the two health states, the base-case is highly conservative, assuming that the cost is the same for both early STDR and AdvSTDR. Even when the quality-of-life weight applied to the AdvSTDR health state is increased to that applied to early STDR, the cost per additional QALY gained is still only approximately $30,000.

The major source of uncertainty in the economic evaluation is the cost of treatment for STDR. First, in the model it is assumed that patients only receive one course of treatment. Second, as discussed above, the base-case assumes that all treatment is laser photocoagulation, but intra-vitreal injection of anti-VEGF agents is increasingly being used as the primary treatment for patients with CSMO. Based on a recent publication (Schmidt-Erfurth et al. 2014), the cost of treatment with intra-vitreal injections of ranibizumab, administered over 3 years, was estimated to be approximately $24,250. Treatment costs of this magnitude increase the ICER to $42,500 per QALY gained.

The results of the secondary comparison with standard medical practice indicate that, while RP-NMRC was more effective than dilated ophthalmoscopy performed by a GP, it was also the more expensive strategy. However, as previously discussed, the use of dilated

ophthalmoscopy by a GP as a triage test for DR is low, and its relevance as a comparator for RP-NMRC is therefore limited. In addition, due to the poor quality of data available for this comparison, the results are highly uncertain. In comparison with CEE performed by either an optometrist or an ophthalmologist, regular testing by RP-NMRC was marginally less expensive than CEE but was also slightly less effective in terms of QALYs gained. Given that CEE is more accurate than RP-NMRC, and is more likely to detect other non–DR-related lesions, it would be inappropriate for RP-NMRC to replace the use of CEE in patients who are currently compliant with testing recommendations.

Both the sensitivity analyses assessing the impact of diagnostic test accuracy (see Table 54) and the Monte Carlo microsimulation for ophthalmoscopy by a GP indicate that, due to the high frequency of testing, even tests with relatively low diagnostic accuracy are reasonably effective in preventing progression to advanced stages of DR. Any patients with DR who have a false negative test result may progress in the intervening interval, but they are still likely to be diagnosed prior to development of any major vision impairment. This indicates that ensuring compliance with testing is more important than the type of testing used. In addition, RP-NMRC will only be effective if provisions are made to ensure appropriate follow-up of results, compliance with referrals for further examination by an ophthalmologist, and prompt treatment of STDR when indicated.

The viability of RP-NMRC may also depend on the size of the primary care setting. The equipment component ($20 per service) of the proposed fee for RP-NMRC was based on a 5-year amortisation of a $50,000 camera (including set-up costs and training) and an average of 10 services per week. For non-Indigenous patients a fee may only be charged every 2 years. Therefore, a service provider must have a client base of approximately 1,000 patients with diabetes in order to cover the initial set-up costs. It is also possible that practitioners with small caseloads may be unable to adequately maintain their diagnostic skills (Tu et al. 2004).

In addition to the cost of the camera, and the current absence of a Medicare rebate for RP-NMRC, an Australian pilot study of DR screening using RP-NMRC (Askew et al. 2009) reported that GPs perceived the following as barriers to more widespread implementation of screening in general practice:

- the necessity of having a darkened room for the camera
- time required for training of GPs and practice staff
- time involved in taking and reading the photos.

It is clear that, while RP-NMRC may, in theory, be a cost-effective method of identifying cases of DR in patients who would previously not have received any eye examination, there are many other important factors in ensuring that these outcomes are realised in the practical setting, especially within remote and marginalised communities.

Estimated financial impact

Due to the presence of a pool of undiagnosed patients with DR when RP-NMRC is introduced, the initial lower uptake of RP-NMRC and the fact that (non-Indigenous) patients are only tested every 2 years, the first 3–4 years of the analysis are not reflective of the ongoing number of patients likely to be tested each year. After this time, with the majority of the initial pool of patients with DR having been diagnosed, the number of patients tested as a proportion of the prevalent cases of diabetes remains relatively stable; the cases of DR detected are largely newly incident cases. Consequently, the estimated cost to the MBS for RP-NMRC testing also becomes reasonably steady at approximately $4.3 million per year, increasing gradually in line with the increase in the number of patients with diabetes. In contrast, the costs associated with CEE continue to increase as more patients are diagnosed with DR, requiring ongoing monitoring for disease progression. The cost attributable to CEE rapidly becomes the major source of the cost to the MBS, exceeding $8 million per year by 2020–21 in the base-case scenario.

The majority of the cost to patients results from the out-of-pocket cost for CEE performed by an ophthalmologist to monitor patients who have been diagnosed with DR as a result of RP-NMRC testing. Due to the high rate of bulk-billing by GPs for patients with chronic diseases such as diabetes, the total cost to the patient population for RP-NMRC is minimal.

Most of the issues contributing to uncertainty in the results of the financial analysis relate to the estimated population likely to be tested by RP-NMRC. The two major sources of uncertainty are the proportion of patients who are not currently receiving regular eye examinations and the likely uptake of RP-NMRC testing in this population. Some studies have reported the estimated rate of compliance with the NHMRC guideline recommendations regarding the frequency of eye examinations, but there is no evidence on which to base the likely uptake of RP-NMRC within the population for which it is intended. In the primary scenario, in which a relatively high rate of uptake is assumed, the annual cost to the MBS is estimated to be in the range $4–$12.5 million over the first 6 years of listing. Assuming a high uptake, this increases to approximately $6–$14 million, whereas if the uptake is low the cost to the MBS decreases to $1–$9 million.

Another source of uncertainty is the average frequency of CEEs performed in patients diagnosed with DR, which is largely dependent on clinical judgement. The base-case scenario assumes an average of 1.5 CEEs per year in non-Indigenous patients and 2 per year in Indigenous patients. Increasing this to 2 per year and 3 per year, in non-Indigenous and Indigenous patients, respectively, has only a relatively small effect on the annual cost to the MBS. Similarly, variations in the diagnostic accuracy of RP-NMRC do not have a substantial impact on the outcome of the financial analysis.

While there is considerable uncertainty in the estimated financial implications, it is evident that listing RP-NMRC on the MBS is likely to result in considerable costs to the MBS. The majority of the cost results from the increase in the utilisation of CEE services for ongoing monitoring of patients with DR, and therefore the total costs will continue to rise as more patients are diagnosed.

It has been proposed that alternative mechanisms for the funding of non-mydriatic retinal cameras may be considered. Depending on the uptake of RP-NMRC, the provision of alternative funding for the initial set-up costs of RP-NMRC would potentially result in savings to the MBS in the order of $5–$9 million over the first 6 years of listing on the MBS. Assuming an initial set-up cost of $50,000, as proposed in the justification of the proposed MBS fee for RP-NMRC, these potential savings would be sufficient to fund the purchase of approximately 100–180 cameras. However, there would also be a requirement for ongoing financial support for replacement of outdated equipment, and ongoing training and quality assurance measures. As discussed above, an alternative funding mechanism may be necessary to ensure that access to RP-NMRC is provided to those primary care facilities where the need is greatest, and that cameras are placed in areas where they can be used most efficiently. However, the introduction of this service also needs an investment in time and space by the healthcare provider, and provision of fully funded equipment lowers the incentive to use the technology to its full potential.

Conclusions

Is RP-NMRC safe?

There was no literature that reported safety outcomes related to the use of RP-NMRC, and little literature investigating adverse events associated with the use of mydriasis for RP-NMRC or comparator tests. However, based on the available evidence, it would appear that mydriasis-related angle-closure glaucoma attack is very rare in the relevant population.

RP-NMRC was found to be highly acceptable to the majority of patients. Up to one-fifth of patients experienced some level of discomfort during the procedure, but very few experienced severe discomfort as a result of high-power Polaroid flash, which is not applicable to current digital systems. Using current systems, any discomfort should be rare according to the evidence available. Most patients would prefer RP-NMRC to CEE. Ninety per cent of a small sample of Indigenous Australian diabetes patients (n=11) were very positive about having RP-NMRC as part of their local Indigenous health service.

Is RP-NMRC effective?

Is RP-NMRC accurate?

Meta-analyses of studies investigating the diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE showed that there was little or no difference between studies based on the use of chemical mydriasis with RP-NMRC for detection of any level of DR or for DR requiring urgent referral. However, the use of mydriasis did greatly reduce the number of UIs.

Analysis by way of an LR scattergram strongly indicated that a negative test result is likely to be correct, placing RP-NMRC as a useful test for exclusion of any DR. Thus, RP-NMRC would effectively triage patients for further examination by an ophthalmologist.

Subgroup analyses for the detection of any DR based on the number of fields in the eye that were photographed showed that the sensitivity increased from 83% (95%CI 71, 90) to 97% (95%CI 87, 99), and the specificity decreased from 79% (95%CI 69, 86) to 66% (95%CI 52, 77), when more than one field was photographed, although the 95%CIs were overlapping. This is reflected in the HSROC curve and the LR scattergram, and indicates that multiple-field RP-NMRC can be successfully used as a triage tool, as there is a high likelihood that patients without DR who would not require any further investigations by an ophthalmologist would be correctly identified by RP-NMRC.

It should be noted that, in nearly all the studies included above, the photographs were read by ophthalmologists or retinal specialists, as opposed to GPs or other professionals with minimal training in settings such as community or rural primary care. Agreement studies emphasised the importance of adequate training and quality assurance if non-medical and non-specialist staff are to be a feature of an RP-NMRC program. This is less of an issue in contexts where an ophthalmologist or retinal specialist remotely interprets the photographs using telemedicine.

Does RP-NMRC change patient management?

The included evidence (1 RCT and 2 level III-3 studies) suggests that patients are much more likely to undergo RP-NMRC in a primary care setting than make and attend an appointment with an eye care specialist. One study (level III-2 evidence) indicated that patients invited to attend screening by either RP-NMRC or CEE are more likely to attend RP-NMRC.

An Australian study by Spurling et al. (2010) found that GPs' referrals resulted in greater attendance of Indigenous patients at an eye specialist when RP-NMRC was implemented, compared with 1 year earlier when a traditional surveillance model operated (90% vs 15% of patients, respectively; $p<0.001$).

Overall compliance with invitations to attend CEE versus RP-NMRC was found to be poor (45% vs 50%, respectively), and the small difference observed (OR 1.22, 95%CI 1.07, 1.40) is unlikely to be of clinical significance.

Two case series (level IV evidence) reported compliance rates of 87% and 89% for annual or 2-yearly RP-NMRC screening following an invitation; however, without comparative results for compliance with CEE or other services, it is difficult to interpret these findings.

A survey of GPs found that less than 60% were compliant with all patient referral recommendations from a screening program, but additional patients complied with recommendations without going through their GPs.

The evidence on change in management as a whole suggests that RP-NMRC may be an effective triage tool but is not as accurate as CEE for diagnosing DR, and should not replace CEE. A small number of patients receiving a false negative result from RP-NMRC will not be referred on to an eye specialist following screening, and their treatment may be delayed until later detection. Given that these patients are unlikely to have attended an eye examination in the absence of RP-NMRC, the impact of false negative results is likely to be small. Patients who receive a false positive result for DR by RP-NMRC are not likely to be

negatively affected, as DR would be excluded on subsequent referral for ophthalmologist follow-up.

Is RP-NMRC cost-effective?

RP-NMRC is likely to be a cost-effective option for diagnosing DR in patients with diabetes who would not otherwise receive regular eye examinations. The estimated incremental cost per QALY is $14,870 in the broader Australian population and $12,380 in the Indigenous population, and the cost per blindness prevented is approximately $51,600 and $46,600, respectively. The model is most sensitive to the cost of treatment and the quality-of-life weight applied to the advanced STDR health state, but the ICER remains below $45,000/QALY in all modelled scenarios.

The comparison of RP-NMRC with standard medical assessment indicates that, while RP-NMRC is more effective than dilated ophthalmoscopy performed by a GP, it is also more expensive. However, the relevance of dilated ophthalmoscopy as a comparator for RP-NMRC is limited. Given that CEE is more accurate than RP-NMRC, and is more likely to detect other non-DR related lesions, it would be inappropriate for RP-NMRC to substitute for CEE in patients currently receiving this service.

The introduction of RP-NMRC will only be effective if provisions are made to ensure compliance with regular testing, appropriate follow-up of results and prompt treatment of STDR when indicated.

Costing

If the new listing for RP-NMRC testing is approved, within 3 years the cost to the MBS is likely to exceed $10 million per year. The cost attributable to CEE initially increases markedly as more patients are diagnosed with DR and require ongoing monitoring for disease progression. This rapidly becomes the major source of the cost to the MBS. The main sources of uncertainty are the proportion of patients with diabetes who are not receiving regular eye examinations, and the likely uptake of RP-NMRC testing in this population.

The total cost to the non-Indigenous patient population increases to approximately $4.5 million by 2020–21. The majority of the cost to patients results from the out-of-pocket cost for CEE performed by an ophthalmologist to monitor patients who have been diagnosed with DR as a result of RP-NMRC testing. Due to the high rate of bulk-billing by GPs for patients with chronic diseases such as diabetes, the total cost to patients for RP-NMRC is minimal.

Depending on the uptake of RP-NMRC, the provision of alternative funding for the initial set-up costs of RP-NMRC would potentially result in savings to the MBS in the order of $5–$9 million over the first 6 years of listing on the MBS. Assuming an initial set-up cost of $50,000, these potential savings are sufficient to fund approximately 100–180 cameras.

Appendix B

Health Expert Standing Panel and Assessment Group

Health Expert Standing Panel (HESP)

Member	Expertise or affiliation
Rohan Essex	Senior Lecturer, Australian National University; Senior Staff Specialist (Ophthalmology), Canberra Hospital
Tim Fricke	Director of Specialty & Community Services, Australian College of Optometry
David Pye	Associate Professor, School of Optometry and Vision Science, University of New South Wales
Paul Zimmet	Director Emeritus, Victor Smorgon Diabetes Centre, Baker IDI Heart and Diabetes Institute; Adjunct Professor, Monash University
Geoffrey Spurling	Senior Lecturer, Discipline of General Practice, University of Queensland; Senior Medical Officer, Inala Indigenous Health Service

Assessment group

AHTA, University of Adelaide, South Australia

Name	Position
Ben Ellery	Research Officer
Joanne Milverton	Research Officer
Skye Newton	Team Leader (Medical HTA)
Judy Morona	Senior Research Officer
Debra Gum	Senior Research Officer
Jacci Parsons	Team Leader (Medical HTA)
Arlene Vogan	Health Economist
Stefan Fischer	Visiting Fellow (Health Economics), Ludwig Boltzmann Institut für Health Technology Assessment, Austria
Tracy Merlin	Managing Director

Noted conflicts of interest

There were no conflicts of interest.

Appendix C

Search strategies

Bibliographic databases

Electronic database	Period covered
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1985 – 2/2014
Current Contents	1985 – 2/2014
Embase	1985 – 2/2014
PubMed	1985 – 2/2014
Web of Science – Science Citation Index Expanded	1985 – 2/2014
Cinahl	1985 – 2/2014
Econlit	1985 – 2/2014
PsychINFO	1985 – 2/2014

Additional sources of literature

Source	Location
Internet	
NHMRC – National Health and Medical Research Council (Australia)	http://www.nhmrc.gov.au/
US Department of Health and Human Services (reports and publications)	http://www.hhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.greylit.org/
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.nihr.ac.uk/Pages/NRRArchive.aspx
Google Scholar	http://scholar.google.com/
Australian and New Zealand Clinical Trials Registry	www.anzctr.org.au
Pearling	
All included articles had their reference lists searched for additional relevant source material	
Guidelines search (last step linked evidence)	
Guidelines International Network (G-I-N)	http://www.g-i-n.net/
NHMRC Clinical Guidelines Portal	http://www.clinicalguidelines.gov.au

HTA websites

AUSTRALIA	

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/sphpm/divisions/mars/cce.html
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications.html
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUIs)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://dsi.dk/english/
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.thl.fi/en_US/web/en
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://www.otago.ac.nz/christchurch/research/nzhta/
NORWAY	
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
SPAIN	

Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://www.oregon.gov/oha/OHPR/HRC/Pages/index.aspx
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Specialty websites

Optometrists Association Australia	http://www.optometrists.asn.au
Australian College of Optometrists	http://www.aco.org.au
Optometry Board of Australia	http://www.optometryboard.gov.au
American Optometric Association	http://www.aoa.org/
World Council of Optometry (WCO)	http://www.who.int/workforcealliance/members_partners/member_list/wcoptometry/en/

American Academy of Ophthalmology	http://www.aao.org/
Centre for Eye Research Australia	http://www.cera.org.au/
Australian Society for Ophthalmologists	http://www.aso.asn.au/
Diabetes Australia	http://www.diabetesaustralia.com.au/
Australian Diabetes Society	https://www.diabetessociety.com.au/
American Diabetes Association	http://www.diabetes.org/
Royal Australian College of General Practitioners	http://www.racgp.org.au/
Vision 20/20 Australia	http://www.vision2020australia.org.au/
Baker IDI Heart and Diabetes Institute	https://www.bakeridi.edu.au/
Type 1 diabetes network (reality check forum)	http://t1dn.org.au/
Retina Australia	http://www.retinaaustralia.com.au/index.htm

Additional databases searched for economic evaluations

Electronic database	Time period
Cost-effectiveness Analysis (CEA) Registry	1985 – 2/2014
Database of Abstracts of Reviews of Effects or Reviews of Effects (DARE)	1985 – 2/2014
Health Technology Assessment database	1985 – 2/2014
NHS Economic Evaluation Database (NHS EED)	1985 – 2/2014
European Network of Health Economics Evaluation Databases (EURONHEED)	1985 – 2/2014

Appendix D

Diagnostic accuracy results from studies included in the review

Table 92 Diagnostic accuracy of RP-NMRC compared with SLBM and/or CEE for all included studies

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
Ahmed et al. (2006) USA Level III-1 Some risk of bias	N=482 eyes (243 patients)	Fundus photography with a non-mydriatic camera – 3-field imaging without mydriasis Reader GPs	Dilated fundoscopic examination	171 / 482 (35.5%) Excluded from 2x2 data	Any DR without UIs 85.7% [72.8, 94.0] Sev NPDR+ 100% [40.2, 100]	Any DR without UIs 86.6% [81.9, 90.5] Sev NPDR+ 100% [98.8, 100]	Any DR without UIs 54.5% [42.8, 65.9] Sev NPDR+ 100% [40.2, 100]	Any DR without UIs 97.0 [93.3, 98.8] Sev NPDR+ 100% [98.8, 100]	Any DR without UIs 6.42 [4.62, 8.91] Sev NPDR+ -	Any DR without UIs 0.16 [0.08, 0.33] Sev NPDR+ 0.00
Aptel et al. (2008) France Level II Some risk of bias	N=158 eyes (79 patients)	Fundus photography with a non-mydriatic camera – 1- and 3-field imaging with and without mydriasis Reader Ophthalmologists	SLBM	No mydriasis: 1-field 11.4% 3-field 13.3% With mydriasis: 1-field 2.5% 3-field 3.8% Unknown if included in analysis	Any DR No mydriasis: 1-field 76.92% 3-field 92.31% With mydriasis: 1-field 89.74% 3-field 97.44%	Any DR No mydriasis: 1-field 99.16% 3-field 97.48% With mydriasis: 1-field 98.32% 3-field 98.32%	-	-	Any DR No mydriasis: 1-field 91.6 3-field 36.6 With mydriasis: 1-field 53.4 3-field 0.10	Any DR No mydriasis: 1-field 0.23 3-field 0.08 With mydriasis: 1-field 58.0 3-field 0.03
Cavallerano, AA et al. (2003) USA Level II Some risk of bias	N=535 eyes (268 patients)	Fundus photography with a non-mydriatic camera – 3-field imaging without mydriasis	CEE by a retinal specialist	41 / 535 (8%) Included in 2x2 data	Any DR with UIs 94.2% [91.0, 96.5] Sev NPDR+ 81.7%	Any DR with UIs 79.9% [74.2, 85.0] Sev NPDR+ 89.0%	Any DR with UIs 86.7% [82.6, 90.1] Sev NPDR+ 57.3%	Any DR with UIs 90.9% [85.9, 94.5] Sev NPDR+ 96.4%	Any DR with UIs 4.69 [3.61, 6.10] Sev NPDR+ 7.40	Any DR with UIs 0.07 [0.05, 0.11] Sev NPDR+ 0.21

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
		Reader Certified JVN readers			[71.6, 89.4]	[85.7, 91.7]	[47.8, 66.4]	[94.2, 98.0]	[5.59, 9.80]	[0.13, 0.33]
Chia & Yap (2004) Singapore Level II Low risk of bias	N=78 eyes (39 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis Reader Ophthalmologist	SLBM and indirect ophthalmoscopy	4 / 78 (5.1%) Included in 2x2 data	Any DR with UIs 95.8% [85.7, 99.4] Sev NPDR+ MO 100% [78.0, 100]	Any DR with UIs 86.7% [69.3, 96.2] Sev NPDR+ MO 100% [94.3, 100]	Any DR with UIs 92.0% [92.2, 97.7] Sev NPDR+ MO 100% [78.0, 100]	Any DR with UIs 92.9% [76.5, 98.9] Sev NPDR+ MO 100% [94.3, 100]	Any DR with UIs 7.19 [2.88. 17.93] Sev NPDR+ MO -	Any DR with UIs 0.05 [0.01, 0.19] Sev NPDR+ MO 0.00
Conlin et al. (2006) USA Level III-1 High risk of bias	N=140 patients	Fundus photography with a non-mydriatic camera – 3-field imaging mydriasis NS Reader Beetham Eye Institute certified readers	CEE	80 / 223 (35.9%) Excluded from 2x2 data	Any DR without UIs 92.9% [80.5, 98.4] Sev NPDR+ 100% [54.1, 100]	Any DR without UIs 61.2% [50.9, 70.9] Sev NPDR+ 87.3% [80.5, 92.4]	Any DR without UIs 60.6 [39.0, 62.2] Sev NPDR+ 26.1% [10.3, 48.4]	Any DR without UIs 95.2 [86.7, 98.9] Sev NPDR+ 100% [96.9, 100]	Any DR without UIs 2.39 [1.84, 3.11] Sev NPDR+ 7.88 [5.06, 12.29]	Any DR without UIs 0.12 [0.04, 0.35] Sev NPDR+ 0.00
Diamond et al. (1998) Australia Level III-I Some risk of bias	N=328 eyes (164 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging with mydriasis if needed Reader Ophthalmologist	Indirect ophthalmoscopy	13% Eyes with 'inadequate' images were re-photographed with mydriasis and included in the 2x2 data	Any DR with UIs 56.8% [41.0, 71.6]	Any DR with UIs 89.4% [85.3, 92.8]	Any DR with UIs 45.5% [32.0, 59.4]	Any DR with UIs 93.0% [89.3, 95.8]	Any DR with UIs 5.38 [3.52, 8.23]	Any DR with UIs 0.48 [0.34, 0.68]
Ding et al. (2012) Thailand	N=531 patients	Fundus photography with a	SLBM	A: 1-field without	Any DR with UIs:	Any DR with UIs:	-	-	Any DR with UIs:	Any DR with UIs:

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
Level III-I Some risk of bias		non-mydriatic camera – 1- and 2-field imaging with and without mydriasis <u>Reader</u> NS		mydriasis 27.1% [23.4, 31.1] B: 1-field with mydriasis 8.3% [6.1, 11.0] C: 2-field without mydriasis 28.2% [24.5, 32.3] D: 2-field with mydriasis 8.9% [6.6, 11.6] Included in analysis	A: 82.4% [74.3, 88.7] B: 79.0% [70.6, 85.9] C: 93.3% [87.2, 97.1] D: 86.6% [79.1, 92.1] Sev NPDR+ Ma: A: 75.6% [59.7, 87.6] B: 73.2% [57.1, 85.5] C: 87.8% [73.8, 95.9] D: 90.2% [76.9, 97.3]	A: 58.3% [53.3, 63.1] B: 69.7% [65.0, 74.1] C: 56.8% [51.9, 61.6] D: 68.4% [63.7, 72.9] Sev NPDR+ Ma: A: 68.8% [64.5, 72.9] B: 84.3% [80.8, 87.4] C: 64.7% [60.3, 68.9] D: 81.6% [77.9, 85.0]			A: 2.0 B: 2.6 C: 2.2 D: 2.7 Sev NPDR+ Ma: A: 2.4 B: 4.7 C: 2.5 D: 4.9	A: 0.3 B: 0.30 C: 0.12 D: 0.20 Sev NPDR+ Ma: A: 0.35 B: 0.32 C: 0.19 D: 0.12
Freyberger et al. (1995) Germany Level III-2 Low risk of bias	N=80 patients	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis <u>Reader</u> Ophthalmologist	Ophthalmos-copy by a retinal specialist	83 patients had both tests and were included in 2x2 data	Any DR without UIs 95.7% [78.0, 99.3]	Any DR without UIs 93.3% [83.8, 98.1]	Any DR without UIs 84.6% [65.1, 95.6]	Any DR without UIs 98.3% [90.6, 99.7]	Any DR without UIs 14.35 [5.54, 37.13]	Any DR without UIs 0.05 [0.01, 0.32]
Gomez-Ulla et al. (2002) Spain Level II Some risk of bias	N=126 eyes	Fundus photography with a non-mydriatic camera – 4-field imaging without mydriasis	SLBM	14 / 140 (10%) Excluded from 2x2 data	Any DR without UIs 100% [94.7, 100] Sev NPDR+ 76.9%	Any DR without UIs 100% [93.7, 100] Sev NPDR+ 100%	Any DR without UIs 100% [94.7, 100] Sev NPDR+ 100%	Any DR without UIs 100% [93.7, 100] Sev NPDR+ 97.4%	Any DR without UIs - Sev NPDR+ -	Any DR without UIs 0.00 Sev NPDR+ 0.23

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
		Reader Ophthalmologist			[46.2, 94.7]	[96.8, 100]	[69.0, 100]	[92.6, 99.4]		[0.09, 0.62]
Harding et al. (1995) USA Level II Some risk of bias	N=320 diabetes patients	Fundus photography with a non-mydriatic camera – 3-field imaging with mydriasis Reader Experienced ophthalmic clinical assistant	SLBM	46 / 320 (14.4%) Included in 2x2 data	Sev NPDR+ 46.7% [21.3, 73.4]	Sev NPDR+ 100% [98.8, 100]	Sev NPDR+ 100% [58.9, 100]	Sev NPDR+ 97.4% [95.0, 98.9]	Sev NPDR+ -	Sev NPDR+ 0.53 [0.33, 0.86]
Herbert et al. (2003) UK Level II Low risk of bias	N=288 eyes (145 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging with mydriasis as required Reader Retinal specialist	SLBM	13 / 301 (4%) Excluded from 2x2 data	Any DR without UIs 38.2% [26.7, 50.8]	Any DR without UIs 95.5% [91.8, 97.8]	Any DR without UIs 72.2% [54.8, 85.8]	Any DR without UIs 83.3% [78.2, 87.7]	Any DR without UIs 8.4 [4.3, 16.6]	Any DR without UIs 0.65 [0.54. 0.78]
Kuo et al. (2005) Taiwan Level III-2 Low risk of bias	N=200 eyes (100 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging, mydriasis NS Reader 1 Endocrinologist Reader 2 Retinal specialist	SLBM	Reader 1: 47 / 200 (23.5%) Reader 2: 16 / 200 (8%) Excluded from 2x2 data	Any DR without UIs Reader 1: 45.0 [33.9, 56.5] Reader 2: 53.8 [43.1, 64.2]	Any DR without UIs Reader 1: 75.3 [63.9, 84.7] Reader 2: 89.0 [80.7, 94.6]	Any DR without UIs Reader 1: 66.7 [52.5, 78.9] Reader 2: 83.3 [71.5, 91.7]	Any DR without UIs Reader 1: 55.6 [45.2, 65.5] Reader 2: 65.3 [56.3, 73.4]	Any DR without UIs Reader 1: 1.83 [1.14, 2.92] Reader 2: 4.89 [2.65, 9.04]	Any DR without UIs Reader 1: 0.73 [0.58, 0.93] Reader 2: 0.52 [0.41, 0.65]
Lawrence (2004)	N=103	Fundus	CEE	H-DVRI (high	Any DR with	Any DR with	Any DR with	Any DR with	-	-

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
USA Level III-I Low risk of bias	patients (H-DVRI) N=151 patients (L-DVRI)	photography with two non-mydriatic cameras – 1-field imaging without mydriasis; 3-field imaging with mydriasis <u>Reader</u> Ophthalmologist		resolution) 0 / 103 (0%) L-DVRI (low resolution) 1 / 151 (0.7%) Included in analysis	UIs H-DVRI: No mydriasis 81% With mydriasis 87% L-DVRI: No mydriasis 79% With mydriasis 80%	UIs H-DVRI: No mydriasis 45% With mydriasis 69% L-DVRI: No mydriasis 68% With mydriasis 85%	UIs H-DVRI: No mydriasis 66% With mydriasis 78% L-DVRI: No mydriasis 61% With mydriasis 78%	UIs H-DVRI: No mydriasis 66% With mydriasis 81% L-DVRI: No mydriasis 84% With mydriasis 87%		
Lee, VS et al. (1993) USA Level III-1 Low risk of bias	N=795 eyes (410 patients)	Fundus photography with a non-mydriatic camera – 2-field imaging with mydriasis <u>Reader</u> University of Wisconsin Fundus Photograph Reading Centre	SLBM and indirect ophthalmos-copy	Photography 61 / 795 (7.7%) Ophthalmos-copy 9 / 795 (1.1%) Included in 2x2 data	Any DR with UIs 87.2% [84.0, 89.9] PDR 75.9% [62.4, 86.5]	Any DR with UIs 80.4% [75.1, 85.0] PDR 99.1% [98.1, 99.7]	Any DR with UIs 89.9% [87.0, 92.4] PDR 85.4% [72.2, 93.9]	Any DR with UIs 75.8% [70.4, 80.7] PDR 98.3% [97.0, 99.1]	Any DR with UIs 4.44 [3.47, 5.68] PDR 80.37 [37.87, 170.6]	Any DR with UIs 0.16 [0.13, 0.20] PDR 0.24 [0.15, 0.39]
Lin et al. (2002) USA Level III-I Some risk of bias	N=197 patients	Fundus photography with a non-mydriatic camera – 2-field imaging without mydriasis <u>Reader</u> Ophthalmologist	SLBM	16 / 197 (8.1%) Included in 2x2 data	Any DR with UIs 100% [92.8, 100] Sev NPDR+ 28.8% [4.5, 70.7]	Any DR with UIs 46.9% [38.7, 55.3] Sev NPDR+ 99.5% [97.1, 99.9]	Any DR with UIs 39.1% [30.6, 48.1] Sev NPDR+ 66.7% [11.6, 94.5]	Any DR with UIs 100% [94.7, 100] Sev NPDR+ 97.4% [94.1, 99.2]	Any DR with UIs 1.88 [1.62, 2.19] Sev NPDR+ 54.29 [5.56, 530.15]	Any DR with UIs 0.00 Sev NPDR+ 0.72 [0.45, 1.15]
Lopez-Bastida, Cabrera-Lopez &	N=1,546 eyes (773	Fundus photography with a	SLBM and indirect	7.2% Excluded from	Any DR without UIs	Any DR without UIs	Any DR without UIs	Any DR without UIs	-	-

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
Serrano-Aguilar (2007) Spain Level II Low risk of bias	patients)	non-mydriatic camera – 2-field imaging without mydriasis (also with if needed) Reader Retinal specialist	ophthalmos-copy	analysis 56 patients had mydriasis due to small pupils	92% [90, 94] Sev NPDR+ 100% Any DR + mydriasis of UIs 100%	96% [95, 98] Sev NPDR+ 100%	955 93, 97] Sev NPDR+ 100%	94% [93, 96] Sev NPDR+ 100%		
Maberley et al. (2002) Canada Level III-2 Low risk of bias	N=200 eyes (100 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging with mydriasis Reader Retinal specialists at Queen's University, Ontario, and the Lu Esther T. Mertz Retinal Research Unit, New York	SLBM	Reader 1 3 / 200 (1.5%) Reader 2 1 / 200 (0.5%) Included in 2x2 data	Any DR with UIs 83.8% [73.8, 91.1] PDR 100% [48.0, 100]	Any DR with UIs 79.2% [70.8, 86.0] PDR 99.5% [97.2, 99.9]	Any DR with UIs 72.8% [62.6, 81.6] PDR 83.3% [36.1, 97.2]	Any DR with UIs 88.0% [80.3, 93.4] PDR 100% [98.1, 100]	Any DR with UIs 4.02 [2.80, 5.77] PDR 195.0 [27.6, 1377.4]	Any DR with UIs 0.21 [0.12, 0.34] PDR 0.0
Mizrachi et al. (2013) Israel Level III-3 High risk of bias	N=362 patients	Fundus photography with a non-mydriatic camera – 2-field imaging, mydriasis NS Reader Retinal specialist	Retinal examination	144 / 1,002 photographs (14.4%) Unknown if included in analysis	Any DR 99.3%	Any DR 88.3%	Any DR 85.3%	-	-	-
Mohan et al. (1988) UK	N=165 eyes (85 patients)	Fundus photography with a non-mydriatic	Direct ophthalmos-copy by an	Photography: 16 / 165 (9.7%)	Any DR with UIs 87.4%	Any DR with UIs 61.4%	Any DR with UIs 75.5%	Any DR with UIs 78.2%	Any DR with UIs 2.27	Any DR with UIs 0.21

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
Level III-1 Low risk of bias		camera – 1-field imaging without mydriasis Reader Retinal specialist	ophthalmolo-gist with mydriasis	Ophthalmos-copy: 9 / 165 (5.5%) Included in 2x2 data	[79.0, 93.3]	[49.0, 72.8]	[66.3, 83.2]	[65.0, 88.2]	[1.67, 3.07]	[0.12, 0.36]
Mollentze, Stulting & Steyn (1990) South Africa Level III-1 Low risk of bias	N=172 eyes (86 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging with and without mydriasis Reader Ophthalmologist	Direct ophthalmos-copy with mydriasis	Photography: Without mydriasis 19 / 172 (11.0%) With mydriasis 6 / 172 (3.5%) Ophthalmosco py: 12 / 172 (8.0%) Included in 2x2 data	No mydriasis: Any DR with UIs 54.0% [40.9, 66.6] PDR 100.0% [16.6, 100.0] With mydriasis: Any DR with UIs 46.3% [35.3, 57.7] PDR 100.0% [19.3, 100.0]	No mydriasis: Any DR with UIs 75.2% [66.0, 83.0] PDR 95.3% [91.0, 98.0] With mydriasis: Any DR with UIs 78.9% [69.0, 86.8] PDR 89.4% [83.8, 93.6]	No mydriasis: Any DR with UIs 55.7% [42.5, 68.5] PDR 11.1% [1.84, 48.26] With mydriasis: Any DR with UIs 66.7% [52.9, 78.6] PDR 10.0% [1.5, 31.7]	No mydriasis: Any DR with UIs 73.9% [64.7, 81.8] PDR 100.0% [97.7, 100.0] With mydriasis: Any DR with UIs 61.7% [52.2, 70.6] PDR 100.0% [97.6, 100.0]	No mydriasis: Any DR with UIs 2.18 [1.46, 3.25] PDR 21.38 [10.9, 42.1] With mydriasis: Any DR with UIs 2.20 [1.38, 3.49] PDR 9.44 [6.10, 14.62]	No mydriasis: Any DR with UIs 0.61 [0.46, 0.82] PDR 0.00 With mydriasis: Any DR with UIs 0.68 [0.54, 0.85] PDR 0.00
Moriarty et al. (1993) UK Level II Low risk of bias	N=74 eyes (37 patients)	Fundus photography with a non-mydriatic camera – fields NS; with mydriasis Reader Ophthalmologist	SLBM, indirect and direct ophthalmos-copy	0% Included in 2x2 data	Any DR with UIs 100% [76.7, 100] PDR+ Ma 91.7% [61.5, 98.6]	Any DR with UIs 93.3% [83.8, 98.1] PDR+ Ma 98.4% [91.3, 99.7]	Any DR with UIs 77.8% [52.4, 93.5] PDR+ Ma 91.7% [61.5, 98.6]	Any DR with UIs 100% [93.6, 100] PDR+ Ma 98.4% [91.3, 99.7]	Any DR with UIs 15.0 [5.82, 38.7] PDR+ Ma 56.83 [8.07, 400.1]	Any DR with UIs 0.00 PDR+ Ma 0.08 [0.01, 0.55]
Murgatroyd et al. (2004)	N=398 patients	Fundus photography with a non-mydriatic	SLBM	A: 1-field without mydriasis	Any DR with UIs: A: 83%	Any DR with UIs: A: 91%	Any DR with UIs: A: 85%	Any DR with UIs: A: 90%	-	-

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
UK Level II Low risk of bias		camera – 1-field with and without mydriasis; 3-field with mydriasis <u>Reader</u> Ophthalmologist and diabetologist		36% B: 1-field with mydriasis 7% C: 3-field with mydriasis 6.5% Included in analysis	[78, 88] B: 85% [82, 90] C: 90% [86-93 Sev NPDR+: A: 77% [71, 84] B: 81% [76, 87] C: 83% [78, 88]	[88, 94] B: 91% [89, 94] C: 90% [88, 93] Sev NPDR+: A: 95% [93, 97] B: 92% [90, 94] C: 93% [91, 96]	[80, 90] B: 87% [83, 91] C: 86% [82, 90] Sev NPDR+: A: 85% [79, 91] B: 79% [73, 85] C: 82% [77, 87]	[87, 93] B: 91% [88, 94] C: 93% [91, 95] Sev NPDR+: A: 92% [89, 95] B: 93% [91, 95] C: 94% [92, 96]		
O'Hare et al.(1996) UK Level III-1 Low risk of bias	N=1,010 patients with diabetes: N=517 examined by GPs N=493 examined by opticians	Fundus photography with a non-mydriatic camera – 1-field imaging with mydriasis <u>Reader 1</u> GPs <u>Reader 2</u> Opticians	Ophthalmos-copy by GP (this was a comparator for the purposes of this review, as specified *a priori*. O'Hare et al. used ophthalmos-copy as the reference standard)	NS Unknown if included in analysis	Sev NPDR+ Ma GP: 68% Optician: 75% Both: 71%	Sev NPDR+ Ma GP: 97% Optician: 99% Both: 99%	Sev NPDR+ Ma GP: 94% Optician: 82% Both: 88%	Sev NPDR+ Ma GP: 97% Optician: 99% Both: 99%		
Penman et al. (1998) Egypt / USA Level III-2: Some risk of bias	N=427 patients (right eyes)	Fundus photography with a non-mydriatic camera – 1-field imaging with mydriasis <u>Reader</u>	Binocular indirect ophthalmos-copy	Photography: 92 / 427 (21.5%) Ophthalmos-copy: 23 / 427 (5.4%)	Any DR with UIs 81.9% [73.2, 88.7] PDR+ Ma 60.0% [15.4, 93.5]	Any DR with UIs 65.2% [59.7, 70.4] PDR+ Ma 96.7% [94.5, 98.2]	Any DR with UIs 43.4% [36.4, 50.7] PDR+ Ma 17.7% [4.0, 43.5]	Any DR with UIs 91.7% [87.4, 94.9] PDR+ Ma 99.5% [98.3, 99.9]	Any DR with UIs 2.35 [1.98, 2.80] PDR+ Ma 18.09 [7.49, 43.68]	Any DR with UIs 0.28 [0.18, 0.42] PDR+ Ma 0.41 [0.14, 1.21]

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
		University of Wisconsin Fundus Photograph Reading Center		Included in 2x2 data						
Peters et al. (1993) USA Level III-2 Some risk of bias	N=522 patients had photos N=189 patients included in analysis	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis <u>Reader</u> Diabetologist	CEE by ophthalmolo-gist	334/1,044 (32%) Excluded from analysis	Any DR without UIs 85%	Any DR without UIs 93%	-	-	-	-
Scanlon et al. (2003a) UK Level III-1 Low risk of bias	N=478 eyes (239 patients)	Fundus photography with a non-mydriatic camera – 2- and 7-field imaging with mydriasis <u>Reader</u> Ophthalmologist	SLBM	7-field: 73 / 478 (15.3%) Included in 2x2 data 2-field: 6 / 478 (1.3%) Excluded from 2x2 data	7-field: Any DR with UIs 99.4% [97.9, 99.9] Sev NPDR+ 69.6% [60.3, 77.8] 2-field: Mod NPDR+ Ma 82.8% [77.4, 87.4]	7-field: Any DR with UIs 51.5% [42.7, 60.3] Sev NPDR+ 89.5% [85.9, 92.5] 2-field: Mod NPDR+ Ma 92.9% [88.9, 95.8]	7-field: Any DR with UIs 84.3% [80.4, 87.7] Sev NPDR+ 67.8% [58.6, 76.1] 2-field: Mod NPDR+ Ma 91.9% [87.4, 95.2]	7-field: Any DR with UIs 97.1% [90.0, 99.6] Sev NPDR+ 90.3% [86.7, 93.1] 2-field: Mod NPDR+ Ma 84.7% [79.8, 88.9]	7-field: Any DR with UIs 2.05 [.72, 2.45] Sev NPDR+ 6.65 [4.81, 9.19] 2-field: Mod NPDR+ Ma 11.65 [7.34, 18.48]	7-field: Any DR with UIs 0.01 [0.00, 0.05] Sev NPDR+ 0.34 [0.26, 0.45] 2-field: Mod NPDR+ Ma 0.18 [0.14, 0.25]
Scanlon et al. (2003b) UK Level III-1 Low risk of bias	N=1,542 patients	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis; 2-field	SLBM and direct ophthalmos-copy by ophthalmolo-gist	321 / 1,542 (20.8%) Included in 2x2 data	<u>No mydriasis</u>: Any DR + UIs 82.9% [79.2, 86.3] Mod NPDR+ Ma	<u>No mydriasis</u>: Any DR + UIs 64.6% [61.7, 67.5] Mod NPDR+ Ma	<u>No mydriasis</u>: Any DR + UIs 49.7% [46.1, 53.3] Mod NPDR+ Ma	<u>No mydriasis</u>: Any DR + UIs 90.0% [87.7, 92.0] Mod NPDR+ Ma	<u>No mydriasis</u>: Any DR + UIs 2.34 [2.14, 2.57] Mod NPDR+ Ma	<u>No mydriasis</u>: Any DR + UIs 0.26 [0.21, 0.32] Mod NPDR+ Ma

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
		imaging with mydriasis Reader Specialist registrar in ophthalmology			57.5% [50.0, 64.9] With mydriasis: Any DR + UIs 87.4% [84.0, 90.3] Mod NPDR+ Ma 82.8% [76.5, 88.0]	96.5% [95.4, 97.4] With mydriasis: Any DR + UIs 63.3% [60.3, 66.1] Mod NPDR+ Ma 91.8% [90.2, 93.2]	68.2% [60.2, 75.5] With mydriasis: Any DR + UIs 50.1% [46.6, 53.6] Mod NPDR+ Ma 56.9% [50.6, 63.0]	94.5% [93.2, 95.7] With mydriasis: Any DR + UIs 92.2% [90.1, 94.1] Mod NPDR+ Ma 97.6% [96.6, 98.4]	16.34 [12.0, 22.2] With mydriasis: Any DR + UIs 2.38 [2.18, 2.59] Mod NPDR+ Ma 10.03 [8.30, 12.11]	0.44 [0.37, 0.52] With mydriasis: Any DR + UIs 0.20 [0.16, 0.25] Mod NPDR+ Ma 0.19 [0.14, 0.26]
Suansilpong & Rawdaree (2008) Thailand Level II Some risk of bias	N=495 eyes (248 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis Reader Endocrinologist	SLBM	93 / 495 (18.8%) Excluded from 2x2 data	Any DR without UIs 65.6% [54.8, 75.3] Sev NPDR+ 100% [30.5, 100]	Any DR without UIs 84.9% [80.5, 88.7] Sev NPDR+ 94.2% [91.5, 96.3]	Any DR without UIs 55.7% [45.7, 65.3] Sev NPDR+ 11.5% [2.6, 30.2]	Any DR without UIs 89.5% [85.5, 92.8] Sev NPDR+ 100% [99.0, 100]	Any DR without UIs 4.35 [3.21, 5.89] Sev NPDR+ 17.35 [11.7, 25.8]	Any DR without UIs 0.41 [0.30, 0.54] Sev NPDR+ 0.00
Tanterdtham et al. (2007) Thailand Level III-2 Some risk of bias	N=225 eyes (142 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis Reader Ophthalmologist	SLBM and indirect ophthalmos-copy by retinal specialist	59 / 284 (26.2%) Excluded from analysis	Any DR without UIs 68.6% [57.0, 78.2]	Any DR without UIs 92.3% [87.0, 95.5]	Any DR without UIs 80.0% [68.2, 88.2]	Any DR without UIs 86.7% [80.6, 91.0]	-	-
Tu et al. (2004) UK Level III-2 Some risk of bias	N=874 patients	Fundus photography with a non-mydriatic camera – 4-field imaging with mydriasis	SLBM by optometrist of referrals and sample audit (10%) of screen-	NS Excluded from 2x2 data	Sev NPDR+ 80.0 [68.7, 89.2]	Sev NPDR+ 98.7 [97.8,99.4]	Sev NPDR+ 82.8 [70.6, 91.4]]	Sev NPDR+ 98.5 [97.4, 99.2]	Sev NPDR+ 65.1 [34.7, 122.1]	Sev NPDR+ 0.20 [0.12, 0.34]

Study, country, evidence level and risk of bias	Population	Index test	Reference standard	Unreadable images (%)	Sensitivity % [95%CI]	Specificity % [95%CI]	PPV % [95%CI]	NPV % [95%CI]	LR+	LR–
		Reader Ophthalmologist	negative patients (inferred false negative rate)							
Williams, R et al. (1986) UK Level III-2 Some risk of bias	N=120 eyes (62 patients)	Fundus photography with a non-mydriatic camera – 1-field imaging without mydriasis Reader Ophthalmologist	Direct and indirect ophthalmos-copy by an ophthalmolo-gist	7/120 (5.8%) Excluded from 2x2 data	Any DR without UIs 95.8% [88.1, 99.1]	Any DR without UIs 97.6% [87.4, 99.6]	Any DR without UIs 98.6% [92.2, 99.8]	Any DR without UIs 93.2% [81.3, 98.5]	Any DR without UIs 40.23 [5.8, 279.1]	Any DR without UIs 0.04 [0.01, 0.13]

DR = diabetic retinopathy; H-DVRI = high-resolution digital-video retinal imaging; JVN = Joslin Vision Network; L-DVRI = low-resolution digital-video retinal imaging; Ma = maculopathy; MO = macular oedema; NPDR = non-proliferative DR; PDR = proliferative DR; mod NPDR+ = moderate NPDR or worse; Sev NPDR+ = severe NPDR or worse; SLBM = slit-lamp biomicroscopy; UIs = unreadable images

Appendix E

Study profiles included in the review

Table 93 Study profiles of included studies on safety

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Index test – RP-NMRC	Safety outcomes assessed
Maberley et al. (2002) Canada	Level IV: case series Quality: 5/6 (high)	N=100 Age, mean (range): 54.6 (24–82) years Sex: 69% female Ethnicity: Predominantly Cree, native to Canada	Inclusion Consecutive participants in retinopathy screening program Exclusion NS	Setting Remote communities of Moose Factory and Moosonee, Ontario Camera TRC-NW5SF, Topcon Medical systems, NJ, USA 1 x 45° images per eye Photographer Ophthalmic photographer 30 eyes re-photographed by minimally trained healthcare worker (1 hour training) Reader Retinal specialist Mydriasis Tropicamide 1%, phenylephrine 2.5%	Mydriasis-related angle-closure glaucoma

NS = not stated; RP-NMRC = retinal photography with a non-mydriatic retinal camera

Table 94 Study profiles of included comparative studies on patient acceptability

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria Objectives	Intervention – RP-NMRC	Outcomes assessed
Massin et al. (2005) France	Level III-2: prospective cohort study Quality: 15/26 (poor) Reporting: 6/10 External validity: 3/3 Bias: 4/7 Confounding: 2/6	N=834; 417 in each of two groups Age, mean: 60 years Sex: 62% male Ethnicity: NS Duration of diabetes, RP-NMRC group / ophthalmologist assessed group mean: 6.4 / 8.1 years	Inclusion Consecutive patients with diabetes at two locations (control group matched based on geographic location, density of private ophthalmologists, similar social and demographic characteristics) Exclusion If evaluated in previous 12 months, documented DR, refusal to participate, or preference to consult ophthalmologist directly Objectives To evaluate RP-NMRC compared with dilated examination by ophthalmologist	Setting Primary care Camera Topcon TRC-NW6S 5 x 45° images per eye Photographer Orthoptist Reader Trained ophthalmologists Mydriasis None	Patient-reported: - acceptability of testing duration - visual impairment due to flash - accessibility - preparedness to undergo next annual screen
Taylor, DJ et al. (1999) UK	Level II: cross-over study Quality: 19/26 Reporting: 6/10 External validity: 3/3 Bias: 5/7 Confounding: 5/6	N=118 Age, range: 60–79 years Sex: 66 (56%) female Ethnicity: NS Duration of diabetes: Range 6–10 years	Inclusion Randomly selected people with diabetes attending GP retinal screening on 2-year cycle Exclusion NS Objectives To evaluate digital RP-NMRC compared with Polaroid-based systems, against ophthalmologist assessment	Setting GP-based mobile retinal screening clinic Camera Topcon/Imagenet system, Canon CR5/Ris-Lite system and 45° CR4NM Polaroid photography Photographer NS Reader Experienced grader Mydriasis 0.5% tropicamide	Patient-reported discomfort

RP-NMRC = retinal photography with a non-mydriatic retinal camera; NS = not stated; GP = general practitioner

Table 95 Study profiles of included non-comparative studies on patient acceptability

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Index test – RP-NMRC	Outcomes assessed
Boucher, Nguyen & Angioi (2005) Canada	Level IV: case series Quality: 3/6 (medium)	Recruitment by intensive multimedia communication campaign (296 responded) N=291 diabetes patients (85.9% type 2) Age, median (range): 59 (17–87) years Sex: 59% male Ethnicity: NS Duration of diabetes, mean: 9.6 years Insulin therapy: 27.4% of patients	Inclusion NS Exclusion NS	Setting Community-based Camera TRC-NW5S, Topcon Medical systems, NJ, USA 4 x per eye Photographer NS Reader Ophthalmologist	Patient acceptability of RP-NMRC Satisfaction with screening Preference vs standard medical assessment Patient-reported future compliance
Cavallerano, JD et al. (2005) USA	Level IV: survey Quality: 4/6 (medium)	N=52 patients with no or mild NPDR at previous examination (type 2 diabetes: 63.5%) Age, mean: 47.7 years Sex: 55.8% male Ethnicity: 77% Caucasian, 11.5% African American Duration diabetes, mean: 11.5 years Insulin therapy: 21.2% of patients	Inclusion Examined more than 11 months prior, and diagnosed with no DR or mild NPDR and no DMO by retinal specialist Exclusion NS	Setting Eye institute, diabetes centre Camera TRC-NW5S, Topcon Medical systems, NJ, USA 3 x per eye Photographer Certified imagers Reader Certified readers	Overall experience with RP-NMRC Patient intention to return for RP-NMRC on a yearly basis Preference for RP-NMRC vs dilated eye examination
Kurji et al. (2013) Kenya	Level IV: survey Quality: 4/6 (medium)	N=26 out of 57 diabetes patients who completed a survey following teleophthalmology using RP-NMRC and a traditional clinical screening exam Age, mean male / female: 52.4 / 46.5 years Sex: 15 / 26 (58%) male Ethnicity: NS	Inclusion Patients were selected from a database at a multidisciplinary diabetes clinic and must have undergone both an ophthalmologist-based and RP-NMRC screening examination during July 2005 – July 2010 Exclusion NS	Setting Diabetic clinic, Nairobi, Kenya Camera Topcon TRC-NW100, Topcon Corp, Tokyo, Japan Photographer Trained nurses Reader Ophthalmologist	Patients preference for teleophthalmology RP-NMRC vs in-person examination Satisfaction with teleophthalmology

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Index test – RP-NMRC	Outcomes assessed
Leese et al. (1992) UK	Level IV: case series Quality: 3/6 (medium)	N=312 diabetes patients Age: NS Sex: NS Ethnicity: NS	Inclusion Known diabetes patients, or recruited through community radio Exclusion NS	Setting Mobile van Camera Canon CR4-45NM Polaroid Photographer NS Reader Hospital physicians, with doubtful films assessed by ophthalmologists Mydriasis NS	Proportion of patients with unfavourable, favourable and neutral views on mobile RP-NMRC
Massaro, Curry & Quillen (2010) USA	Level IV: survey Quality: 4/6 (medium)	N=87 diabetes patients Age, mean: 60 years Sex: 44 / 87 (50.6%) male Ethnicity: 80% Caucasian, 10% African American, 10% other Duration of diabetes, mean: 7 years	Inclusion Patients on diabetes registry 18 years or older with type 1 or type 2 DM No retinal screening more than 1 year prior Exclusion Blind Unable to provide informed consent	Setting Primary care setting Camera Canon CR-DG Photographer Trained medical student Reader Certified ophthalmic retinal photographer and an ophthalmologist	Intention to return for annual digital retinal scan Perceived benefit of digital retinal scan
Mohan et al. (1988) UK	Level IV: case series Quality: 3.5/6 (medium)	N=85 diabetes patients (165 eyes) Indian/European Age, mean: 54.9 / 62.1 years Sex: NS Ethnicity: 45 (86 eyes) / 40 (79 eyes) Duration of diabetes, median: 8 / 12 years Fasting glucose, mean: 10.8 / 12.1 mmol/L BMI, mean: 26.2 / 25.8	Inclusion Age at diagnosis: 20 years or older Known duration of diabetes 4 years or more No history of ketosis Exclusion NS	Setting Diabetes clinic Camera Canon CR3-45NM Photographer Unclear Reader Unclear Mydriasis None	Level of discomfort during RP-NMRC

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Index test – RP-NMRC	Outcomes assessed
		N patients with hypertension: 10 / 13			
Murgatroyd, MacEwen & Leese (2006) Scotland	Level IV: case series Quality: 1/6 (poor)	Group 1: N=292 patients attending a diabetes clinic with previous experience of mydriasis Age, median (range): 63 (20–94) years Sex: NS Ethnicity: NS Group 2: N=103 patients attending mobile RP-NMRC screening Age, median (range): 68 (29–96) years Sex: NS Ethnicity: NS	Inclusion NS Exclusion NS	Setting Diabetes clinic and mobile DR screening Camera NS Photographer NS Reader NS Mydriasis Group 1 only, type NS	Patient views on mydriasis Patient-reported intentions for future screening attendance if mydriasis were to be introduced (Group 2)
Newman et al. (2012) USA	Level IV: case series Quality: 3/6 (medium)	N=274 patients with diabetes screened with new point-of-care system Age, mean: 58.2 years Sex: 63% female Ethnicity: 66% African American, 33% Caucasian Systolic blood pressure, mean: 131.4 mmHg	Inclusion Adult patients with established diagnosis of diabetes Exclusion NS	Setting Primary care centre Camera Retasure DRI system (Digital Healthcare) Photographer Trained individual Reader Remote retinal specialist Mydriasis None	Mean satisfaction (Likert scale) Patient views on convenience and personal economic benefit of RP-NMRC in primary care
Spurling et al. (2010) Australia	Level IV: case series Quality: 4/6	N=11 Indigenous Australian diabetes patients Patient characteristics below based on 132 patients (data for n=11 sample not available)	Inclusion Patients chosen for their likelihood of agreeing to talk to researcher	Setting Urban Indigenous primary healthcare clinic Camera	Patient views on RP-NMRC in Indigenous Health Service

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Index test – RP-NMRC	Outcomes assessed
		Age, mean (range): 52 (24–78) years Sex: 72/132 (55%) female Duration of diabetes, mean (range): 6 (1–37) years Systolic blood pressure, mean ± SD: 130 ± 19.9 mmHg	Exclusion NS	Canon CR-DGi Photographer 2 GPs with relevant training Reader Same GPs as above Ophthalmologist	

NS = not stated; DR = diabetic retinopathy; NPDR = non-proliferative DR; DM = diabetes mellitus; DMO = diabetic macular oedema; SD = standard deviation

Table 96 Study profiles of included studies on diagnostic accuracy

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
Ahmed et al. (2006) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ? Flow and timing ☹ C1 P1	N=243 patients (486 eyes) Age, mean ± SD: 60 ± 11.3 years Male: 54% Sex: NS Ethnicity: NS Duration of diabetes, mean ± SD: 8.9 ± 6.4 years 4 eyes not included due to transmission difficulties	Inclusion Attendance at a routine diabetic examination at four clinic locations Dilated eye examination Exclusion Dilated eye examination more than 12 months apart from NMRI	Setting RP-NMRC as part of a diabetes management program in outlying suburbs of Washington, DC Camera Topcon TRC-NW5S (2 sites) and (TRC-NW6S (2 sites) 3 x 45° images per eye Photographer One of five technicians who underwent a 3-day training course Reader GP Mydriasis No	Dilated fundoscopic eye examination performed by an ophthalmologist or optometrist	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse
Aptel et al. (2008) France	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality:	N=79 patients (158 eyes) Age, mean (range): 52.4 (16–89) years Sex: NS	Inclusion Diabetic Exclusion Previous treatment such as laser photocoagulation or	Setting Retinopathy screening Camera Topcon TRC-NW6S linked to a Sony CCD camera	Eye examination by ophthalmologist using three-mirror lens and entire fundus scan with mydriasis	Unknown if UIs included in analysis Sensitivity, specificity, LR+, LR– per eye, for any DR

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ? C1 P1	Ethnicity: NS Duration of diabetes, mean: type 1, 8.5 years; type 2, 17.2 years	vitrectomy ophthalmological fundus examination in the previous 12 months	1 and 3 x 45° images per eye Photographer Trained ophthalmologist or nurse Reader 2 trained blinded ophthalmologists Mydriasis With and without		
Cavallerano, AA et al. (2003) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ? Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P1	N=525 enrolled patients (268 underwent both index test and reference standard) Age, mean (range): 49 (18–88) years Sex: 51.4% female Ethnicity: NS Mean duration of diabetes (range): 13 years (1 week – 61 years)	Inclusion Patients with type 1 or type 2 diabetes Exclusion NS	Setting JVN screening program, single centre Camera Topcon TRC NW-5S NM 3 x 45° images per eye Photographer Photographer NS Reader Certified JVN readers in consultation with a senior ophthalmologist Mydriasis No	CEE with retinal evaluation through dilated pupils by a retinal specialist	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse
Chia & Yap (2004) Singapore	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ? Index test ☺ Reference standard ☺ Flow and timing ☺ C1 P1	N=39 patients (78 eyes) Age, mean male / female (range): 62.4 (43–76) / 61.2 (37–84) years Sex: 22 (56%) female Ethnicity: 30 (77%) Chinese, 5 (13%) Indian, 4 (10%) Malay	Inclusion Known history of DM, referral from a polyclinic doctor, recently taken retinal photograph Exclusion Patients not attending the outpatient eye clinic	Setting Urban tertiary hospital outpatients clinic Camera NM fundus 1 x 45° image per eye Photographer NS Reader Ophthalmologist Mydriasis No	Clinical eye examination using indirect ophthalmoscopy and SLBM	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse plus MO

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
Conlin et al. (2006) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ? Index test ☺ Reference standard ☹ – only performed if patient attended CEE Flow and timing ☹ C1 P2 – Veterans Affairs health system, predominantly men	N=448 patients, of whom 223 had retinal photography and 140 completed CEE follow-up Age, mean: 67 years Sex: 98% male Ethnicity: 88% Caucasian, 10% African American, 2% other Duration of diabetes, mean: 11.6 years	Inclusion Diagnosis of DM Exclusion NS	Setting Teleretinal group – RP-NMRC in ambulatory care clinic (Veterans Affairs healthcare system) Camera Topcon TRC NW-5S, Topcon, Paramus, NJ 3 x 45° images per eye Photographer NS Reader Certified readers at a reading centre, Beetham Eye Institute Mydriasis NS	Comprehensive dilated eye examination	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse
Diamond et al. (1998) Australia	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ? Index test ☺ Reference standard ☺ Flow and timing ? C1 P1	N=164 patients (328 eyes) Age, mean (range): 48.2 (16–81) years Sex: 100 (61.0%) female Ethnicity: Australian Aboriginal Duration diabetes, mean (range): 7.5 (1–35) years	Inclusion Diabetes patients identified from medical records of Aboriginal communities in Western Australia during 1 week in July 1995 Exclusion NS	Setting Five rural Aboriginal communities in Western Australia Camera Canon CR5-45 1 x 45° image per eye Photographer Ophthalmic photographer Reader Second ophthalmologist Mydriasis If required Eyes with 'inadequate' images were re-photographed with mydriasis and included in the analysis	Indirect ophthalmoscopy through dilated pupils by an ophthalmologist	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR
Ding et al.	Level III-1:	N=531 patients	Inclusion	Setting	SLBM with 90-diopter	UIs included in

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
(2012) China / Thailand	A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ? Reference standard ? Flow and timing ☺ C1 P1	Age, range: 35–84 years Sex: 331 (62.3%) female Ethnicity: NS Duration of diabetes less than 5 years: 260 (48.9%)	Type 1 diabetes and aged 12 years or older Type 2 diabetes of any age and disease duration Exclusion Previous retinal laser surgery or treatment Blindness in both eyes Diagnosed with or suspected of angle-closure glaucoma	Urban community health centres, Beijing Camera Canon CR6-45 NM fundus 1 and 3 x 45° images per eye Photographer Ophthalmic photographer Reader UKNSC grading classifications Mydriasis With and without	lens by an ophthalmologist	analysis Sensitivity, specificity, LR+, LR– per patient, for any DR and severe NPDR or worse plus maculopathy
Freyberger et al. (1995) Germany	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ☺ Reference standard ? Flow and timing ☹ C1 P2 – no reasons given for excluding patients from the analysis	N=305 diabetes patients (80 included in analysis) Type 1 diabetes 17% / type 2 diabetes 83% Age, mean: 37.6 / 68.7 years Sex: NS Ethnicity: NS Duration of diabetes, mean: 12.4 / 10.5 years	Inclusion Diabetes patients who attended clinic Exclusion NS	Setting Hospital diabetes clinic Camera Canon CR4.45 non-mydriatic 1 x 45° image per eye Photographer Experienced retinal specialists Reader Ophthalmologist Mydriasis No	Ophthalmologist assessment	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per patient, for any DR
Gomez-Ulla et al. (2002) Spain	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: Patient selection ☺	N=70 diabetes patients (133 eyes) Age: NS Sex: NS Ethnicity: NS	Inclusion Diabetes patients attending an ophthalmology unit or endocrinology unit Exclusion Patients with cataracts	Setting Hospital ophthalmology and endocrinology units Camera Canon CR5-45 NM fundus 4 x 45° images per eye Photographer	SLBM by ophthalmologist using a 90-diopter lens	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis			Trained technician Reader Ophthalmologist Mydriasis No		
Harding et al. (1995) USA	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: Patient selection ☺ Index test ☺ Reference std ? Flow and timing ☹ C1 P1	N=320 diabetes patients Age, mean: 60.2 years Sex: NS Ethnicity: NS Insulin therapy: 24.9%	Inclusion Diabetes patients from four general practices in Liverpool who attended community-based photography at their local health centre and were subsequently examined in the hospital clinic Exclusion NS	Setting Community-based retinal photography in a mobile unit Camera Canon CR4-45NM fundus camera 3 x 45° images per eye Photographer Trained technician Reader Experienced ophthalmic clinical assistant with arbitration from ophthalmologist Mydriasis Yes	SLBM by retinal disease ophthalmologist using a 60- and 90-diopter indirect lens	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per patient, for severe NPDR or worse
Herbert et al. (2003) UK	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	N=145 patients (288 eyes) Type 1 / type 2 diabetes: 27% / 73% Age: NS Sex: NS Ethnicity NS	Inclusion Patients due to attend diabetes screening Exclusion Technical failures (blurred images, despite mydriasis)	Setting RP-NMRC in hospital setting Camera Digital TRC NW5-S model, 800 x 600 Sony 3-Chip 1 x 45° image per eye Photographer Member of nursing staff unless images difficult to obtain Reader Retinal specialist with extensive experience Mydriasis	SLBM by retinal specialist with extensive experience of screening for and treating DR	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
				If images inadequate		
Kuo et al. (2005) Taiwan	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ☺ Reference standard ? Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	N=100 patients (200 eyes) Age, mean (range): 59 (31–88) years Sex: 61 (61%) male Ethnicity: NS	Inclusion Consecutive patients with diabetes Exclusion Undergone vitrectomy	Setting RP-NMRC in hospital setting Camera Digital CR6-45NM, Canon, Tokyo, Japan 1 x 45° image per eye Photographer Trained technician (level of training NS) Reader 10 endocrinologists (level of training NS) Retinal specialist Mydriasis NS	SLBM by five ophthalmologists with mydriasis	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR
Lawrence (2004) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ? Index test ☺ Reference standard ☺ Flow and timing ☺ C1 P1	Group A: N=151 patients Group B: N=103 patients Age, mean: 67.5 years Sex: 98.5% male Ethnicity: 93.7% Caucasian, 3.5% African American 2% Hispanic, 0.8% Native American Duration of diabetes, mean (range): 12.4 (0–58) years	Inclusion Diabetes diagnosis Attendee of a Veteran Affairs medical centre Exclusion Previous retinal laser treatment in one or more eyes	Setting Veteran Affairs medical centre eye clinic Camera Two NM digital-video retinal imaging systems: A: Topcon TRC-NW5SF with a 640×480-pixel resolution B: Topcon TRC-NW6S with an 800×600-pixel resolution 3 x 45° images per eye Photographer Trained technician Reader Ophthalmologist Mydriasis With and without	Ophthalmologist examination direct / indirect, with / without SLBM at own discretion	UIs included in analysis Sensitivity, specificity, PPV, NPV per patient, for any DR
Lee, VS et al.	Level III-1:	N=410 patients (795	Inclusion	Setting	SLBM and indirect	2x2 data with UIs

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
(1993) USA	A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P1	eyes) Age, mean ± SD: 60.3 ± 8.4 years Sex: 275 (67%) female Ethnicity: Oklahoma Indians Diabetes duration, mean ± SD: 17.3 ± 5.3 years	Oklahoma Indians with non–insulin-dependent diabetes originally recruited for a study of vascular complications of diabetes between 1972 and 1980 Exclusion NS	Follow-up eye examination after an average follow-up period of 12.7 years Camera Canon CR4-45 NM 2 x 45° images per eye Photographer Experienced retinal specialists Reader University of Wisconsin Fundus Photograph Reading Centre Mydriasis Yes	ophthalmoscopy by experienced retinal specialists	Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and PDR
Lin et al. (2002) USA	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ? Flow and timing ☹ C1 P1	N=197 patients who underwent three screening modalities (after excluding 14 unusable records and ETDRS data sets) Age: 21 years or older Sex: 115 (58%) male Ethnicity: 104 (53%) African American, 45 (23%) Caucasian, 29 (12%) Asian American, 14 (7%) Hispanic, 5 (3%) Other	Inclusion Type 1 or type 2 diabetes Exclusion 21 years of age or younger Previous laser photocoagulation treatment for DR Ophthalmologic assessment for DR within the previous 12 months	Setting Medical centre Camera Canon CR5-45 NM 2 x 45° digital images, 640x480 pixels Photographer Trained research associate Reader Endocrinologists and a retinal specialist separately Mydriasis No	Dilated indirect ophthalmoscopy and SLBM performed by ophthalmologist	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per patient, for any DR and severe NPDR or worse
Lopez-Bastida, Cabrera-Lopez & Serrano-Aguilar (2007) Spain	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: Patient selection ☺	N=773/895 Type 1 / type 2 diabetes: 30.5% / 69.5% Age, mean: 50.8 years Sex: 52% female Ethnicity: NS	Inclusion Consecutive diabetes patients from several primary care centres 18 years of age or older Exclusion	Setting Hospital ophthalmoscopic clinic Camera Topcon TRC-NW6s 2 x 45° and 30° images per eye Photographer	SLBM and indirect ophthalmoscopy through dilated pupils by a retinal specialist	UIs excluded from analysis Sensitivity, specificity, PPV, NPV per eye, for any DR and severe NPDR or worse

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	Duration of diabetes, mean: 9.8 years	Previous ophthalmic treatment such as laser treatment; pregnant; learning or significant physical disability	Experienced specialist in retinal diseases Reader Experienced specialist in retinal diseases Mydriasis If required		
Maberley et al. (2002) Canada	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P1	N=100 Age, mean (range): 54.6 (24–82) years Sex: 69% female Ethnicity: Predominantly Cree, native to Canada	Inclusion Consecutive participants in retinopathy screening program Exclusion NS	Setting Remote communities of Moose Factory and Moosonee, Ontario Camera Topcon TRC-NW5SF 1 x 45° images per eye Photographer Ophthalmic photographer 30 eyes re-photographed by minimally trained healthcare worker (1 hour training) Reader Retinal specialist Mydriasis Yes	Clinical examination of the retina by retinal specialist, including anterior segment SLBM	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and PDR
Mizrachi et al. (2013) Israel	Level III-3: A diagnostic case-control study Quality: Patient selection ☹ Index test ? Reference standard ? Flow and timing ☹ C1 P2 – unknown if patients with UIs excluded from	N=362 (173 type 2 diabetes patients positive for DR by RP-NMRC and 189 patients with negative screening) Age, mean: 63.2 years Sex: 50.9% females Ethnicity: NS	Inclusion 18 years of age or older Type 2 diabetes Underwent both RP-NMRC and retinal examination by ophthalmologist with pupil dilation within 12 months	Setting RP-NMRC community health clinics Camera Digital Topcon TRC NW6S Photographer, imaging Trained ophthalmic photographer 2 x 45° images per eye Reader Retinal specialist Mydriasis NS	Retinal examination by ophthalmologist, with mydriasis Average time between RP-NMRC and retinal ophthalmologist testing 120 days	Unknown if UIs included in analysis Sensitivity, specificity, PPV per patient, for any DR

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	analysis					
Mohan et al. (1988) UK	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☺ C1 P1	N=85 diabetes patients (165 eyes) Indian / European Age, mean: 54.9 / 62.1 years Sex: NS Ethnicity: 45 (86 eyes) / 40 (79 eyes) Duration of diabetes, median: 8/12 years Fasting glucose, mean: 10.8 / 12.1 mmol/L BMI, mean: 26.2 / 25.8 N patients with hypertension: 10 / 13	Inclusion Consecutive patients attending the diabetic clinic who were aged 20 years or older at diagnosis, a known duration of diabetes of at least 4 years, and no history of ketosis Exclusion NS	Setting Hospital diabetic clinic Camera Canon CR3.45 non-mydriatic 1 x 45° image per eye Photographer Photographer not stated Reader Retinal specialist Mydriasis No	Direct ophthalmoscopy by an ophthalmologist	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR
Mollentze, Stulting & Steyn (1990) South Africa	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☺ C1 P1	N=86 diabetes patients, mostly non–insulin-dependent Age: NS Sex: NS Ethnicity: NS Duration of diabetes, mean (range): 9.5 (5–26) years	Inclusion First 9–10 patients per week who were in routine screening program with diagnosis of diabetes more than 5 years ago Exclusion Patients who had undergone previous eye surgery	Setting Hospital diabetic clinic Camera Canon CR4-45 NM 1 x 45° image per eye Photographer Official hospital photographer Reader Independent ophthalmologist Mydriasis With and without	Direct ophthalmoscopy	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and PDR
Moriarty et al. (1993)	Level II: A comparison against	N=37 consecutive patients newly	Inclusion Newly referred to	Setting Hospital diabetic clinic	SLBM (78-dioptre fundus lens) and	2x2 data with UIs Sensitivity, specificity,

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
UK	independent, blinded reference standard among consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P1	diagnosed with diabetes Age, mean: 54.9 (19–73) years Sex: 24 (65%) female Ethnicity: 25 (68%) Afro-Caribbean	diabetic clinic Exclusion NS	Camera Canon CR3 NM ? x 45° images per eye Photographer Unclear Reader Independent ophthalmologist Mydriasis Yes	indirect and direct ophthalmoscopy within 1 week by an independent ophthalmologist	PPV, NPV, LR+, LR– per eye, for any DR and PDR plus maculopathy
Murgatroyd et al. (2004) UK	Level II: A comparison against independent, blinded reference standard among consecutive Quality: Patient selection ? Index test ☺ Reference standard ☺ Flow and timing ☺ C1 P1	N=398 patients with diabetes Age, median: 63.0 years (range 17–88) Sex: 63% female Ethnicity: NS Duration of diabetes, mean [95%CI]: 9.3 [8.5, 10.1] years Insulin therapy: 35%	Inclusion Consecutive patients attending a medical diabetes clinic for annual review, and from ophthalmic diabetes clinics Exclusion Patients who were unable to position at the slit lamp table, or were unable to fixate on the light target of the camera	Setting Diabetes clinic Camera Topcon TRC NW6S NM 1 and 3 x 45° per eye Photographer Trained photographer Reader One ophthalmologist and one diabetologist Mydriasis With and without	SLBM by ophthalmologist	UIs included in analysis Sensitivity, specificity, PPV, NPV per patient, for any DR and severe NPDR or worse
O'Hare et al. (1996) UK	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺	N=1,010 patients with diabetes (517 examined by GPs, 493 examined by opticians) Age: NS Sex: NS Ethnicity: NS	Inclusion Patients attending GP and ophthalmic/optician practices already using ophthalmoscopy as part of their clinical annual review of diabetic patients	Setting Mobile screening unit that travelled to 11 GP practices (screened by 31 GPs) and 12 optician practices (screened by 17 opticians) Camera Canon CR4-45NM 1 x 45° image per eye Photographer Medical photographer	Ophthalmoscopy by GP	Unknown if UIs included in analysis Sensitivity, specificity, PPV, NPV per patient, for severe NPDR or worse

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	Flow and timing ☹ C1 P2 – unknown if patients with UIs excluded from analysis		Exclusion Patients who had been seen in hospital diabetic or ophthalmological clinics in the previous 12 months, were already blind and those unable to mount steps of the retinal screening van	Reader GPs Opticians Mydriasis Yes		
Penman et al. (1998) Egypt / USA	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ☺ Reference standard ☹ Flow and timing ☹ C1 P1	N=456 patients with diabetes Age, mean (range): 53.7 years (20–85) Sex: 297 (65%) female Ethnicity: NS Duration of diabetes, mean: 11.2 years (for 88% of patients)	Inclusion Patients with diabetes sampled from a population-based survey of diabetes and its complications Exclusion NS	Setting Specialist care Camera 45° Canon CR4-45 NM 1 x 45° image per eye Photographer Ophthalmologists Reader University of Wisconsin Fundus Photograph Reading Center Mydriasis Yes	Binocular indirect ophthalmoscopy performed by same ophthalmologist as ophthalmologist photographer	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per right eye, for any DR and PDR plus maculopathy
Peters et al. (1993) USA	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ? Reference standard ☺ Flow and timing ☹	N=522 diabetes patients followed in a health maintenance organisation (HMO) – 436 patients had HMO insurance and received a free referral to examiners; final analyses based on 189 patients with both eyes gradable and	Inclusion Patients followed in an HMO Exclusion NS	Setting HMO-affiliated diabetes program Camera Canon CR4-45 NM 1 x 45° image per eye Photographer Nurse clinicians Reader Diabetologist	Complete ophthalmological examination by two retinal specialists	UIs excluded from analysis Sensitivity, specificity per patient, for any DR

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	C1 P2 – patients with UIs excluded from analysis	report of retinal specialist's diagnosis Age, mean: 50.6 years Sex: 275 (53%) female Ethnicity: NS Duration of diabetes: 7 years		Mydriasis No		
Scanlon et al. (2003a) UK	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P1	N=239 patients attending hospital-based DR screening Age: 18 years or older Sex: NS Ethnicity: NS	Inclusion Patients attending a DR clinic and a diabetes and eye clinic Exclusion Pregnancy Age younger than 18 years Learning or physical disability Unwell	Setting See inclusion criteria Camera Canon CR5 or CR6 retinal cameras 2 and 7 x 45° images per eye Photographer Ophthalmic photographer Reader Ophthalmologist Mydriasis Yes	Ophthalmologist examination using indirect (78-dioptre lens) and direct SLBM	2-field: 2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for moderate NPDR or worse plus maculopathy 7-field: 2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR-– per eye, for any DR and severe NPDR or worse
Scanlon et al. (2003b) UK	Level III-1: A comparison against independent, blinded reference standard among non-consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ? Flow and timing ☺ C1	N=1,579 diabetes patients attending GP clinic (1,542 non-mydriatic group, 7 grading forms were missing) Age, mean: 65 years Sex: NS Ethnicity: NS	Inclusion 80 groups of 50 diabetes patients from individual general practices were randomly selected for inclusion Exclusion Unable to climb stairs (to ophthalmologist) or unwilling to have mydriasis for mydriatic	Setting RP-NMRC in general practices Camera Topcon NRW5S 1 x 45° image per eye without mydriasis 2 x 45° images per eye with mydriasis Photographer Nurse technician Reader Specialist Registrar in Ophthalmology Mydriasis	SLBM and direct ophthalmoscopy by ophthalmologist	2x2 data with UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per patient, for any DR and moderate NPDR or worse plus maculopathy

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	P1		photography	With and without		
Suansilpong & Rawdaree (2008) Thailand	Level II: A comparison against independent, blinded reference standard among consecutive patients Quality: Patient selection ☺ Index test ☺ Reference standard ☺ Flow and timing ☹ C1 P2 –patients with UIs excluded from analysis	N=248 patients (495 eyes) Age, mean ± SD: 61.1 ± 10.4 years Sex: 68.1% female Ethnicity: NS Diabetes duration less than 10 years: 60.5%	Inclusion Diabetic patients referred to the ophthalmology department Exclusion Previous eye laser or surgical treatment for DR	Setting Hospital-based diabetic centre Camera Topcon TRC-NW 100 1 x 45° image per eye Photographer Trained nurse practitioner Reading and grading Trained endocrinologist Mydriasis No	Indirect ophthalmoscopy followed by SLBM with high plus lens performed by an experienced ophthalmologist	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR and severe NPDR or worse
Tanterdtham et al. (2007) Thailand	Level III-2 A prospective, blinded comparison Quality: Patient selection ? Index test ☺ Reference std ? Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	N=142 patients (225 eyes) Mean age ± SD: 57.97 ± 11.35 years Sex: 65% female Ethnicity: NS	Inclusion Patients with diabetes attending an ophthalmological unit Able to give informed consent Exclusion History of laser or surgical treatment	Setting Hospital-based diabetes centre Camera Kowa VX-10 1 x 45° image per eye Photographer NS Reader General ophthalmologist Mydriasis No	Examination using SLBM and indirect ophthalmoscopy by retinal specialist with 10 years' experience	UIs excluded from analysis Sensitivity, specificity, PPV, NPV per eye, for any DR
Tu et al. (2004) UK	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺	N=1,643 diabetes patients Optometric screening / photographic screening: 769 / 874 patients Age, mean:	Inclusion Patients attending diabetic eye screening under two models (optometric and digital photography)	Setting See inclusion criteria Camera Topcon NM model TRC-NW5S 4 x 45° images per eye Photographer	SLBM conducted by screening-accredited optometrists for referrals, and sample audit (10%) of screen-negative patients by consultant	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per patient, for severe NPDR or worse

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	Intervention	Reference standard	Accuracy outcomes assessed
	Index test ☺ Reference standard ☹ Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	62.8 / 61.2 years Sex: 55.7% / 52.1% male Ethnicity: 98.9% Caucasian	Exclusion NS	Professional photographer Reader Experienced intermediate-grade ophthalmologist Mydriasis Yes	ophthalmologist using SLBM	
Williams, R et al. (1986) UK	Level III-2: A prospective comparison with valid reference, but blinding NS Quality: Patient selection ☺ Index test ☺ Reference standard ☹ Flow and timing ☹ C1 P2 – patients with UIs excluded from analysis	N=62 patients Age NS Sex NS Ethnicity NS	Inclusion Patients attending general diabetic clinic and diabetic eye disease clinic Exclusion NS	Setting See inclusion criteria Camera Kowa or Canon CR5 NM fundus cameras 1 x 45° image per eye Photographer NS Reader NS Mydriasis No	Ophthalmologist assessment using direct and indirect ophthalmoscopy	2x2 data without UIs Sensitivity, specificity, PPV, NPV, LR+, LR– per eye, for any DR

CEE = comprehensive eye examination; DM = diabetes mellitus; DR = diabetic retinopathy; DVRI = digital video retinal imaging; ETDRS = Early Treatment Diabetic Retinopathy Study; HMO = health maintenance organisation; JVN = Joslin Vision Network; NS = not stated; NM = non-mydriatic; NPV = negative predictive value; PPV = positive predictive value; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SD = standard deviation; SLBM = slit-lamp biomicroscopy; UKNSC = United Kingdom National Screening Committee; ☺ = low risk; ☹ = high risk; ? = unclear risk

Table 97 Study profiles of included studies on agreement among readers

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	RP-NMRC	Outcomes assessed
Andonegui et al. (2010) Spain	Level IV: case series Quality: Sample: 1 Inclusion criteria: 1 Entry point: 0 Follow up: 0 Outcomes:1 3/5 (medium quality)	N=200 patients (1,000 retinal images), of whom 100 had some degree of DR Age: NS Sex: NS Ethnicity: NS	Inclusion Patients with diabetes Exclusion NS	Setting Primary care Camera Digital TRC NW6S, Topcon, Paramus, NJ, USA 5 x per eye Photographer Trained nurse Reader Four GPs trained for 8 hours, followed by online training, until the level of agreement with ophthalmologist was 85% Mydriasis None	Agreement (kappa) between GP and ophthalmologist readers
Andonegui et al. (2012) Spain	Level IV: case series Quality: Sample: 1 Inclusion criteria: 1 Entry point: 0 Follow up: 0 Outcomes:1 3/5 (medium quality)	N=2,750 Patients recruited through general practices in urban and rural settings in Spain 2,036 considered normal 714 positives (26%) referred to ophthalmologist 240 'normals' also assessed by ophthalmologist Age: NS Sex: NS Ethnicity: NS	Inclusion Patients with diabetes Exclusion Visual acuity loss Previous retinal laser treatment Previous vitreoretinal surgery Age-related macular degeneration Other visually disabling diseases Those under care of an endocrinologist due to poor glycaemic control	Setting Primary care Camera TRC NW6S, Topcon, Paramus, NJ, USA 5 x each eye Mydriasis if required Photographer Trained nurses at other GP practices Reader GPs (trained) Ophthalmologist	Proportion of false positives from GP diagnoses among patients with suspected DR or UIs Proportion of false negatives from GP diagnoses among random sample of non-referred patients

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	RP-NMRC	Outcomes assessed
Bhargava et al. (2012) Singapore	Level IV: case series Quality: Sample: 0.5 Inclusion criteria: 0 Entry point: 0 Follow up: 0 Outcomes:1 1.5/5 (low quality – inadequate reporting)	N=367 diabetes patients (706 eyes) of 'polyclinics' (public primary health clinics) in Singapore Patient characteristics for 334 who did not have DR Age, mean: 62.9 ± 11.0 years Sex: 185 (55.4%) female Ethnicity: 83.8% Chinese	Inclusion NS Exclusion NS	Setting Primary healthcare setting Camera Canon CR-DGi, Tokyo, Japan 1 x 45° per eye Photographer Trained nurse Reader Trained non-physician graders Mydriasis As required	Agreement (kappa) between: A: non-physician readers and retinal specialist; B: physician and retinal specialist
Castro, Silva-Turnes & Gonzalez (2007) Spain	Level IV: case series Quality: Sample: 1 Inclusion criteria: 1 Entry point: 0 Follow up: 0 Outcomes:1 3/5 (medium quality)	N=194 consecutive patients with diabetes and/or hypertension (776 digital images) Diabetes only: n=64 (33.0%) Hypertension only: n=59 (30.4%) Diabetes and hypertension, n=71 (36.5%) Age: NS Sex: NS Ethnicity: NS	Inclusion NS Exclusion Known retinal lesions	Setting Primary care setting Camera Topcon TRC-NW5S, Paramus., NJ, USA 2 x per eye (1 x 45° and 1 x 20°) Photographer Unclear Reader GP Ophthalmologist Mydriasis None	Agreement (kappa) between GP and ophthalmologist on presence/absence of retinal lesions among patients with diabetes only and with diabetes and hypertension
Cavallerano, J D et al. (2012) USA	Level IV: case series Quality: Sample: 1 Inclusion criteria: 0 Entry point: 0	N=158 consecutive patients with diabetes (316 eyes) Age, mean (range): 56.5 (22–86) years	Inclusion NS Exclusion NS	Setting Primary care setting Camera Model/make NS (used JVN protocol) Number per eye NS	Agreement (kappa) between certified imagers and optometrists on sight-threatening DR diagnoses

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	RP-NMRC	Outcomes assessed
	Follow up: 0 Outcomes:1 2/5 (medium quality)	Sex: 54% female Duration of diabetes, mean (range): 7.0 (0.1–42.0) years Ethnicity: NS		Photographer Two certified imagers (intensive 3-day program) Reader Optometrists Mydriasis NS	
Farley et al. (2008) USA	Level IV: case series Quality: Sample: 1 Inclusion criteria: 0.5 Entry point: 0 Follow up: 0 Outcomes: 1 2.5/5 (medium quality)	N=1,040 diabetes patients Age: NS Sex: NS Ethnicity: NS Insurance: 75% none, 6% Medicaid, 9% Medicare, 10% privately insured	Inclusion Non-pregnant 18 years of age or older Diagnosis of diabetes At least two visits to the clinic over the 3 years of the study Exclusion NS	Setting Community health setting Camera Canon NM camera 1 x per eye Photographer Trained camera operators Reader Trained primary care clinician Retinal specialist Mydriasis All patients	Sensitivity, specificity, PPV and NPV of RP-NMRC by primary care clinicians relative to retinal specialist reader diagnoses for any DR and referrable DR
Owens et al. (1998) UK	Level IV: case series Quality: Sample: 1 Inclusion criteria: 1 Entry point: 0 Follow up: 0 Outcomes:1 3/5 (medium quality)	N=613 attending DR screening Age, mean insulin-treated / non-insulin treated patients: 52.0 / 66.3 years Sex: 343 (56%) male Ethnicity: NS	Inclusion Patients of four general practices in Wales Exclusion Treatment for glaucoma or previous anterior lens implant; excluded by GP if blind, had terminal illness or dementia	Setting General practice Camera Canon CR4 45NM producing 35mm colour transparencies mounted as slides Photographer Study optometrist Readers GPs Readers at a diabetic retinopathy reading centre Mydriasis	Sensitivity, specificity, and PPV of RP-NMRC by GPs relative to reading centre diagnoses for any DR and sight threatening DR

Study	Study design / Quality appraisal	Study population	Inclusion criteria / Exclusion criteria	RP-NMRC	Outcomes assessed
				All patients	

DR = diabetic retinopathy: GP = general practitioner; JVN = Joslin Vision Network; NM = non-mydriatic; NS = not stated; RP-NMRC = retinal photography with a non-mydriatic retinal photography

Table 98 Study profiles of included studies on change in management

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
Conlin et al. (2006) USA	Level II: RCT Quality: 20/26 (moderate) Reporting: 8/10 External validity: 2/3 Bias: 5/7 Confounding: 4/6	N=448 diabetes patients RP-NMRC group, n=223 Control group, n=225 Mean age ± SE: 67 ± 1 years Sex: 98% male Ethnicity: 88% Caucasian Mean duration of diabetes ± SE: 11.6 ± 0.5 years	Inclusion Diagnosis of DM Exclusion NS Objectives To test the hypothesis that patients with DM who have teleretinal imaging added to their usual ambulatory care will have greater adherence to follow-up eye care (i.e. dilated eye exam)	Setting Teleretinal group – RP-NMRC in ambulatory care clinic (Veterans Affairs healthcare system) Camera Topcon TRC NW5S, Topcon, Paramus, NJ 3 x 45° stereoscopic fields per eye Photographer Trained imagers Reader Remote certified readers Mydriasis None	Usual care (no teleretinal imaging)	Adherence to annual comprehensive dilated eye examination – defined as documented evidence of comprehensive dilated eye examination during the ensuing 12 months (ITT analysis)
Creuzot-Garcher et al. (2010) France	Level III-2: cohort study with concurrent control Quality: 17/26 (moderate–poor) Reporting: 6/10 External validity: 2/3 Bias: 4/7	2005: n= 676 diabetes patients 2006: n=1,298 diabetes patients Age: NS Sex: NS Ethnicity: NS	Inclusion Patients with diabetes who responded to a GP recommendation of an eye examination as a result of an eye screening campaign Exclusion NS	Setting Mobile screening unit, screening campaign advertised by various media Camera Digital, model/make NS Photographer Orthoptist Reader Certified ophthalmologist	No access to mobile screening unit (no eye examination)	Compliance with eye examination recommendations for screened and non-screened areas

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
	Confounding: 2/6		Objectives To evaluate the impact of a mobile DR screening program on the overall ophthalmological follow-up of people with diabetes	Mydriasis None		
Lee, SJ et al. (1999) Australia	Level IV: case series Quality: 4/6 (Moderate)	N=253 GPs who received questionnaires regarding follow-up of patients referred for DR by screening program Age, sex, ethnicity of patients NS	Inclusion No eye examination in the previous 2 years Exclusion NS Objectives To assess compliance by GPs with recommendations for follow-up after their patients' participation in a screening program for DR	Setting Community-based DR screening in two urban and two rural areas of Victoria Camera Model/make NS, Polaroid photographs Photographer NS Reader Ophthalmologist Mydriasis NS	NA	GP and patient compliance with follow-up recommendations from screening
Lee, SJ et al. (2000) Australia	Level IV: case series Quality: 4/6 (Moderate)	N=652 people with diabetes who had either never had an eye examination, or not in the previous 2 years Analysis based on 543 (83%) of people for whom results were available Age: NS Sex: NS Ethnicity: NS	Inclusion No eye examination ever or no eye examination in the previous 2 years Exclusion NS Objectives To examine eye care practices of people with diabetes who had not previously accessed eye care services on a regular basis	Setting Community-based DR screening throughout urban and rural Victoria Camera Model/make NS Polaroid photographs Photographer NS Reader Ophthalmologist Mydriasis NS	NA	Referral rates and patient compliance with follow-up recommendations from screening

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
Leese et al. (2005) Scotland	Level IV: case series (moderate)	N=5,150 patients (appointments sent in the first 12 months of new screening program) N=5,208 patients (screened in the last 18 months of previous screening program) Age, median (IQR): 66.8 (56.1–74.7) years Sex: NS Ethnicity: NS	Inclusion Living within a 12-mile radius of screening centre Exclusion NS Objectives To examine the impact of a new retinal screening program (which follows the Health Technology Board Scotland and Diabetic retinopathy Screening Implementation Guideline) on the ophthalmology services of Dundee	Setting New retinal screening program at hospital-based diabetes centre Camera Topcon TR6-NW6S Photographer Dedicated screener trained in nationally recognised course Reader Level 1 grading (identification of abnormal photos) performed by screener Level 2 grading (identification photos requiring referral) performed by an ophthalmic photographer Quality assurance of grading performed by an ophthalmologist Mydriasis Mydriasis used if image assessed as unacceptable	Previous screening program (results of 18 months prior to implementation of the new program)	Screening attendance, referrals to the ophthalmology clinic, compliance with recommendations
Leiner et al. (2009) USA	Level III-3: A comparative study with historical control Quality: 12/26 (Moderate–poor) Reporting: 4/10 External validity: 3/3 Bias: 3/7 Confounding: 2/6	N=2,438 diabetes patients Age: NS Sex: NS Ethnicity: NS	Inclusion Patients with diabetes attending at University of Virginia medical centre Exclusion NS Objectives To examine the impact of a retinal screening program	Setting Screening program at primary care clinic (mostly patients with no medical insurance or of lower socioeconomic status) Camera Optos Inc., Optomap retinal imaging machine 200° digital images Photographer NS	Screening prior to implementation of the new program in mid-2006	Annual patient screening rates, non-attendance rates for ophthalmological appointments pre and post implementation of RP-NMRC screening

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
				Reader Ophthalmologist Mydriasis NS		
Mansberger et al. (2013) USA	Level II: RCT Quality: 19/27 (Moderate) Reporting: 7/10 External validity: 3/3 Bias: 4/7 Confounding: 5/6	N=567 diabetes patients Mean age ± SD: 51.1 ± 11.8 years Sex: 51.7% female Ethnicity: 53% White, 17% American Indian or Alaskan Native, 50% American Indian or Alaskan Native heritage (1st, 2nd or 3rd degree), 72% non-white heritage (1st, 2nd or 3rd degree heritage)	Inclusion Diabetes patients 18 years of age or older scheduled to see primary care provider Exclusion Cognitive impairment or inability to transfer to a chair for RP-NMRC Objectives To determine the effectiveness of telemedicine for DR screening with RP-NMRC compared with traditional surveillance in community health clinics with a high proportion of minorities, including American Indian / Alaskan Natives	Setting RP-NMRC in primary care setting, performed opportunistically before, during or after primary care appointment Camera NIDEK NM-1000 digital 6 x 45° per eye Photographer Technicians provided with 3 days of training and ongoing feedback Reader Study investigators, training unclear Mydriasis None	'Traditional surveillance' at primary care appointments for other preventive diabetic exams such as HbA1c testing A recommendation provided to see an eye care specialist once a year	Compliance with recommendations of following eye examination
Romero-Aroca et al. (2010) Spain	Level IV: case series Quality: 5/6 (high)	Group 1: N=4,551 patients Mean age ± SD: 64.52 ± 12.46 years Sex: 54.08% female Mean duration of diabetes ± SD: 7.56 ± 4.09) years	Inclusion Patients with type 2 diabetes attending one of 12 primary health care centres Exclusion Diabetes type 1 patients Objectives	Setting Health-centre-based screening program with two different techniques for reading photos Camera Topcon TRC-NW6S 2 x non-stereoscopic 45° photos per eye	Group 2: fundus images read by ophthalmologists	Screening rate, referral to screening rate, referral to ophthalmologist rate, non-attendance rate, waiting time for screening

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
		Group 2: N=884 patients Mean age ± SD: 64.47 ± 12.13 years Sex: 54.42% female Mean duration of diabetes ± SD: 7.54 ± 4.12) years	To compare the results from a 2-year prospective study (2008–09) using two different techniques of DR screening	Photographer Trained technician Reader Group 1: GP Mydriasis No mydriasis unless image was unsatisfactory		
Spurling et al. (2010) Australia	Level III-3: cohort study with historical control Quality: 14/26 (moderate–poor) Reporting: 6/10 External validity: 2/3 Bias: 4/7 Confounding: 2/6	N=132 patients (out of a total of 147 patients attending the clinic) Age, mean (range): 52 (24–78) years Sex: 72 (55%) female Ethnicity: Indigenous Australian	Inclusion Attendance at the health care clinic for annual check Exclusion NS Objectives To determine the impact of a screening program on access to appropriate screening and referrals, and to determine the feasibility and acceptability of the service to patients	Setting Government primary healthcare facility for Indigenous Australians Camera Cannon CR-DGi digital Photographer Trained technician Reader GP Mydriasis No mydriasis unless image was unsatisfactory	No RP-NMRC screening	Screening rate and rate of compliance with recommendations pre and post RP-NMRC screening implementation
Tu et al. (2004) UK	Level III-2: retrospective cohort study Quality: 15/26 (moderate) Reporting: 7/10 External validity: 1/3 Bias: 5/7 Confounding: 2/6	N=1,643 diabetes patients Optometric screening / photographic screening: 769 / 874 patients Age, mean: 62.8 / 61.2 years Sex: 55.7% / 52.1% male Ethnicity: 98.9%	Inclusion Patients attending diabetic eye screening under two models (optometric and digital photography) Exclusion NS Objectives To compare two DR screening models – an	Setting See inclusion criteria Camera Topcon NM model TRC-NW5S 4 x 45° field non-stereoscopic images Photographer Professional photographer Reader Experienced intermediate-grade	Clinical eye examination using SLBM conducted by screening accredited optometrists (n=14)	Referral rates following RP-NMRC or clinical eye examination

Study	Study design / Quality appraisal/	Study population	Inclusion criteria / Exclusion criteria/ Objectives	Intervention	Comparator	Clinical management outcomes assessed
		Caucasian	optometric screening program and a digital photographic screening	ophthalmologist Mydriasis 1% tropicamide		
Williams, R et al. (1986) UK	Level III-2: cross-over study Quality: 15/26 (moderate) Reporting: 5/10 External validity: 2/3 Bias: 5/7 Confounding 3/6	N=62 randomly sampled patients (120 eyes) attending general diabetes clinic and diabetic eye disease clinic Age: NS Sex: NS	Inclusion Patients attending general diabetic clinic and diabetic eye disease clinic Exclusion NS Objectives To assess RP-NMRC compared with direct examination by an ophthalmologist as a means of detecting diabetic retinopathy	Setting See inclusion criteria Camera Kowa or Canon CR5 NM fundus cameras, with either Polaroid 600 colour prints or Kodachrome ASA 200 colour transparency film Single 45° image Photographer NS Reader ophthalmologist Mydriasis None	Dilated fundus examination by ophthalmologist	Management recommendations following RP-NMRC or ophthalmologist clinical examination

DM = diabetes mellitus; DR = diabetic retinopathy; GP = general practitioner; ITT = intention to treat; IQR = interquartile range; NM = non-mydriatic; NS = not stated; RCT = randomised controlled trial; RP-NMRC = retinal photography with a non-mydriatic retinal camera; SD = standard deviation; SE = standard error

Appendix F

Excluded studies

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Appendix F

Additional information related to the economic evaluation

Table 99 Annual indexation adjustments for health state costs used in the economic model

Financial year	% change from previous financial year [a]	No complications			Microvascular complications			Micro- and macrovascular complications		
		Mean	Lower 95%CI	Upper 95%CI	Mean	Lower 95%CI	Upper 95%CI	Mean	Lower 95%CI	Upper 95%CI
2004–05	6.40%	$2,357	$1,850	$2,863	$3,051	$2,356	$3,745	$5,935	$4,692	$7,178
2005–06	5.01%	$2,475	$1,943	$3,006	$3,204	$2,474	$3,933	$6,232	$4,927	$7,538
2006–07	4.46%	$2,586	$2,029	$3,141	$3,347	$2,584	$4,108	$6,510	$5,147	$7,874
2007–08	4.09%	$2,691	$2,112	$3,269	$3,484	$2,690	$4,276	$6,777	$5,357	$8,196
2008–09	4.80%	$2,820	$2,214	$3,426	$3,651	$2,819	$4,481	$7,102	$5,615	$8,589
2009–10	5.00%	$2,961	$2,324	$3,597	$3,833	$2,960	$4,705	$7,457	$5,895	$9,019
2010–11	4.98%	$3,109	$2,440	$3,776	$4,024	$3,108	$4,940	$7,828	$6,189	$9,468
2011–12	3.97%	$3,232	$2,537	$3,926	$4,184	$3,231	$5,136	$8,139	$6,435	$9,844
2012–13	3.64%	$3,350	$2,629	$4,069	$4,336	$3,349	$5,323	$8,436	$6,669	$10,202
2013–14	6.51%	$3,568	$2,801	$4,334	$4,619	$3,567	$5,669	$8,985	$7,103	$10,866

CI = confidence interval

[a] Source: derived from ABS 6401.0 Consumer Price Index, Australia, March 2014, Table 7, http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/6401.0Mar%202014?OpenDocument

Note: 2004–05 costs were sourced from Lee, CM et al. (2013).

Appendix G

Additional information for the financial and costing analysis

Table 100 MBS data report item 104, specialist, referred consultation

MBS Item 104		2007–08	2008–09	2009–10	2010–11	2011–12	2012–13	Derivation
Medicare data								
Number of services:	A	4,169,401	4,274,558	4,307,645	4,332,251	4,529,791	4,611,462	
In hospital	B	142,170	146,352	154,954	161,494	177,956	190,057	
Out-of-hospital	C	4,027,231	4,128,206	4,152,691	4,170,757	4,351,835	4,421,405	
Fee charged:	D	$469,850,044	$503,365,246	$525,508,568	$546,516,146	$588,790,892	$621,949,839	
Average per service	E	$112.69	$117.76	$121.99	$126.15	$129.98	$134.87	
Benefits paid:	F	$280,459,766	$295,866,746	$305,749,512	$313,370,545	$334,530,122	$347,613,931	
Average per service	G	$67.27	$69.22	$70.98	$72.33	$73.85	$75.38	
% of services bulk billed	H	18.3%	18.4%	19.0%	19.4%	20.5%	20.9%	
Extended Medicare Safety Net	I	$10,058,759	$12,512,439	$13,879,095	$13,935,576	$16,013,370	$16,870,299	
Derived data								
Fee-benefit per service		$45.42	$48.54	$51.02	$53.82	$56.13	$59.49	E-G
Average fee patients not bulk-billed	J	$121.62	$127.94	$133.57	$139.04	$144.75	$151.29	(I-H*$72.75)/(1-H) [a]
Average out-of-pocket cost per service (out-of-hospital-billed)	K	$55.58	$59.52	$63.01	$66.81	$70.61	$75.22	J/(1-H)
Average EMSN payment per service covered by EMSN		$42.78	$46.72	$50.21	$54.01	$57.81	$62.42	K-$12.80[a]
Average EMSN payment/service		$3.06	$3.72	$4.13	$4.15	$4.63	$4.82	I/(A*(1-H))

EMSN = Extended Medicare Safety Net; MBS = Medicare Benefits Schedule

[a] Medicare scheduled fee, item 104, $85.55, 85% rebate $72.75, patient co-payment $12.80

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