



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1181– Non-mydriatic retinal photography (NMP) in people with diagnosed diabetes

Applicant: Centre for Eye Research Australia (CERA)

Date of MSAC consideration: MSAC 62nd Meeting, 26-28 November 2014

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting Medicare Benefits Schedule (MBS) listing of retinal photography with a non-mydriatic retinal camera (RP-NMRC), for the identification of retinopathy in people with diabetes, was received from the Centre for Eye Research Australia by the Department of Health in December 2012.

The application requested an additional new item for RP-NMRC, which would be used in patients with diabetes. It also proposed a change in the descriptors of the current MBS item numbers 11215 (RETINAL PHOTOGRAPHY, multiple exposures of 1 eye with intravenous dye injection) and 11218 (RETINAL PHOTOGRAPHY, multiple exposures of both eyes with intravenous eye injection). These items are usually referred to as fluorescein angiography.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding for bilateral non-mydriatic retinal photography for initial or repeat assessment for diabetic retinopathy in patients with medically diagnosed diabetes.

MSAC agreed that MBS funding should promote uptake where most needed, particularly in primary care in remote and rural settings. MSAC advised the Department to consider a hybrid model of funding, such as separating capital costs from service costs and separating image taking from image interpretation. MSAC considered that initial training and maintaining quality control of image interpretation were significant factors and should also be encouraged by the funding model.

MSAC considered that, to optimise photographic performance, the proposed item descriptor should also specify photography of multiple fields rather than a single field.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that in people with diagnosed diabetes, detecting changes in the retina and associated structures enables early identification of diabetic retinopathy (DR) and vision loss. Currently, RP-NMRC is usually provided by an ophthalmologist or optometrist, as part of a comprehensive eye examination (CEE).

Current Australian guidelines for the management of DR recommend 2-yearly assessment of vision and retinal examinations for non-Indigenous Australians with asymptomatic diabetes (i.e. those without visual impairment), and yearly examinations for Indigenous Australians. MSAC noted the current standard of eye care in Australians with diabetes varies considerably, with data suggesting 40-80% of Indigenous people and 20-50% of non-Indigenous people are not monitored in keeping with guidelines (Harper *et al.* 1998; Taylor *et al.* 2009, Ku *et al.* 2013).

MSAC agreed that, given this current gap in monitoring, there was a well-defined clinical need for RP-NMRC, especially in rural and remote regions where access to CEE is poor and among Indigenous populations where the incidence of diabetes is high. It was observed that the portability of NMP cameras makes them more accessible for monitoring than CEE.

MSAC noted the intent to use RP-NMRC as a triage test in the general practice setting for patients with diagnosed diabetes, but without evidence of DR. If a patient tests positive with RP-NMRC, the intent is to refer that patient to an optometrist or ophthalmologist for verification via a CEE. If the image is of inadequate quality, the intent is also to refer, but without charging the patient. If the patient tests negative with RP-NMRC, the intent is to re-assess according to the current Australian guidelines.

Comparative safety and clinical effectiveness of RP-NMRC were appropriately evaluated against:

- Standard medical assessment, either:
 - CEE (includes slit lamp biomicroscopy of the fundus) by an optometrist or ophthalmologist, with or without mydriasis; or
 - ophthalmoscopy with mydriasis by a GP.
- No eye examination beyond visual acuity testing.

No studies on the comparative safety of NMP were presented. Instead indirect evidence was used to inform safety considerations associated with this procedure. It was observed that in the general population, the rate of acute glaucoma from mydriasis was low (1:18,000). Mydriasis is not used with RP-NMRC, unlike CEE where it is always used. Therefore it was considered that RP-NMRC is likely to be safer than CEE, but less safe than no exam. RP-NMRC was also reported to be 'highly acceptable' among patients (Spurling *et al.* 2010), with a rate of discomfort less than 3% (Taylor DJ *et al.* 1999). Overall, MSAC concluded that RP-NMRC was a low risk intervention.

In the absence of direct evidence on the comparative effectiveness of RP-NMRC, a linked evidence approach was utilised to synthesise indirect evidence from studies reporting on diagnostic accuracy and change in management.

The accuracy of RP-NMRC to detect any DR was determined in a meta-analysis of 7 studies. Unreadable images were considered a positive result. Overall, in the context of a triage test, NMP demonstrated acceptable sensitivity (92%, 95%CI: 79, 97; positive likelihood ratio (LR+) 3.58, 95%CI: 2.26, 5.66) with reasonable specificity (74%, 95%CI: 61, 84; negative likelihood ratio (LR-) 0.11, 95%CI: 0.04, 0.30) to detect any diabetes retinopathy against slit lamp biomicroscopy and/or CEE as the reference standard. An extended meta-analysis of 13 studies of retinal photography further demonstrated that, although this diagnostic accuracy was not affected by use or non-use of mydriasis, sensitivity was increased by the use of multiple fields (97%, 95%CI 87, 99) rather than a single field (83%, 95%CI 71, 90). MSAC considered that this improvement in sensitivity was important in the context of a triage test.

However, it was noted that in all of these studies, photographs were read by ophthalmologists or retinal specialists, which is not how RP-NMRC would be used in the proposed Australian context. Six concordance studies examined agreement between GPs and ophthalmologists in interpreting retinal photographs, reporting kappa statistics between 0.40 (fair) and 0.95 (almost complete agreement). This suggests that training in interpreting the photographs is also important.

MSAC also noted there was reasonable evidence to suggest that a substantial change of behaviour might occur if RP-NMRC was initiated within the primary care setting – with substantially more individuals presenting for RP-NMRC monitoring than for CEE monitoring. The strongest evidence came from a randomised trial of telemedicine with RP-NMRC versus traditional surveillance by an eye care provider in community health clinics conducted in the United States (Mansberger *et al.* 2013, N=596), which showed that the RP-NMRC group was more likely to receive a diabetic retinopathy screening examination within a year of enrolment than in the traditional surveillance group (94% vs 56% of patients, respectively; $p < 0.001$). This evidence also included data from an Australian before and after study (Spurling *et al.* 2010, N=132), which found that more Indigenous patients had appropriate surveillance and follow-up in the year after the introduction of clinic-based retinal photography than in the year before (94% vs 15% of patients, respectively; $p < 0.001$).

Overall, MSAC considered that the assessment of RP-NMRC provided a convincing causal pathway to improved health in patients who develop diabetic retinopathy. In particular, RP-NMRC is safe and there is reasonable evidence for acceptable accuracy when interpreted by trained individuals.

MSAC discussed the economic models used to evaluate RP-NMRC for this application. The architecture of the decision model was considered appropriate. When compared with no test, RP-NMRC was associated with an estimated incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) of approximately \$14,870 in the broader Australian population and \$12,380 in the Indigenous population, and an incremental cost per blindness prevented of approximately \$51,600 and \$46,600, respectively. MSAC noted that the base case ICER per QALY of \$14,870 was robust to relevant sensitivity analyses. Compared with ophthalmoscopy performed by a GP, the estimated ICER for RP-NMRC was approximately \$26,000 in both the broader population and the Indigenous population. In comparison with CEE performed by either an ophthalmologist or an optometrist, regular monitoring by RP-NMRC was marginally less expensive, but also slightly less effective in terms of QALYs gained.

MSAC noted that funding RP-NMRC as proposed was estimated to increase the MBS budget by more than \$10 million per year within the first four years of listing. These estimates were associated with substantial uncertainties of the uptake of RP-NMRC by primary practice, the

increasing rates of referral for CEE with increasing prevalence of diabetic retinopathy, and maintaining the accuracy of RP-NMRC sufficient for triage, including with respect to equivocal images.

MSAC identified areas of uncertainty regarding the implementation of RP-NMRC, such as:

- The adequacy of the proposed MBS item fee (\$50) to provide sufficient incentive for primary care to invest in the capital and training required, especially for practices who would see relatively few patients with diabetes annually. Accordingly, MSAC considered alternative models of healthcare funding;
- Ensuring sufficient coverage for rural and remote regions where the biggest benefits and best value of monitoring might be achieved due to the relative scarcity of optometrists and ophthalmologists. MSAC suggested that consideration be given to provide program funding for the capital costs to target uptake in these areas, with a commensurate reduction in the proposed fee for each subsequently rendered service. This might be extended by a differential fee to provide an incentive for updating equipment over time;
- Quality control for taking, reading and interpreting RP-NMRC images –suitable training for GPs and practice staff needs to be provided, both before starting to provide the service, and subsequently to maintain quality over time. MSAC suggested consideration be given to unbundling the service to take an RP-NMRC image from the service to read and interpret the RP-NMRC image, whilst ensuring that all images taken are sent on for for interpretation. This would open up the possibility of having the image interpreted by an optometrist or ophthalmologist, noting a precedent exists for this with the reading of echocardiograms.
- The need to limit use of RP-NMRC to the item descriptor intention of monitoring to detect diabetic retinopathy and not also subsequently to monitor the diabetic retinopathy once detected.

4. Background

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

5. Prerequisites to implementation of any funding advice

Numerous non-mydriatic cameras have been registered with the Therapeutic Goods Administration on the Australian Register of Therapeutic Goods (ARTG). These devices are not exempt from the regulatory requirements of the Therapeutic Goods Act 1989.

6. Proposal for public funding

RP-NMRC is a non-contact, non-invasive [digital] imaging technique that provides images of the retina and optic disc. NMP provides a means for earlier detection of diabetic retinopathy and vision loss in people with diagnosed diabetes who do not attend an eyecare practitioner for a mydriatic fundus assessment.

RP-NMRC does not currently receive public reimbursement as a stand-alone service. The service is usually provided by an ophthalmologist or optometrist, concurrent to a

comprehensive eye examination (CEE), with the additional costs of photography being an out-of-pocket expense to the patient. The existing MBS items for “retinal photography” (11215 & 11218) are considered to be synonymous with fluorescein angiography, an imaging method used specifically to assess severe retinopathy in order to guide treatment.

Diabetic retinopathy (DR) is a disease of the retina that eventually develops in nearly all patients with diabetes mellitus and is directly related to poor control of blood sugar, blood pressure and blood lipids.

DR progresses in a predictable fashion from minimal to more severe changes if there is no intervention. The earliest clinical signs of DR include microaneurysms and haemorrhages. Visual loss results mainly from macular oedema and/or proliferative diabetic retinopathy.

The proposed MBS item is summarised below. 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).

Proposed MBS item descriptor for retinal photography in people with diabetes

<p>Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS And Group A10 – OPTOMETRIC SERVICES</p>
<p>MBS [item number (Note: this will be assigned by the Department if listed on the MBS)]</p> <p>Bilateral retinal photography with a non-mydratric retinal camera for initial or repeat assessment for presence or absence of diabetic retinopathy in people with medically diagnosed diabetes.</p> <p>Fee: \$50.00</p> <p>Explanatory notes:</p> <p>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 distance vision means unaided distance vision or the vision obtained with the current spectacles or contact lenses, if normally worn for distance vision.</p> <p>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).</p> <p>This item is intended for the provision of retinal photography with a non-mydratric 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).</p> <p>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.</p> <p>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.</p> <p>Detection of any diabetic retinopathy must be followed by referral to an optometrist or ophthalmologist.</p> <p>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.</p> <p>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.</p> <p>Charging of a fee must be accompanied by a report detailing the presence or absence of diabetic retinopathy, based on photos of readable quality.</p>

7. Summary of Public Consultation Feedback/Consumer Issues

During the public consultation period a consumer interest group 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.

Delegation of this procedure could save costs without compromising safety and quality.

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 or optometrists to claim the interpretation portion of the service.

Public submissions raised issues related to eligibility and the need to prioritise/target education and testing.

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-mydratic 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.

There is also some evidence that patients with identified DR from the RP-NMRC are more likely to attend an ophthalmologist or optometrist to begin a treatment regime than they are if advised to see the eye specialist for testing to see if treatment is needed.

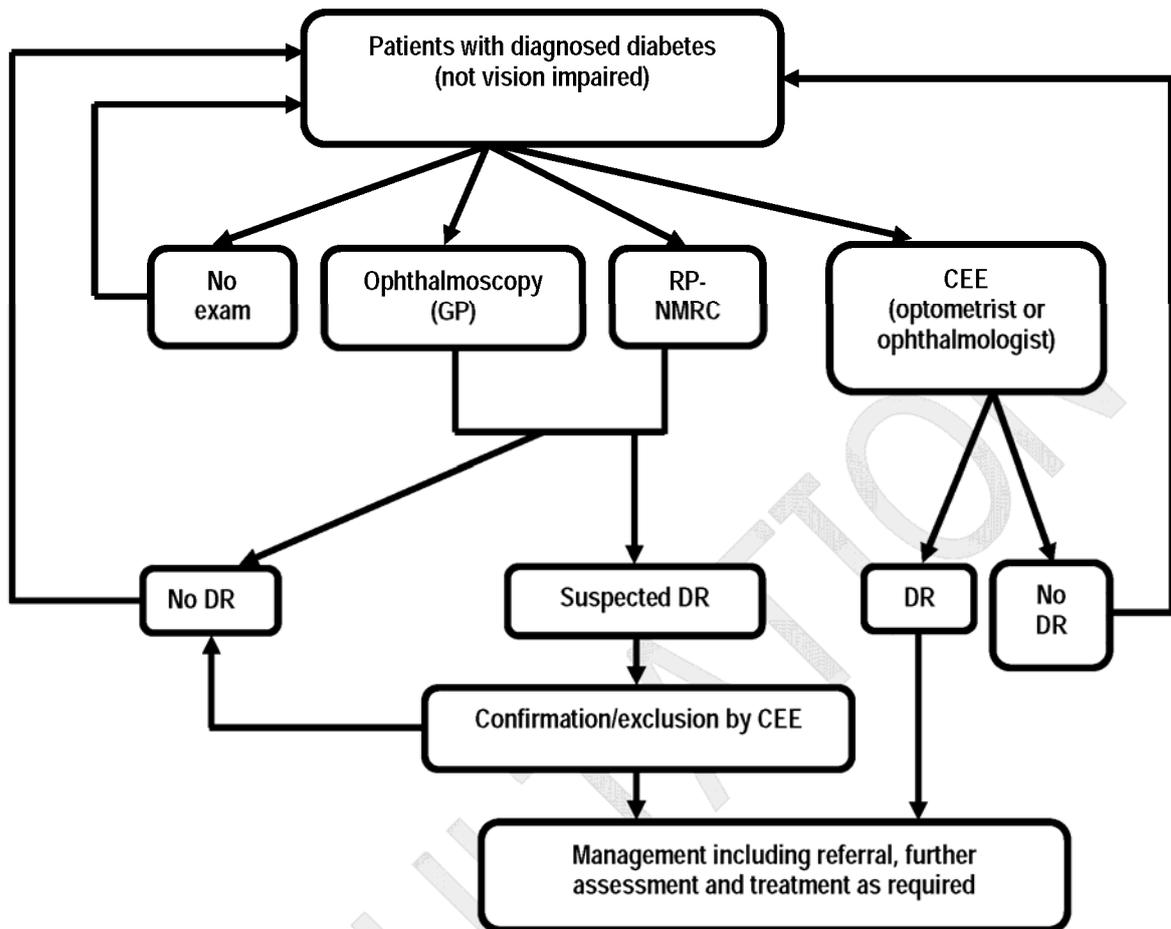
Consumer advice noted that the more comfortable and less intrusive nature of the procedure could encourage uptake and early intervention, as would community and targeted education.

8. Proposed intervention's place in clinical management

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).

The management algorithm for detection of diabetic retinopathy in patients with diagnosed diabetes, with the proposed service available i.e retinal photography using a non-mydratic retinal camera is shown below.



Abbreviations: CEE, comprehensive eye examination; RP-NMRC, retinal photography with a non-mydratic retinal camera; DR, diabetic retinopathy; GP, general practitioner

Note: CEE by an optometrist or ophthalmologist will include fundus examination using a slit-lamp biomicroscope and may also involve retinal photography with use of mydriasis; examination conducted by a GP through an ophthalmoscope may also involve instillation of a mydratic in the eyes. NHMRC guidelines on DR recommend CEE and ophthalmoscopy are repeated every two years and yearly among non-Indigenous and Indigenous persons with diabetes, respectively (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.

9. Comparator

The most commonly used diagnostic intervention for diabetic retinopathy at present is a CEE, performed either by an ophthalmologist or optometrist, which includes visual acuity testing and an ocular fundus examination through dilated pupils (mydriasis). In comparison to CEE, RP-NMRC is less costly but also less effective.

Effectively RP-NMRC would be used as a triage test, i.e for instances where no evidence of DR is detected, a CEE would not be considered necessary, whereas any sign of DR would be an indication for referral to CEE. The proposed comparators for the assessment of RP-NMRC are:

- Standard medical assessment, either:
 - a) CEE (includes slit lamp biomicroscopy of the fundus) by an optometrist or ophthalmologist, with or without mydriasis; or
 - b) ophthalmoscopy with mydriasis by a GP.
- No eye examination beyond visual acuity testing.

10. Comparative 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). One Australian study that interviewed 11 Indigenous diabetes patients found that 10 were positive towards RP-NMRC (Spurling et al. 2010).

11. Comparative 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.

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 slit lamp biomicroscopy (SLBM) and/or CEE to detect any level of DR. Unreadable images were considered a positive result (i.e treated as a finding of probable DR which should be assessed further). 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.

Subgroup analysis was also undertaken to investigate the effect of chemical mydriasis, publication year, sample size and the number of fields photographed.

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.

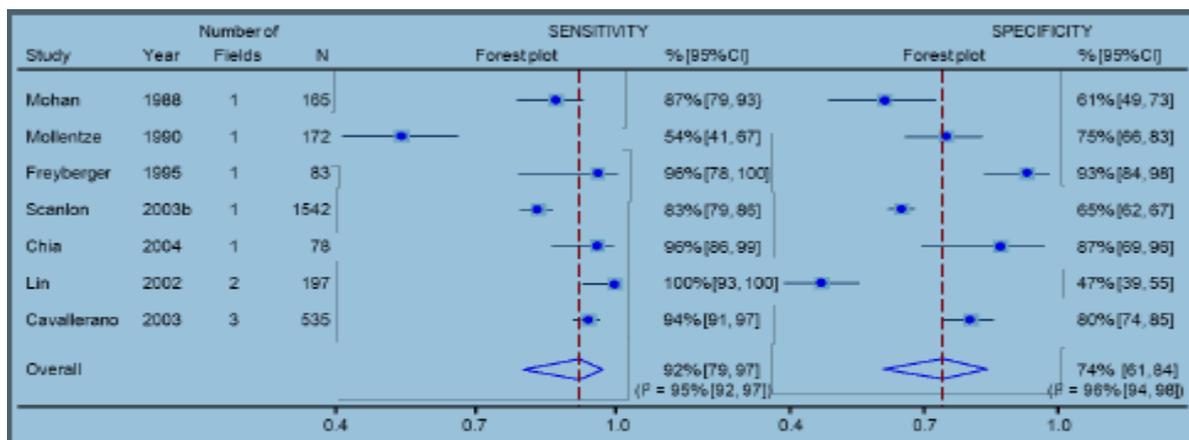


Figure 4 Forest plot of sensitivity and specificity for detection of any DR by RP-NMRC compared with SLBM and/or CEE for studies that did not use chemical mydriasis

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 (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, 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.

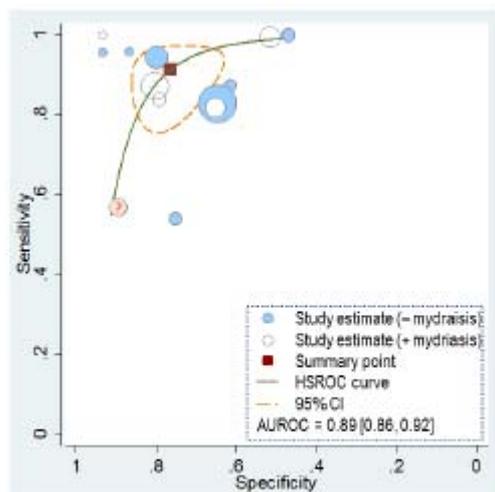


Figure 5 HSROC curve for all studies investigating sensitivity and specificity of RP-NMRC versus SLBM and/or CEE in the detection of any DR according to the use of mydriasis

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

Subgroup analysis showed similar differences according to publication year, with greater sensitivity of RP-NMRC in studies published after 2000, probably due to imaging with multiple fields as opposed to a single field.

Subgroup analysis for the detection of any DR based on the number of fields in the eye that were photographed showed that 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). 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).

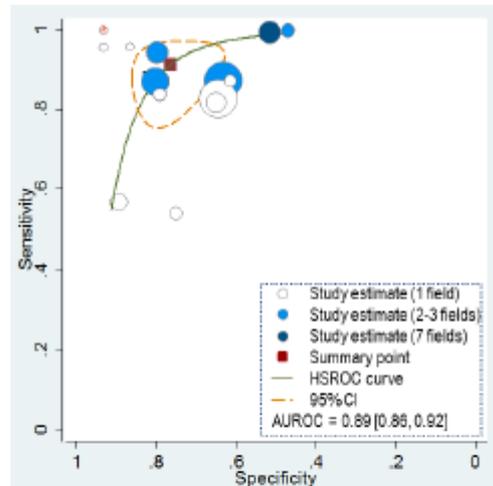


Figure 8 HSROC curve for all studies investigating sensitivity and specificity of RP-NMRC versus SLBM and/or CEE in detection of any DR according to the number of fields photographed

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

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 more Indigenous patients had appropriate surveillance and follow-up in the year after the introduction of clinic-based retinal photography than in the year before (94% 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 of 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 requested that consideration be given to alternative (non-MBS) funding arrangements in the evaluation of RP-NMRC.

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.

12. Economic evaluation

A modelled economic evaluation was 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 was 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) was also presented.

The structure of the economic model was 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).

In the RP-NMRC arm, transitioning to a diagnosed health state was dependent on the diagnostic accuracy of RP-NMRC. In comparison, in the 'no testing' arm of the model, patients were presumed to progress to the AdvSTDR health state before undergoing eye testing due to deteriorating vision. The economic evaluation was conducted from the perspective of the Australian healthcare system. The model had 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 was similar in structure to that for RP-NMRC. The incremental effectiveness of the alternative strategies was dependent on the relative accuracy of the respective testing methods.

Two populations were assessed - the broad Australian diabetic population and the Indigenous Australian diabetic population - 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 below.

Primary comparison of RP-NMRC versus no testing

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
<i>Broader Australian population</i>					
RP-NMRC	\$52,381	\$1,054	10.964	0.071	\$14,875
No testing	\$51,327		10.894		
<i>Indigenous population</i>					
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-mydratric retinal camera

A conservative approach was 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.

The cost of treatment was a major source of uncertainty in the economic model. In the base-case analysis it was assumed that all patients are treated with laser photocoagulation, at an average cost of \$2,214. However, intra-vitreous injection of anti-vascular endothelial growth factor (VEGF) was 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 was 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.

The economic evaluation suggested 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 was most sensitive to the cost of treatment and the quality-of-life weight applied to the AdvSTDR health state, but the ICER remained below \$45,000/QALY gained in all modelled scenarios.

It must be noted that if GPs had cameras they would use them for triage of people they now send to CEE. This would likely be a net saving.

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.

13. Financial/budgetary impacts

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 below.

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						
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-mydratic retinal camera

From the table above, if a 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.

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 with a compensating reduction in the MBS fee would potentially result in savings to the MBS of \$5–\$9 million over the first 6 years of listing on the MBS. Assuming an 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.

14. Key issues from ESC for MSAC

ESC considered that the patient population who would derive the greatest benefit from the availability of RP-NMRC would be in the primary care setting in rural and regional Australia for patients who are less likely to attend the optometrist for a comprehensive eye examination.

Although RP-NMRC is not as effective as a CEE, ESC noted that the proposed use of RP-NMRC will be to triage the need for a CEE and, in this context; the savings from triaging are likely to more than offset the costs of the service.

ESC suggested that MSAC may wish to consider a funding model outside of the MBS to ensure the cameras and trained personnel are made available for patients with the greatest unmet clinical need. ESC further noted there would need to be co-ordinated follow-up services and treatments if this service identifies patients with diabetic retinopathy, particularly in rural and remote areas who would not have been detected otherwise.

ESC was concerned that the estimate of differential costs provided by the applicant was based on the costs of care for patients with diabetes, i.e. it included the costs of all microvascular complications not just costs associated with optical care. The implications of this approach to costing for the value of the ICER calculated was unclear.

ESC considered that the overall costs were very uncertain and likely over-estimated based on extremely optimistic take-up rates, particularly given that GPs would need to purchase cameras, train themselves or staff and have sufficient eligible patients to make it worthwhile.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The applicant believes that it is extremely important that this Medicare item number not be restricted solely to general practitioners and that it be available to all Medicare providers as proposed in the initial application (11.12.2012) and in parts C and D (17.1.2013). This

recommendation was also included in the finalised Consultation Protocol (October 2013). To prevent inappropriate use the proposed item could not be claimed in conjunction with other items by optometrists or ophthalmologists.

The intent is to promote screening for diabetic retinopathy in primary care. However, up to 25% of people with diabetes receive their ongoing primary care from consultant physicians including diabetologists and endocrinologists. It is very important that these people with diabetes are not excluded from the service provided by this item.

The finalised Consultation Protocol (page 18) states “PSC have advised that the service should be reserved exclusively for use in primary care settings (eg GP rooms, diabetes clinics and Indigenous health clinics).”

As diabetic clinics may be run by consultant physicians they must also be able to access this item number.

It is important to remember that up to 98% of the blindness from diabetes can be prevented with appropriately timed treatment and yet only 50% receive the NHMRC recommended eye exams (only 20% for Indigenous Australians) and this item is aimed at providing a mechanism to address this.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.