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Primary Screening for Diabetic Complications: A Systematic Review

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Abstract

Background: Diabetic complications contribute significantly to morbidity in Canada. Regular and effective primary screening for these complications can detect them in their early stages. Early detection may allow for more effective interventions, which may decrease the burden of disease.

Objectives: To systematically review the effectiveness and cost-effectiveness of population-based primary screening models for diabetic retinopathy, nephropathy, and foot ulcers and to document the published literature about screening among those who are indigenous.

Methods: We searched MEDLINE, EMBASE, Cochrane Central Register of Randomized Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL from 2009-present for studies examining primary screening programs for diabetic retinopathy, foot complications, or diabetic nephropathy. Studies were reviewed in duplicate and sorted into three categories: randomized controlled trials (RCTs) to assess effectiveness of screening models, economic evaluations, and studies addressing screening among Indigenous peoples. Studies were appraised for quality with Joanna Briggs Institute tools.

Results: We identified six RCTs, 14 economic studies, and four studies among Indigenous peoples. Nearly all studies discussed screening for retinopathy, except one RCT which addressed all three complications, one economic study investigated each of foot and kidney complications. The RCTs addressed different populations and interventions, but generally found that reminders for patients to screen, comprehensive support programs, and convenient teleophthalmology were associated with higher rates of screening. Economic studies all reported that screening would be considered reasonable value for money by the country-specific threshold. Three of the four studies among indigenous peoples included a qualitative component, and one study was a retrospective audit. Due to the differences in people studied, heterogeneity of study designs and the different evaluated outcomes, no conclusions can be drawn from these data.

Conclusions: There is an emerging, disparate literature about primary screening for diabetic complications. The available clinical efficacy and cost-effectiveness literature does not identify the most effective, cost-effective approaches or models of care for primary screening for diabetic complications related to retinopathy, foot ulcers and nephropathy at a population level. Before widespread implementation within Canada could be considered, a well-designed high-quality study to assess effectiveness and cost-effectiveness should be undertaken. In addition, existing high-quality, validated and comprehensive economic models could be used to inform the design of such a study.

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1 Introduction

Diabetic complications of the eye, foot, and kidney may be severe and life-altering. They are significant contributors to morbidity: in Canada, diabetic macular edema (DME) is the leading cause of blindness in people older than 18 years, and adults with diabetes are twenty times more likely to be hospitalized for a non-traumatic lower limb amputation.[1,2] Up to one half of people with diabetes will have signs of kidney damage at some point in their lives.[3]

Diabetic complications are largely treatable when treatment is begun early in the course of the disease. For example, appropriate early intervention decreases risk of serious vision loss from proliferative retinopathy by 90%, and from diabetic macular edema by 50%.[4] An effective screening model that increases rates of screening for diabetic complications may significantly decrease the burden of disease.[1-3]

Diabetes Canada recommends regular annual eye and kidney screening for all type 1 diabetics aged 15 years old or older, starting five years after diagnosis[1]. It recommends type 2 diabetes patients are screened at diagnosis, and again every 1-2 years.[1] Foot screenings should take place every year. Yet many people with diabetes in Canada do not receive appropriate screening.[5] When considering a screening model, the cost-effectiveness and people who may have different needs and perspectives, such as indigenous peoples, should also be considered.

1.1 Objective

The objective of this review is to establish the effectiveness, and cost-effectiveness, of a primary screening program for diabetic complications, specifically retinopathy, foot ulcers, and nephropathy. In particular, this review will answer the following research questions:

> What are the effective approaches/models of care for population-based primary screening of diabetes complications related to retinopathy, nephropathy, and foot ulcers?
>
> What are the cost-effective approaches/models of care for population based primary screening of diabetes complications related to retinopathy, nephropathy, and foot ulcers?
>
> What does the published literature document about screening among those who are indigenous?

2 Methods

2.1 Search strategy

A systematic review of the literature was completed. MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and CINAHL were searched from 2009-present. The searches were performed on October 30, 2018. Terms capturing diabetic complications of interest (e.g. “diabetic retinopathy,” “diabetic nephropathy,” “diabetic foot”) were searched in combination with terms capturing screening programs (e.g. “mass screening,” “preventative health services,” “screening”). The search was limited to exclude animal studies, editorials, letters, reviews, and case reports. The full search strategies are reported in Appendix 1: Search Strategies.

2.2 Study selection

Four reviewers screened abstracts in duplicate using *a priori* inclusion and exclusion criteria as listed in Table 1. Studies were included if they fell into one of three categories: randomized controlled trials comparing screening models and groups with no screening, economic evaluations, or studies of Indigenous peoples. Studies were excluded if: 1) they did not report on a primary screening model for diabetic retinopathy, foot ulcers, or nephropathy, 2) they did not satisfy the study design criteria for one of the three categories (for example non-comparative studies), 3) they did not study an adult population, and 4) they did not report proportion of patients screened or cost as an outcome. Abstracts marked for inclusion by any reviewer progressed to the next screening stage. Full-texts were retrieved and sorted into three categories: effectiveness, economic evaluations, and those that report studies including Indigenous peoples. Two reviewers screened each full text independently. Discrepancies between reviewers were resolved through discussion and consensus.

Table 1: Inclusion and exclusion criteria

	Inclusion Criteria			**Exclusion Criteria**
Study	• Studies published at or after 2009			• Studies published before 2009
Population	• Adults (18+) with Type 1 and Type II diabetes			• Animals • Children • Gestational diabetes

Intervention (Exposure)	• Models of screening interventions programs (Single or Multifactorial)
	  • Patient oriented
	  • Healthcare provider oriented
				• Effectiveness of screening **procedure** to prevent complication

Comparison	• Different type of screening intervention or program/model • No intervention/program/model of screening			
Outcomes	**Effectiveness of Screening programs/models** • Effective screening programs to reduce diabetes related loss of vision due to retinopathy, chronic kidney disease and lower limb amputation. (Measured as number/proportion of people referred, or taking part in screening program)	**Cost Effective studies** • Cost effectiveness or changes in cost of screening programs to reduce diabetes related complications (retinopathy, kidney disease, foot ulcers)	**Indigenous peoples** • Any outcome related to screening programs	
Design	• RCTs	• Cost minimization • Cost-Effectiveness • Cost Utility	All study designs	Excluded study designs: • Conference proceedings • Editorials or commentaries • Reviews • Summaries • Costing studies

2.3 Data extraction

For all studies, one reviewer extracted year of publication, country, study design, a description of the population, a description of the screening program and comparator, and a description of the outcomes reported into a table. For the economic evaluations, additional methodological data elements were extracted including modelling approach, perspective adopted, time horizon and discount rate. A second reviewer verified the accuracy of the data extracted. *A priori*, a meta-analysis was planned for the studies of effectiveness. However, given the heterogeneity of the literature identified, a meta-analysis was not possible. Thus, all studies were synthesized narratively.

2.4 Quality assessment

All quality assessment was completed in duplicate by two independent reviewers. Randomized controlled trials were assessed with the Joanna Briggs Institute critical appraisal checklist for randomized controlled trials.[6] Economic studies were evaluated with the Joanna Briggs Institute critical appraisal checklist for economic studies.[7] Discrepancies between reviewers were resolved through discussion and consensus. Due the variability of study designs in the review of studies of Indigenous peoples, quality assessment was not performed on these papers.

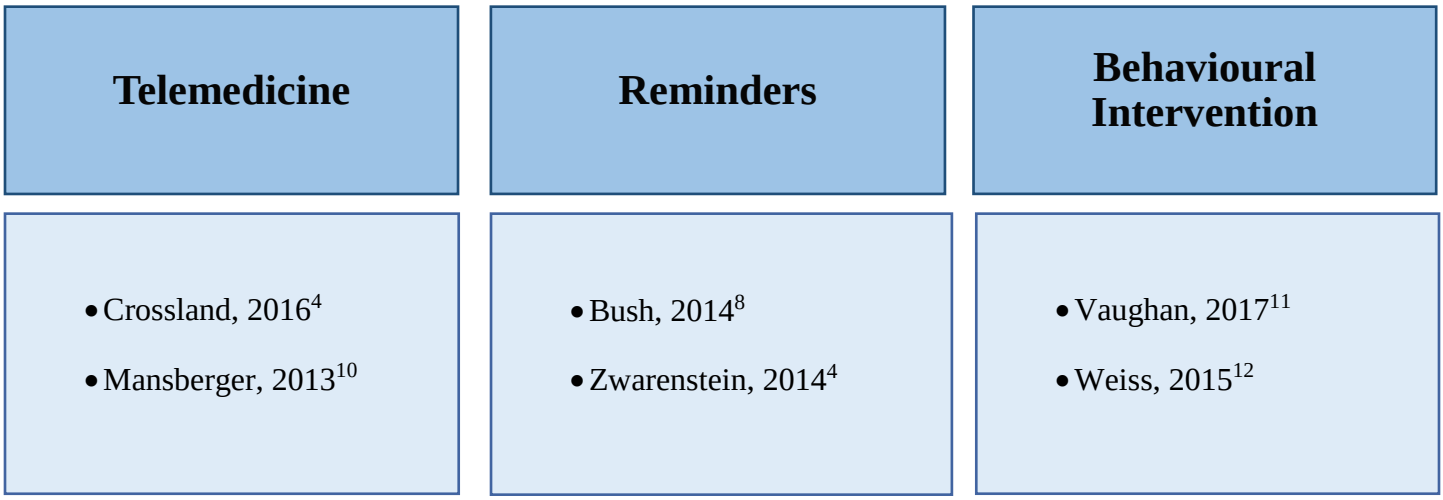
3 Effectiveness

3.1 Results

3.1.1 Included studies

A detailed diagram of study selection can be found in Appendix 2: PRISMA flow-chart. Six randomized controlled trials addressing primary screening for the included diabetic complications were identified.[4,8-12] All six studies examined screening for retinopathy; one study also examined nephropathy and foot complications.[11] Three studies were published in the United States,[10-12] one in Australia,[9]one in the United Kingdom,[8] and one in Canada[4] (Table 2). The studies used different types of interventions: two of the studies used telemedicine for retinopathy,[9,10] two studies used reminders for retinopathy screening and two studies used some form of behavioral intervention (one specific to retinopathy screening; [12] and one for retinopathy, foot complications, and nephropathy [11]) (Figure 1).

Figure 1. Summary of studies included by type of interventions used



Bush et al examined the impact of Link Workers providing patients with telephone reminders to attend their retinopathy screening.[8] The study randomized ten general practices with "a high proportion of patients of South Asian ethnicity" in the United Kingdom. Five practices were assigned to send appointment reminders by post to patients who missed their initial screening appointment (usual care) (patient n=1692). Five practices had multi-lingual Link Workers call patients who missed their first appointment on the day before their second appointment (intervention) (patient n=988). The mean proportion of screening attendance was significantly higher in practices assigned to the intervention (0.89) than in practices assigned to the control condition (0.74), a difference of 0.15 (95% CI: 0.04-0.27). Of the patients who missed their first appointment in the intervention practices (n=271, 160 of whom were contacted by Link Workers), 53% attended the second appointment. Of patients who missed their first appointment in control practices (n=580), 21% attended the second appointment; a difference of 34% (95% CI: 27%-41%).[8]

Crossland et al examined an enhanced care pathway for retinopathy detection in Australia.[9] Five general practices were assigned to continue usual care by sending patients written or verbal reminders to access their local screening services (patient n=577). Five general practices were assigned to the intervention group (patient n=447), in which GPs completed a four-hour online training program and accreditation assessment. Intervention practices were also given a non-mydriatic camera, staff training to operate and maintain the camera, and were partnered with a remotely located ophthalmologist. All (100%) of eligible intervention patients received reminders or referrals to screening, and nearly 100% of intervention patients (446/447) received appropriate screening based on guidelines established by the Australian National Health and Medical Research Council (NHMRC). Sixty-two percent of control patients received reminders or referrals, and 33% received NHMRC-appropriate screening. Screening rates in all intervention practices exceeded national population average screening rates.[9]

Mansberger et al examined retinopathy screening in patients from two clinics serving a large proportion of people with diabetes who have difficulty accessing retinopathy screening in the United States.[10] Patients were randomized to a control group undergoing traditional surveillance (n=271) and an intervention group screened by telemedicine (n=296). Patients in the control group were asked by their primary care providers to seek screening for retinopathy. The patients in this group arranged their own screening appointment with local eye care providers. Patients assigned to the intervention group were screened by technicians in their primary care clinic before, during, or after their usual primary care visit. Ninety-four percent of intervention patients were screened within 12 months of enrollment, whereas 56% of control patients were screened within 12 months ($p<0.001$).[10]

Vaughan et al examined the integration of Community Health Workers (CHWs) into diabetic care for low-income Hispanic adults in the United States.[11] Patients in the control arm (n=31) continued with their usual care and received a bathroom scale and glucometer upon patient or provider request. Patients in the intervention group (n=31) attended monthly 3-hour group meetings, involving lab checks and education about screening and prevention of diabetic sequelae (among other topics). Intervention participants were assigned a CHW, who contacted them between group sessions with reminders about diabetes care, including screening appointments. Intervention participants were all supplied with a bathroom scale, a glucometer, and a log for weight, glucose, and medication. With respect to retinal screening, patients in the intervention arm received care that was significantly more concordant with practice guidelines than the care received by the participants in the control arm (90.5% concordant with guidelines in the intervention group, vs. 13.3% concordant in the control group, $p<0.001$). Similarly, with respect to foot exams, 57.1% of intervention participants received care that was concordant with practice guidelines vs. 0.0% of control participants ($p<0.001$). Lastly, 81.0% of intervention participants vs. 28.6% of control participants received care that was concordant with practice guidelines for urine microalbumin testing ($p<0.01$).[11]

Weiss et al examined the role of behavioral activation for retinopathy screening in African American diabetes patients aged 65 years or older.[12] The control participants (n=103) received a structured placebo intervention consisting of in-home supportive therapy; a race/ethnicity-concordant community health worker (CHW) visited patients and used open-ended, nonjudgmental questions to encourage them to reflect on their care. If requested, the CHW provided contact information for local ophthalmologists. In the intervention group, participants received education about diabetes and behavioral therapy from a race/ethnicity-concordant CHW. The intervention used a health belief model to help patients set goals, problem-solve barriers, and evaluate success. If requested, the CHW assisted patients in making appointments with ophthalmologists. Of the 91 patients in the intervention arm who completed the study, 85.7% reported having a dilated fundus exam (DFE) in 6 months. Of the 88 patients in the control arm who completed the study, 51.1% reported having a DFE in 6 months. The risk difference of a self-reported DFE between the groups was 0.346 (95% CI: 0.20-0.46). A higher proportion of intervention participants had a medically confirmed DFE in the 6 months of the study (87.9% vs 34.1%), with a risk difference of 0.538 (95% CI: 0.40-0.64). Overall, the intervention group was more likely to receive a DFE than the control group, with a risk difference of 2.58 (95% CI: 1.91-3.48).[12]

Finally, Zwarenstein et al examined the impact of printed educational messages regarding diabetic retinopathy screening sent to Ontario family practitioners.[4] In this study, family practices randomized to the control arm continued to receive a free peer-reviewed primary care newsletter called *Informed*, with

no additional materials included (total physician n=1282). Family practices randomized to the intervention condition received *Informed*, plus additional printed educational material. The educational material consisted of two components: a two-page insert with background, the summary of an evidence-based guideline, and references, and a short, post-card sized 'outsert' with a simple directive about retinopathy screening. One intervention group received *Informed* with the insert (physician n=1273). Another intervention group received *Informed* with the outsert (physician n=1252), and a third group received *Informed* with both the insert and the outsert (physician n=1241). The two groups (outsert, and outsert+insert) were further randomized to receive a pad of reminders to distribute to their patients, or no pad of reminders (outsert + reminder: physician n=629; insert + outsert + reminder: physician n= 621). Success was defined as an eye exam (including retinal screening) of a patient with diabetes who was not screened in the prior 12 months, with the screening event taking place within 90 days of the patient visiting their family physician.. Success rates did not differ significantly between any of the groups, even after adjusting for patient- and physician-level covariates. The median success rate was 31.0% for the control group, 30.9% for the insert group, 30.8% for the outsert only group, 30.4% for the outsert + reminders group, 30.3% for the insert + outsert group, and 30.4% for the insert + outsert + reminders group.[4]

Table 2: Studies included in the effectiveness review

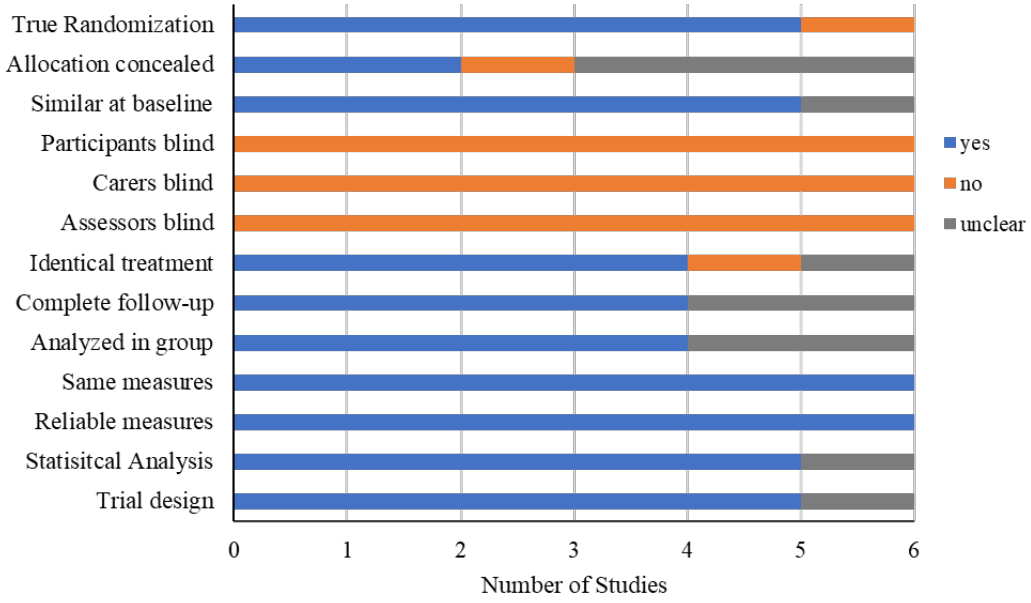
Author, country, date	Study design	Population	Comparator	Number in the Compar.	Intervention	Number in the Interven.	Outcomes reported	Findings
Bush United Kingdom 2014[8]	Cluster RCT (randomized by practice)	10 General Practices with high proportion of South Asian patients	Reminder to screen sent by post	5 practices, 1692 patients	Link Workers providing telephone reminders	5 practices, 988 patients	Attendance at diabetic retinopathy screening	**Attended Screening (first or second):** Intervention: 87% Comparator: 73% Difference: 14% (95% CI 11%-17%)
Crossland Australia 2016[9]	Open controlled trial (randomized by practice)	General practices in Queensland Australia with at least 50 patients with type 2 diabetes receiving diabetes care	Usual referral pathway (internet reminder letter or verbal reminder to patient)	5 practices, 577 patients	In-house screening by trained GPs and nurses, and teleophthalmic support for patients with mild-moderate DR, and quarterly videoconference education for first 12 months for GPs and ophthalmologists	5 practices, 447 patients	Screening rates; appropriate follow-up recorded	**Referral or reminder to screen recorded (range of % across 5 practices):** Intervention: 100% Comparator: 22%-53% **Screening outcome reported:** Intervention: 99% in one practice; 100% in the other 4 practices Comparator: 22 to 57% in 5 practices **Follow-up recorded for patients identified with mild-moderate DR:** Intervention: 71% in one practice; 100% in the other 4 practices Comparator: 27 to 57% in 3 practices; 2 practices did not report follow-up
Mansberger US 2013[10]	RCT	Diabetic patients; 18 years or older scheduled to visit their clinic primary care provider	Traditional surveillance with an eye care provider	271	Telemedicine with a nonmydriatic camera	296	Proportion of diabetic retinopathy screening; state of diabetic retinopathy; risk factors for DR; referral patterns	**Proportion DR screening:** Intervention: 94% Comparator: 56%

Vaughan US 2017[11]	RCT with delayed control	Low income Hispanic adults with type 2 diabetes receiving care in a community clinic	No community health workers (CHWs)	25	Monthly 3 hour comprehensive diabetes group visits with CHWs, with weekly individual CHW contact	25	Adherence to guidelines (% screened); participant acceptability	**Adherence to guidelines (% Screened)** **Retinal eye exam:** intervention 90.5%; comparator 13.3% **Comprehensive foot exam:** Intervention 57.1%; comparator 0% **Urine microalbumin:** Intervention 81.0%; comparator 28.6%
Weiss US 2015[12]	RCT	African American individuals 65 years or older with diabetes mellitus and no DR screening in past 12 months, recruited from an academic medical centre or community care programs	Supportive therapy-structured placebo treatment	88	Behavioral activation for DR- education, behavioral therapy, health belief model	91	Medical documentation of dilated fundus examination at 6 months follow-up; National eye institute vision function questionnaire	**Medical documentation of dilated fundus examination at 6 months follow-up** Intervention: 87.9% Comparator: 34.1%
Zwarenstein Canada 2014[4]	Pragmatic 2x3 cluster RCT (randomized by practice)	Ontario family practices active in Ontario in 2003/2004	Professional newsletter with no printed educational materials	1051 family practices	1. Newsletter + full educational insert 2. Newsletter + educational outsert stapled to front; further randomized to receive pad of patient reminders, or no pad. 3. Newsletter + insert + outsert; further randomized to receive pad or no pad	1: 1042 2 with pad: 523; 2 w/o pad: 519 3 with pad: 519; 3 w/o pad: 527	Retinal screening within 90 days after visiting the family practitioner for patient with diabetes who was not screened in the previous 12 months	**Percentage of patients obtaining retinal screening in 90 days of mail out (Crude success rate, Median %)** **Comparator**: 31.6% (25th and 75th percentile 25.0%- 37.0%) **Interventions:** Newsletter + insert: 30.9% (25.3% - 37.8%) Newsletter+ outsert, no reminder notepad: 30.8% (25.0%- 37.1%) Newsletter+ outsert and reminder notepad: 30.4% (25.0%- 37.5%) Newsletter+ insert and outsert, no reminder notepad: 30.3% (25.0% - 37.3%) Newsletter+ insert and outsert and reminder notepad: 30.4% (25.0% - 37.5%) *p*= 0.96 (crude success rate)

3.1.2 Quality assessment

A summary of the quality assessment of the studies using the Joanna Briggs Institute critical appraisal checklist for randomized controlled trials[6] is presented in Figure 2 (individual study quality is in Appendix 3: Table 1). All but one of the studies were deemed to be of high quality in terms of randomization.[4,8,10-12] One study was not randomized nor was the allocation sequence concealed; in this study, general practices were approached to be in the intervention group, then subsequently other practices were allocated as controls.[9] In three studies, allocation concealment was not clearly reported,[8,10,11] and in two studies the allocation sequence was concealed.[4,12] In all but one study, participants were similar at baseline.[4,9-12] In the remaining study, baseline characteristics were not reported; this was a cluster randomized controlled trial randomizing by practice.[8] None of the studies were blinded to participants, providers, or outcome assessors.[4,8-12] In four of the six studies, aspects of treatment other than the intervention were controlled.[4,8,9,12] One study specifically encouraged patients assigned to tele-ophthalmology to access in-person screening as well, but did not account for the number of patients who did so.[10] Another study provided equipment such as a bathroom scale and glucometer to all intervention participants, and also to some control patients (only on request) and also did not account for how many control patients accessed this equipment.[11] No study reported any instance of incomplete follow-up or patients/clinics analyzed in the wrong group, but only some papers provided any information about follow-up and analysis.[4,10-12] Cluster trials and papers with a complete PRISMA chart were considered to have all data analyzed in the group as randomized.[4,8,9,12] All studies used reliable measurements similarly for both intervention groups and control groups. Five studies employed appropriate statistical analyses,[4,8,10-12] and appropriate study designs for their purposes.[4,8,9,11,12]

Figure 2. Quality assessment summary



3.2 Conclusions

In total, only six RCTs specifically evaluated models of screening for diabetic retinopathy, nephropathy, or foot ulcers. Two of these studies evaluated tele-ophthalmology, [9,10] two studies evaluated reminders to screen for retinopathy, [4,8] and two examined the role of support for people with diabetes.[11,12] One study examined a clinic population with a high proportion of South Asian patients, [8]one study included only Hispanic patients, [11] and another study included only African American patients.[12] Given the diversity of interventions, populations, and reported outcomes, a meaningful synthesis of this data was not possible.

The only Canadian study examined the role of various forms of reminders delivered to general practices in Ontario. This study found no significant differences in the screening of diabetic patients for retinopathy.[4] The other study that evaluated the impact of reminders on screening targeted the reminders at patients, and used telephone calls to contact patients immediately before scheduled appointments. This study found a significant difference between patients contacted by phone and patients contacted by post.[8]

Both of the studies examining tele-ophthalmology found significant differences in screening rates between traditional pathways and pathways that included a tele-health component.[9,10] Both of the studies evaluating the impact of additional support on patients' screening behaviors found a significant difference in screening rates; these studies examined the intervention in specific racial/ethnic groups, rather than in a general population.[11,12]

4 Economic Evaluations

4.1 Results

4.1.1 Retinopathy

4.1.1.1 Included studies

Twelve studies were included in the final data set of economic evaluations of screening for retinopathy (Appendix 2: PRISMA flow-chart). Of these, 7 studies compared no screening to a form of screening[13-19] while 5 studies compared different methods of screening without considering a no screening comparator.[20-24] All but one of the studies used a modelling approach, either a simple decision tree or markov model; one study reported direct observations using a historical cohort.[18] The studies are conducted in a variety of populations including 3 studies from the United Kingdom,[20-22] and 1 from each of Canada,[24] Hong Kong,[16] Japan,[19] South Africa,[18] Korea,[17] Singapore,[23] India,[15] China[13] and the United States.[14]

4.1.1.2 Findings

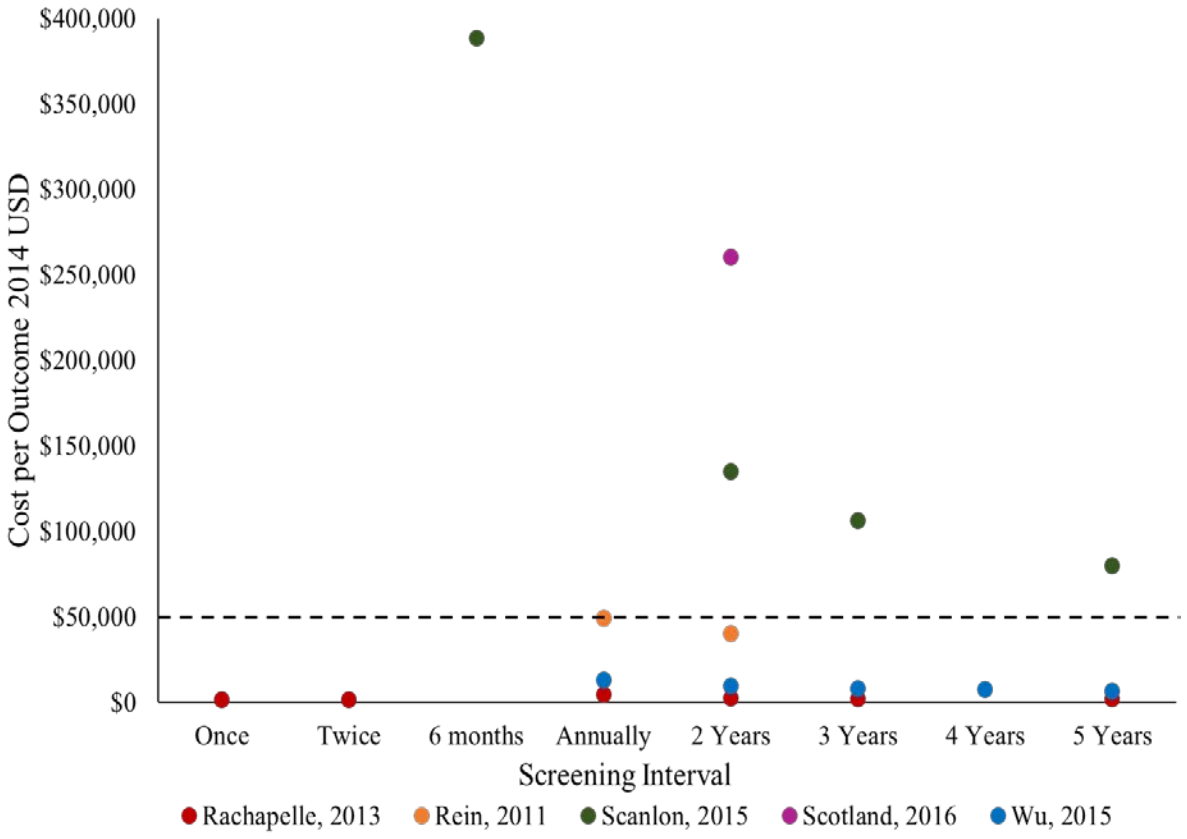
Compared to no screening, all seven studies reported increased costs and increased effectiveness with any screening programme; no studies reported cost savings associated with moving from no screening to some kind of screening programme.[13-19] The incremental cost-effectiveness ratios (ICER) ranged and all the estimates are from different countries limiting their comparability. However, all the estimates were below the country-specific willingness-to-pay-threshold (e.g. $50,000 US, 1100 ZAR, 5,000,000 Yen) meaning that screening could be considered reasonable value for money within their context. There was significant uncertainty in all the models driven by the same two key variables: the effectiveness of screening and the costs of screening. As the effectiveness of screening decreased and the costs increased, screening becomes less economically attractive.

Six studies assessed the time interval of screening.[13-15,19,21,22] The studies assessed a range of intervals from once-in-a-lifetime to as frequently as every 6 months. The ICER for each strategy reported within each study is presented in Figure 3 (Kawasaki is excluded as it did not provide useable comparative data). Each study is represented by a colour and the ICER for each screening strategy, compared to the least frequent screening, is plotted. It is important to note that the baseline strategy varies for each study thus the ICERs are not directly comparable. However, Figure 3 does provide a visual summary of how the ICER changes with screening frequency.

Four of the studies concluded that biennial screening was the most cost-effective option whereas one study concluded that screening every 3 years was the most cost-effective and the final study found that

screening completed every 3-5 years was the most cost-effective option. No study reported that screening more frequently than biennially was the most cost-effective option.

Figure 3. Cost per QALY for various screening intervals for retinopathy, as reported within each study. (Kawasaki is excluded as it did not provide useable comparative data). Each study is represented by a colour. The dashed line at $50,000 per QALY represents the willingness-to-pay threshold that may be considered reasonable value for money within Canada. The comparators vary across the studies.



Three studies compared different screening approaches.[17,20,23] Kim et al compared systematic screening with fundus photography to systematic screening by an ophthalmologist in the Korean population.[17] Systematic screening with an ophthalmologist was more expensive and more effective than fundus photography. However, the QALY gain is small (9.06) resulting in very high incremental cost-effectiveness ratio (308,193,813 Won). This ICER is substantially larger than the ICER resulting from the change from opportunistic screening to systematic screening (43,575,592 Won per QALY gained with systematic screening with fundus photography compared to opportunistic screening). This same pattern is reported within the other two studies that compared technology-enabled screening to human-based screening. Nguyen et al. found that the "real-time" assessment of DR photographs by a centralized team supported by a tele-ophthalmology information technology infrastructure (SiDRP) dominated, was less expensive and more effective, than screening by primary care physicians.[23] Tufail et al. reported that a strategy where all images are run through automated screening software compared to being seen by a level 1 manual grader resulted in a cost reduction of £4.51 per appropriate outcome missed.[20]

The only Canadian study compared screening by a primary care physicians with fundus examination to teleophthalmology within pharmacies.[24] The model simulated a southwestern Ontario semi-urban area. The study found that teleophthalmology within a pharmacy was more costly and more effective than screening in primary care with an incremental cost per case detected of $314. There was limited sensitivity analysis completed (deterministic only). The results were robust to variations in all variables except the cost of the primary care consultation. When the cost of the consult was greater than $77, teleophthalmology within a pharmacy becomes the dominant option (less costly and more effective).

4.1.1.3 Quality assessment

The above studies are all high quality (Appendix 5: Table 1). The research questions are clear, the models capture the appropriate health states and are developed using high-quality inputs. All of the studies have unclear generalizability to the Canadian population. In particular, several of the studies simulate models in emerging nations where the health care systems and access to care may vary from the Canadian context.

4.1.2 Foot Ulcers

One study was identified that assessed the cost-effectiveness of telemonitoring screening for diabetic foot ulcer (Appendix 4: Table 1).[25] The study reported a Markov model simulating population-based and high-risk (those who have already had an ulcer) screening in Canada, based on Ontario data. The study is of high quality with the only area of concern being the establishment of clinical effectiveness (Appendix 5: Table 1). The effectiveness is measured in decreased foot ulcers and the estimate is informed by clinical expert opinion, a weak form of evidence.

The primary outcome of the model was the cost per QALY comparing the current screening approach to the simulated alternatives. The study reports that population-based screening resulted in $50,915 - $120,087 per QALY gained compared to the standard approach. Within the probabilistic sensitivity analysis, all simulations resulted in higher costs and higher QALYs for population-based screening. However, with high-risk screening the study finds an increase in 0.000207-0.00058 QALYS and cost savings of $1.26-$25.55 compared to standard screening. Within the probabilistic sensitivity analysis, all the simulations resulted in cost savings while approximately 25% of the simulations resulted in decreased QALYs.

4.1.3 Nephropathy

Similarly, only one study was identified that assessed the cost-effectiveness of annual microalbuminuria screening (Appendix 4: Table 1).[26] The study reports a Markov model simulating screening with urine dipstick compared to no screening in the Thai population. The study is high quality with no areas of methodological concerns (Appendix 5: Table 1). However, the generalizability of Thai costs, treatment pathways and utility estimates to the Canadian context is unknown.

The study reports the primary outcome of 3,035 THB ($128 CAD) per QALY gained with urine dipstick screening compared to no screening. The results are affected to changes in the PPV of the urine dipstick (the cost per QALY decreases by 76% and increases by 55% when the PPV is varied), the costs of dipsticks (decreases of 59% and increases of 62% in the cost per QALY) and the discount rate (decreases of 18% and increases of 27% in the cost per QALY).

4.2 Conclusions

We identified 14 economic evaluations assessing the cost-effectiveness of primary screening for diabetic complications; 12 screening for retinopathy and 1 screening for each of nephropathy and foot ulcers. All studies were of high-quality and applied best practices for economic modelling. All of the studies that compared any screening programme to no screening found that screening was associated with higher costs and higher effectiveness and an incremental cost effectiveness ratio that would be considered reasonable based on the country-specific thresholds.

The generalizability of this literature to the Canadian context is unknown. Four studies are from countries that may be considered peer nations (the United States and the United Kingdom). However, the majority of studies are from emerging nations (e.g. India, Singapore) with different healthcare systems, access to care and underlying sociodemographic profiles. To understand the transferability of these findings to Canada, the individual model inputs, such as epidemiologic data, costs and health utility values, should be assessed for comparability to those of the Canadian context.

Six of the included studies compared different screening intervals and 3 compared different technology-enabled screening approaches. This literature consistently found that screening intervals of 2 years or more and technology-enabled platforms that reduce the need for human assessment of **all** patients are more cost-effective. As technology continues to advance, screening algorithms that capitalize on technology to segment the population into levels of risk are likely promising to decrease the economic burden of screening.

Only one Canadian study was identified and its contribution to understanding the most cost-effective way to develop a screening programme in Canada is limited. It assessed two models of screening (through primary care or teleophthamology with pharmacies). To bolster this weak body of literature, a simulation of screening including different intervals and technological approaches within the Canadian context should be completed before the widespread adoption of any screening programme.

The currently published literature presents numerous high-quality, validated and comprehensive economic models. These models represent a pre-existing infrastructure that could be leveraged in the Canadian context. To avoid duplication and unnecessary effort, building collaborative links with the existing economic modelling teams, particularly those within the United Kingdom who completed their models for the National Institute of Care and Health Excellence (NICE), should be explored.

Of note, none of the studies reported cost savings. It is likely that within a Canadian context, additional resources would be required to implement a screening programme. Within the context of a fixed healthcare budget, it is important to consider the opportunity cost (the health benefit that could have been derived from funding the next best alternative) associated with programmes.[27] There is a growing body of literature documenting factors other than the cost per QALY are valued in funding decisions. These include 1) whether an intervention is immediately lifesaving, and less so, the expected gain in life expectancy, 2) the impact on quality of life, 3) the number of people eligible for treatment, 4) the age of the potentially treatable patients (younger versus older), 5) whether the treatment was for people with good or poor underlying baseline health, 6) the likelihood of the treatment being successful, and 7) its impact on equality of access to therapy.[28-30] Applying this checklist to primary diabetes screening would be useful as the policy conversation about primary screening continues.

Lastly, the overall budget impact of screening programmes was not reported in any of the studies. This provides important information about the overall required financial expenditure within a specific healthcare system. This analysis, complementing an economic evaluation, within a Canadian context will be required to inform evidence-based policy development.

5 Indigenous peoples

5.1 Placing the research team in context

It is important to acknowledge that research concerning Indigenous peoples in Canada has been largely defined and performed by non-Indigenous researchers in ways that do not reflect Indigenous world views and has not necessarily benefited Indigenous peoples or communities. Research has not typically recognised the diversity of First Nations, Métis and Inuit living in Canada, including diverse languages, cultures, histories and perspectives. While the research team finds the primary screening for diabetic complications among Indigenous peoples to be a crucial research gap worthy of additional attention, it was beyond the scope of this systematic review to provide the appropriate context to interpret the results in Indigenous peoples. We acknowledge that Indigenous researchers, organizations and communities are leaders in performing research that benefits Indigenous peoples and are best positioned to explore, review and contextualize the existing evidence and research in the primary screening of diabetic complications among Indigenous peoples.

5.2 Results

5.2.1 Included studies

We identified four studies considering diabetic complications screening among Indigenous peoples (Table 3*)*.[31-35] All four studies concerned retinopathy screening only. Two studies used mixed methods,[33,35] one study used qualitative methodology only,[31] and one study used a prospective cross-sectional design.[34] One study was Canadian, published in 2013,[31] and three were Australian, published between 2010 and 2018.[33-35] The Canadian study was localized to a Cree First Nation in Alberta.[5] Two of the Australian studies included Indigenous peoples in the Kimberley Region of Western Australia, and the third Australian study was in an urban Indigenous clinic in Brisbane, Queensland.[20-23]

Arora et al. investigated the success of using culturally sensitive tele-ophthalmology screening to overcome sociocultural barriers to retinopathy screening in a Cree First Nation in Alberta.[31] The authors examined a tele-health screening clinic in the Aboriginal Diabetes Wellness Program (ADWP) by interviewing five patients, two program administrators, two nurses, and one cultural liaison from the community. Program nurses were fluent in Cree and hired from local communities. Traditional practices that included cultural artifacts and ceremonies were integrated into the program. Participants discussed their experiences, health, challenges, and goals in a talking circle. Cultural activities related to health behaviors were implemented, such as bracelet making with coloured beads to help remember medication regimens. Appointment attendance rates increased from 20% in 2009 to 85% in 2011. The interviews with program participants revealed four main barriers to healthcare access: economic, geographic, social,

and cultural. Participants discussed feelings of discrimination and communication difficulties with health care professionals in hospital-based clinics. The authors of the study speculate that some of the cultural elements of the screening program, such as the Smudge ceremony, may be difficult to implement in a hospital setting. The tele-health model allows for the incorporation of more appropriate social and cultural aspects of care, and the hiring of local nurses familiar with the language and the community.[31]

Meyer et al. evaluated the impact of an educational video aimed at Indigenous peoples living in Western Australia assessed by a questionnaire and semi-structured interviews.[33] The educational video *Bad Sugars, Bad Eyes* was developed by the Lions Eye Institute in the Kimberley Region of Western Australia in collaboration with Aboriginal Health Workers (AHWs) and local community members. The video was narrated in English with AHWs available to assist in participant interpretation as there are twenty-eight Indigenous languages spoken in the region, English is the most commonly shared language. The questionnaires were tailored with specific language, visuals, and wording to maximize participant comprehension. Eighty-four patients participated. Before watching the video, 29.2% of patients were not aware that annual screening for retinopathy was recommended; the video increased awareness by 35% (p=0.031). Before the video, 15.3% of participants did not believe screening was required unless visual symptoms had presented. Awareness of the need for screening without visual symptoms increased by 13% (p=0.008). Before watching the video, 11.2% of participants were not aware that diabetic retinopathy could be serious enough to cause blindness; after the video, awareness increased by 9.3% (p=0.031). Interviews with AHWs revealed that participants found the video to be understandable, relatable, and culturally appropriate. Participants indicated that the casting of Indigenous people in the video was most important to them, and that the biggest shortcoming of the video was the absence of a female speaker.[33]

Table 3: Studies included in the Indigenous populations review

Author, country, date	Retinopathy, foot ulcers, nephropathy?	Study design	Intervention	Population	Population n=	Outcomes reported	Findings
Arora, Canada, 2013[31]	Retinopathy	Qualitative	Culturally sensitive diabetes tele-ophthalmology screening program	Cree First Nation peoples living in Alberta, Canada with diabetes	5 patients; 2 program administrators; 1 nurse from the hospital; 1 nurse from the remote clinic; 1 cultural liaison of the First Nation community	Participants identified barriers to accessing services: 1. Economic and geographic considerations 2. Societal and cultural barriers 3. Absence of cultural rituals and ceremonies	A culturally-sensitive model of healthcare delivery in a community-based health clinic improved access to tele-ophthalmology services in a First Nation community.
Meyer, Australia, 2016[33]	Retinopathy	Mixed Methods: Pre-post questionnaire with patients; semi-structured interview with Aboriginal health workers	Eye screening education video	14-89 years Indigenous peoples living in Western Australia with a diagnosis of type 1 or 2 diabetes	84 patients; 11 Aboriginal Health Workers	Increase awareness of diabetic retinopathy and annual screening in absence of visual symptoms; cultural appropriateness of video; ease to understand; video content appropriateness	**Awareness of recommendation or annual screening:** Pre-questionnaire 29.2% of presenting patients unaware Post-questionnaire: after watching video 35% increase in awareness **Awareness of need for screening in absence of visual symptoms** Pre-questionnaire 15.3% of participants did not understand the need for screening in absence of visual

							symptoms post-questionnaire: 13% increased in awareness after watching video
Moynihan, Australia, 2017[34]	Retinopathy	Retrospective audit	Impact of a Kimberley diabetic eye health coordinator (KDEHC)	Indigenous peoples living in Western Australia with diabetes	947 Indigenous patients	Increase screening coverage provided by the program for Indigenous peoples with diabetes. Increase in screening sites during study.	Screening coverage: 9.44% in 2010, 29.8% in 2014 Number of participating sites: 4 in 2010, 17 in 2014 70.2% of the Indigenous Australian population did not screen in last year of the program
Spurling, Australia, 2010[35]	Retinopathy	Mixed Methods: quantitative portion measured access to screening and results of screening pre-post first retinal photo; Qualitative measured patient experience	Clinic diabetic retinopathy (DR) screening	Indigenous peoples living in Queensland, Australia with diabetes	132- overall quantitative; 11-qualitative	Access to appropriate screening and ophthalmic follow up. Prevalence of DR. Acceptability and feasibility of clinic-based retinal photography	Appropriate screening and follow up increased more than 6 times from 15% (20/132 participants) before clinical based DR screening program to 93.9% (124/132) after clinical retinopathy screening program

Moynihan et al. examined the employment of a Kimberley diabetic eye health coordinator (KDEHC) to support and coordinate screening for retinopathy in the Kimberley region in Western Australia.[34] The KDEHC trained AHWs and other clinic staff in the use of the retinal camera and provided screening in regions that did not have a retinal camera or operating staff of their own. The position was jointly established between the Lions Eye Institute and the Kimberley Aboriginal Medical Services Council (KAMSC). During the tenure of the KDEHC, screening program coverage increased from 9.44% in 2010 to 29.8% in 2014 ($p<0.05$), and the number of screening sites increased from four to 17. Even so, 70.2% of the Indigenous Australian population did not undergo screening in the last year of the program (2013-2014). Data were collected for 1,029 patients, of whom 916 were Indigenous. Six-hundred and sixty-six Indigenous patients received an initial screening and a recommendation for repeat screening within 12 months, but only 147 (22.1%) of these participants accessed the repeat screening, and of those who eventually did access a second screening, only 44.3% were re-screened within 9-15 months. The authors speculate that many Indigenous people living in Australia did not access screening services at all, and that a portion of this population may have been screened in alternative settings (for example, regional optometrists), which would not have been recorded by the study audit.[34]

Finally, Spurling et al. examined the introduction of a retinal photography screening program for patients with diabetes at the Inala Indigenous Health Service (IIHS), an urban Indigenous primary health clinic in Brisbane, Australia.[35] A retinal camera was purchased and training provided to clinic nurses for the operation of the camera and for two general practitioners (GPs) in the interpretation of the photographs. Participants (n=132) were recruited over two years. Nurses took photographs of each retina, with dilation only used in cases of unreadable photographs. Screening and follow-up rates increased more than six times, from 20 participants screened in the year before introduction of the program to 124 out of 132 the year after. Eleven participants selected by clinic staff as the most likely to speak to investigators were contacted and interviewed by phone (n=10) or in person (n=1) about their experiences. Of these 11 participants, 10 found the program to have improved their screening experience, specifically citing convenience and a culturally safe, comfortable environment. Most interviewees indicated that all Indigenous Health Services should offer the screening. One participant discussed having trepidations about the provision of eye-care by non-specialists, stemming from the perception of inexperience of recently trained nursing staff operating the cameras.[35]

5.2.2 Quality assessment

Due to the variety of methods employed by the studies with Indigenous peoples, quality assessment was not performed.

5.3 Conclusions

Four studies examining an intervention of diabetes complications screening among Indigenous peoples met our inclusion criteria.[31,33,35] Three of the four studies included a qualitative component, and one study was a retrospective audit.[34] Due to the heterogeneity of study designs and the different evaluated outcomes, no conclusions can be drawn from these data.

The only Canadian study evaluated the acceptability of a culturally sensitive diabetes care program, which included a screening component for retinopathy in the context of a Cree First Nation in Alberta.[31] This study demonstrated that incorporation of cultural and social elements into diabetes care can significantly increase the uptake of retinopathy screening in this Cree community. The generalizability of these results to other Indigenous communities in unknown, although likely to be low given the diversity among communities and peoples.

6 Conclusions

There is an emerging, disparate literature about primary screening for diabetic complications. The available clinical efficacy and cost-effectiveness literature does not identify the most effective, cost-effective approaches or models of care for primary screening for diabetic complications related to retinopathy, foot ulcers and nephropathy at a population level. Most of the literature is concentrated in retinopathy screening, with only one clinical study and one cost-effectiveness study exploring screening for foot ulcers and nephropathy.[11,25,26] However, the cost-effectiveness literature does point towards biennial screening intervals, technology-enabled approaches that minimize human resources for lower-risk people and approaches that segment the general population into risk groups. This finding could be incorporated into the planning of a screening programme but has not been validated within the clinical efficacy literature. Before widespread implementation within Canada could be considered, a well-designed high-quality study to assess effectiveness and cost-effectiveness should be undertaken. In addition, existing high-quality, validated and comprehensive economic models could be used to inform the design of such a study. The model could also be used to complete a value-of-information assessment to quantify the value of increased precision in specific variables such as the clinical effectiveness of a screening programme.

7 References

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Appendix 1: Search Strategies

MEDLINE

1. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
2. Diabetic Retinopathy/pc, th [Prevention & Control, Therapy]
3. Diabetic Nephropathies/pc, th [Prevention & Control, Therapy]
4. Diabetic Foot/pc, th [Prevention & Control, Therapy]
5. 2 or 3 or 4
6. Foot Ulcer/
7. Amputation/
8. Renal Insufficiency/
9. exp Renal Insufficiency, Chronic/
10. exp Renal Replacement Therapy/
11. GANGRENE/
12. 6 or 7 or 8 or 9 or 10 or 11
13. 1 and 12
14. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 ((retina* adj3 (complication* or degenerat* or disorder* or lose or losing or loss$2 or problem*)) or retinopath*)).tw,kf.
15. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (foot or feet)).tw,kf.
16. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (amputat* or gangren*)).tw,kf.
17. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement)).tw,kf.
18. 5 or 13 or 14 or 15 or 16 or 17
19. mass screening/ or multiphasic screening/ or vision screening/
20. (detect* or prescreen* or screen*).tw,kf.
21. 19 or 20
22. 18 and 21
23. limit 22 to animals
24. limit 22 to (animals and humans)
25. 23 not 24
26. 22 not 25
27. limit 26 to yr="2009 -Current"
28. limit 27 to (english or french)
29. limit 28 to (case reports or comment or editorial or letter or "review")
30. 28 not 29
31. limit 28 to (meta analysis or systematic reviews)
32. ((systematic or scoping or synthesis or critical) adj (review* or overview*)).tw,kf.
33. 28 and 32
34. 30 or 31 or 33

EMBASE

1. diabetes mellitus/
2. insulin dependent diabetes mellitus/
3. non insulin dependent diabetes mellitus/
4. 1 or 2 or 3
5. diabetic retinopathy/pc, th [Prevention, Therapy]
6. diabetic nephropathy/pc, th [Prevention, Therapy]
7. diabetic foot/pc, th [Prevention, Therapy]
8. 5 or 6 or 7
9. foot ulcer/
10. exp amputation/
11. kidney failure/ or acute kidney failure/ or exp chronic kidney failure/ or end stage renal disease/ or renal replacement therapy-dependent renal disease/ or severe renal impairment/
12. gangrene/
13. toe gangrene/
14. retinopathy/
15. 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 ((retina* adj3 (complication* or degenerat* or disorder* or lose or losing or loss$2 or problem*)) or retinopath*)).tw,kw.
18. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (foot or feet)).tw,kw.
19. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (amputat* or gangren*)).tw,kw.
20. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement)).tw,kw.
21. 8 or 16 or 17 or 18 or 19 or 20
22. mass screening/ or screening/ or multiphasic screening/ or screening test/
23. vision test/
24. (detect* or prescreen* or screen*).tw,kw.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to animal studies
28. limit 26 to (human and animal studies)
29. 27 not 28
30. 26 not 29
31. limit 30 to yr="2009 -Current"
32. limit 31 to (english or french)
33. limit 32 to (conference abstract or editorial or letter or "review")
34. 32 not 33
35. ((systematic or scoping or synthesis or critical) adj (review* or overview*)).tw,kw.
36. 32 and 35
37. 34 or 36

Cochrane Central Register

1. diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/
2. Diabetic Retinopathy/pc, th [Prevention & Control, Therapy]
3. Diabetic Nephropathies/pc, th [Prevention & Control, Therapy]
4. Diabetic Foot/pc, th [Prevention & Control, Therapy]
5. 2 or 3 or 4
6. Foot Ulcer/
7. Amputation/
8. Renal Insufficiency/
9. exp Renal Insufficiency, Chronic/
10. exp Renal Replacement Therapy/
11. GANGRENE/
12. 6 or 7 or 8 or 9 or 10 or 11
13. 1 and 12
14. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 ((retina* adj3 (complication* or degenerat* or disorder* or lose or losing or loss$2 or problem*)) or retinopath*)).tw,kf.
15. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (foot or feet)).tw,kf.
16. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (amputat* or gangren*)).tw,kf.
17. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement)).tw,kf.
18. 2 or 3 or 4 or 13 or 14 or 15 or 16 or 17
19. mass screening/ or multiphasic screening/ or vision screening/
20. (detect* or prescreen* or screen*).tw,kf.
21. 19 or 20
22. 18 and 21
23. limit 22 to yr="2009 -Current"

Cochrane Database of Systematic Reviews

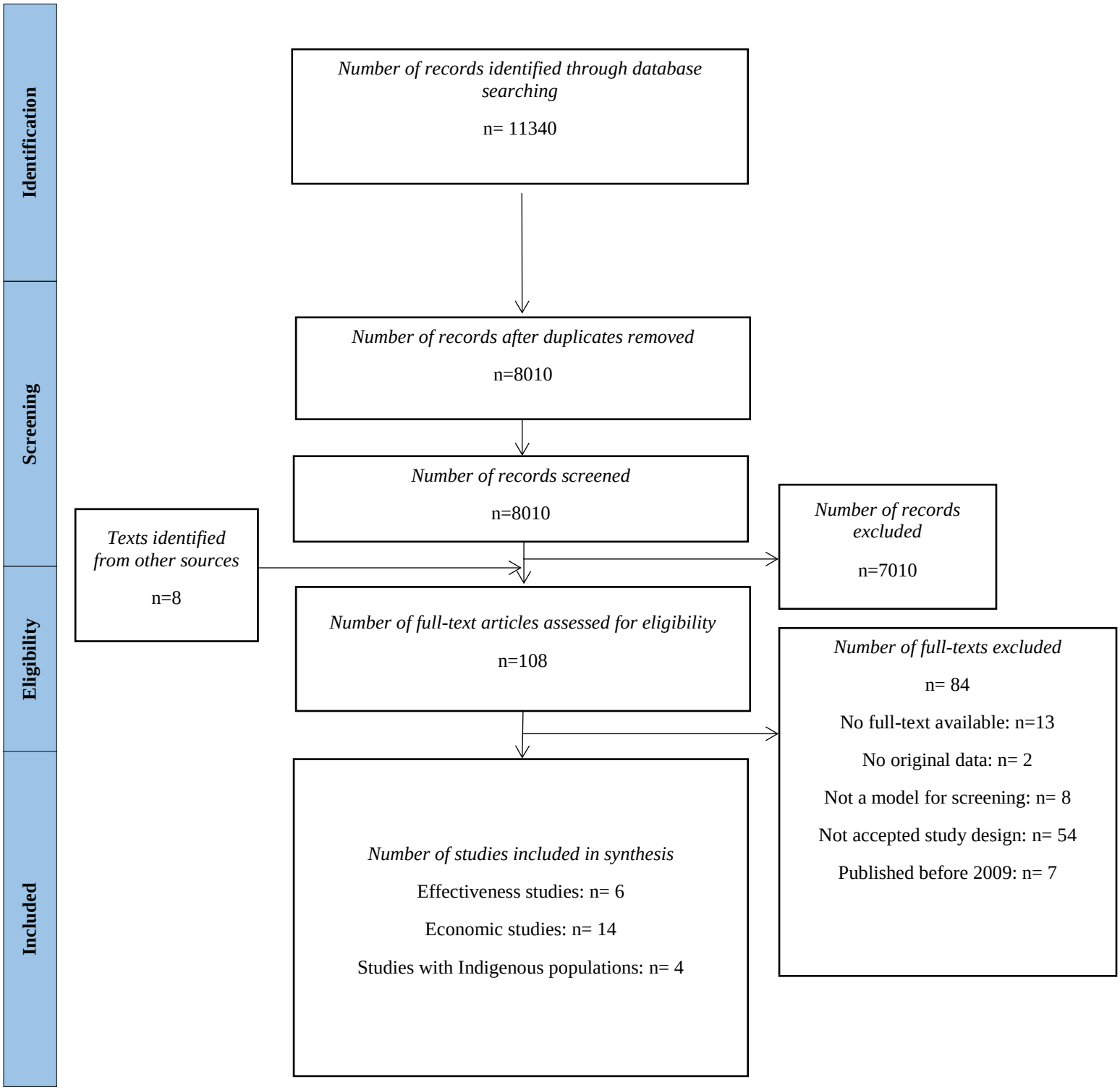
1. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 ((retina* adj3 (complication* or degenerat* or disorder* or lose or losing or loss$2 or problem*)) or retinopath*)).tw,kf.
2. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (foot or feet)).tw,kf.
3. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (amputat* or gangren*)).tw,kf.
4. ((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) adj5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement)).tw,kf.
5. (detect* or prescreen* or screen*).tw,kf.
6. 1 or 2 or 3 or 4
7. 6 and 5
8. limit 7 to last 10 years
9. limit 8 to protocols
10. 8 not 9

CINAHL

1. ((MH "Diabetes Mellitus") OR (MH "Diabetes Mellitus, Type 2") OR (MH "Diabetes Mellitus, Type 1")) OR TI (diabetes or diabetic*) OR AB (diabetes or diabetic*)
2. (MH "Diabetic Retinopathy/PC/TH") OR (MH "Diabetic Foot/PC/TH") OR (MH "Diabetic Nephropathies/PC/TH")
3. (MH "Foot Ulcer") OR (MH "Amputation") OR (MH "Above-Knee Amputation") OR (MH "Below-Knee Amputation") OR (MH "Amputation Stumps") OR (MH "Renal Insufficiency") OR (MH "Renal Insufficiency, Chronic") OR (MH "Renal Replacement Therapy") OR (MH "Gangrene")
4. 1 and 3
5. TI (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 ((retina* N3 (complication* or degenerat* or disorder* or lose or losing or loss* or problem*)) or retinopath*))) OR AB (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 ((retina* N3 (complication* or degenerat* or disorder* or lose or losing or loss* or problem*)) or retinopath*)))
6. TI (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (foot or feet))) OR AB (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (foot or feet)))
7. TI (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (amputat* or gangren*))) OR AB (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (amputat* or gangren*)))
8. TI (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement))) OR AB (((diabetes or diabetic* or Type 1 DM or Type 2 DM or T1DM or T2DM or IDDM or MODY or NIDDM) N5 (Ckd or ESKD or ESRD or chronic kidney or chronic renal or glomerulosclerosis or kidney function or kimmelstiel-wilson syndrome or nephropath* or renal replacement)))
9. 2 or 4 or 5 or 6 or 7 or 8
10. (MH "Health Screening") OR (MH "Vision Screening")
11. (TI (detect* or prescreen* or screen*))) OR AB (detect* or prescreen* or screen*))))
12. 10 or 11
13. 9 and 12
14. Limit 13 to 2009-2018
15. Limit to English or French

Appendix 2: PRISMA flow-chart

Figure 1: PRISMA chart



Appendix 3: Quality assessment for randomized controlled trials

Table 1: Quality assessment of randomized controlled trials

Author, Country, Year	True randomization	Allocation concealed	Similar at baseline	Participants blind	Carers blind	Assessors blind	Identical treatment	Complete follow-up	Analyzed in group	Same measures	Reliable measures	Statistical analysis	Trial design
Bush United Kingdom 2014	Yes	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Crossland Australia 2016	No	No	Yes	No	No	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes
Mansberger US 2013	Yes	Unclear	Yes	No	No	No	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear
Vaughan US 2017	Yes	Unclear	Yes	No	No	No	No	Yes	Unclear	Yes	Yes	Yes	Yes
Weiss US 2015	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zwarenstein Canada 2014	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 4: Included economic studies

Table 1: Studies included in the economic review

Type of Screening Programme	Author, country, date	Population	Model	Perspective	Comparators	Health States	Time Horizon	Discount Rate	Primary Outcome	Currency (year)	Assessment of Uncertainty	Primary result
Retinopathy	Coronado Canada 2016	People with diabetes (type 1 and type 2) residing in semi-urban areas	Simple decision tree	Health care system	1. Primary care examination (fundus exam with pupil dilation) 2. Pharmacy-based teleophthalmology (retinal imaging)	Referral	12 months	Cost: 5% Benefit: not specified	Cost per additional case correctly diagnosed	Canadian Dollars (2013)	Deterministic sensitivity analysis (one-way and two-way)	Compared to primary care examination, pharmacy-based teleophthalmology has an additional cost of $73.24 per case detected.
	Kawasaki Japan 2015	Hypothetical Japanese cohort 50,000 age 40	Markov Model	Societal (National Health Insurance and patient co-pay)	1. No screening (current standard) 2. screening program provided by ophthalmologist using dilated fundus examination	normal pre-diabetes DM NPDR severe NPDR PDR high-risk PDR CSME(low Va or high VA) stabilized DR(low Va or high VA) blindness	lifetime (40 yrs)	Cost:3% Benefit: 3%	Cost per QALY	Japanese Yen (2012)	probabilistic sensitivity analysis	944,981 Yen ($11,857 USD) per QALY gained
	Khan South Africa 2013	14,541 patients with type 2 diabetes screened in three primary health care facilities in Cape town between 2007 and 2010	direct cost and outcome observation, no model	Provincial government as the third party health funder	1. No screening (no screening in place prior to 2007)	Screened referral to ophthalmologist undergoing cataract operations	2007-2010	No discounting applied	cost per blindness case averted	ZAR (not specified)	sensitivity analysis	10,500 Zar ($1206 USD) per case of blindness averted

Retinopathy	Kim Korea 2015	Hypothetical cohort of 10,000 adults aged 40 years with newly diagnosed diabetes	Markov Model	Societal	1. no screening 2. opportunistic screening examination (fundus examination by an ophthalmologist) 3. systematic fundus photography systematic examination by an ophthalmologist	NPDR PDR CSME severe vision loss	lifetime (40 years)	Cost: 5%; Benefit: 5%	cost per QALY	Korean Won (KRW)(2013)	sensitivity analysis	Compared to no screening: Opportunistic screening: 48,961,339 ($56,883 CAD) per QALY Systematic photography: 43,575,592 ($50,626 CAD) per QALY gained Systematic examination by ophthalmologists: 308,193,813 ($358,059 CAD) per QALY
	Lian Hong Kong 2015	Hypothetical cohort of 1,000 individuals with diabetes with mean starting age of 64 years.	Markov Model	Provider and societal	1. No screening 2. Case ascertainment (add on to routine visit) 3. Systematic screening with a co-pay ($60 HK) 4. Systematic screening with no co-pay	no DR background DR pre-proliferative DR proliferative DR maculopathy non-clinically significant macular edema clinically significant macular edema blindness death	Lifetime	Cost: 3.5%; Benefit:3.5%	Cost per QALY	2009 HK dollars	Probabilistic sensitivity analysis	Compared to no screening: Case ascertainment: $73,394 per QALY ($12607 CAD) Co-Pay: $71,179 per QALY ($12227 CAD) No co-pay: $480,479 per QALY ($82,539 CAD)
	Nguyen Singapore 2016	Hypothetical cohort of patients with type 2 diabetes aged 55 years not previously screened for DR	Markov model	healthcare system and societal perspectives	1. Singapore Integrated Diabetic Retinopathy program (SiDRP)-telemedicine-based 4. Existing model (family physician assess photographs)	no DR mild DR moderate/severe DR	Lifetime	Cost: 3% Benefit: 3%	Cost per QALY	Singapore dollar (2015)	Probability sensitivity analysis	Both models have the same effectiveness and SiDRP costs less so it dominates the current model.

Retinopathy	Rachapelle India 2013	Hypothetical cohort of 1000 rural people with diabetes 40 years of age	Markov Model	Societal	1. No screening 2. Once-in-a-lifetime 3. Twice-in-a-lifetime 4. Screening every 5 years 5. Screening every 3 years 6. Screening every 2 years 7. Annual screening	No DR non-STDR STDR clinically significant macula edema Blind from DR	Lifetime (25 years)	Cost: 3% Benefit: unknown	Cost per QALY	2009 USD	Probabilistic sensitivity analysis	Compared to no screening: Once: $2692 per QALY Twice: $2475 per QALY Every 5 yrs: $3134 per QALY Every 3 yrs: $3365 per QALY Every 2 yrs: $3669 per QALY Annually: $5677 per QALY
	Rein United States 2011	Hypothetical mixed-age cohort of people with diabetes at low-risk for progression	Markov Model	Societal	1. Patient self-referral (no screening) 2. Annual screening 3. Screening every 2 years 4. Annual telemedicine screening	Non-vision threatening DR Vision threatening stages of DR	Lifetime (until 90 years of age)	Cost: 3% Benefit: 3%	Cost per QALY	2010 USD	Probabilistic sensitivity analysis	Compared to self-referral: Annual screening: $45,586 per QALY Screening every 2 yrs: $37,531 per QALY Annual Telemedicine screening: $54,979 per QALY
	Scanlon United Kingdom 2015	People with Diabetes	continuos-time hidden Markov model	UK NHS and personal social services	1. Screening every 6 months 2. Screening every year (current practice) 3. Screening every 2 years 4. Screening every 3 years 5. Screening every 5 years	No DR Background in 1 eye, no DR in other Background DR in both Pre-proliferative or proliferative in 1 eye, no DR in other Pre-proliferative or proliferative in both Diabetic maculopathy in 1 eye, any DR in other Maculopathy in both	Lifetime	Cost:3.5% Benefit: 3.5%	Cost per QALY	£ 2012-2013	probabilistic sensitivity analysis	Compared to every 5 years: Every 6 months: £288,497 per QALY gained Every year: £98,085 per QALY gained Every 2 years: £45,684 per QALY gained Every 3 years: £26,156 per QALY

Retinopathy	Scotland United Kingdom (Scotland) 2016	simulated cohort based on a random sample (n=7439) of the Scottish screening cohort	continuos-time hidden Markov model	Healthcare payer	1. annual screening for those with no retinopathy, 6-monthly screening for those with observable retinopathy (current practice) 2. 2-year intervals for those with no retinopathy 3. 2-year intervals for those with no retinopathy at first screen 6. 2-year intervals for those observed with no retinopathy at 2 consecutive screens	Non-referable Referable	Lifetime (30 years)	Cost: 3.5%; Benefit:3.5%	Cost per QALY	£ 2012-2013	Probabilistic sensitivity analysis	Compared to 2-year interval for those with no DR: Current practice: £ 232,290 per QALY gained 2-year intervals for those observed with no retinopathy at 2 consecutive screens: £ 480,006 per QALY gained 2-year intervals for those with no retinopathy at first screen: : £ 73,960 per QALY gained
	Tufail United Kingdom 2016	People with diabetes who attend a routine annual NHS diabetic screening	Simple decision tree	Healthcare payer	1. Manual grading 2. Automated screening followed by human grading for positive, ungradable and a small proportion of negatives (ARIAS 1) 4. Automated screening such that 90% of screened would be invited to annual screening (no level 2 human grading) (ARIAS 2)	R0 R1 R2 R3 M1a M1b U	1 year	Cost: 3.5% Benefit: Not reported	Cost per appropriate screening outcome identified	£ (2013/14)	Deterministic sensitivity analysis (one-way and two-way)	Compared to manual grading: ARIAS 1: reduction of £4.51 per appropriate outcome ARIAS 2: reduction of £2.80 per appropriate outcome

Retinopathy	Wu China 2015	Hypothetical Chinese patients with newly diagnosed type 2 diabetes	Discrete Event Simulation	Chinese healthcare system	1. No screening 3. Diabetic retinopathy screening at 1-yr, 2-yr, 3-yr, 4-yr and 5-yr intervals	No retinopathy Nonproliferative retinopathy Proliferative retinopathy Macular edema	Lifetime	Cost: 3% Benefit: 3%	Cost per QALY	US $ equivalents (2014)(US $1=CNY 6.2)	Probability sensitivity analysis	Compared to no screening: $12 970 for 1-yr screening $9273 for 2-yr screening $7879 for 3-yr screening $7312 for 4-yr screening $6625 for 5-yr screening
Foot Ulcer	Boodoo; Canada; 2018	Hypothetical cohort of Canadian patients aged 60 years with diabetes and no history of ulceration	Markov Model	Not stated	1. Standard care (current screening standards) 2. Population-wide (device given before formation of an ulcer) telemonitoring 3. Targeted (high-risk- given after first diabetic foot ulcer) telemonitoring programs	low risk for foot ulcer moderate risk for foot ulcer Foot ulcer Amputation Death	5 years	Cost: 1.5% Benefit: 1.5%	Cost per QALY, Proportion of diabetic foot ulcers prevented; Cost of screening	Canadian dollars (2015)	Probability sensitivity analysis	Compared to no screening: Population-based screening: $50,915 - $120,087 /QALY gained High-Risk screening: increase in 0.000207-0.00058 in QALYS and cost savings of $1.26-$25.55
Nephropathy	Srisubat Thailand 2014	Simulated cohort of 10,000 45-75 year-old normotensive people with type 2 diabetes	Markov Model	Societal	1. No screening 2. Screening by Urine dipsticks	Normoalbuminuria Microalbuminuria Macroalbuminuria Elevated serum creatinine end stage renal disease death	Lifetime	Cost: 3% Benefit: 3%	Cost per QALY	Thai Baht (not specified)	Probabilistic sensitivity analysis	3,035 THB ($128 CAD) per QALY gained compared to not screening.

Appendix 5: Quality assessment of economic studies

Table 1: Quality assessment of economic studies

Author, Country, Year	Well-defined question	Comprehensive description of alternative	All important/relevant costs and outcomes for each alternative	Established clinical effectiveness	Costs and outcomes measured accurately	Costs and outcome valued credibly	Costs and outcome adjusted for differential timing	Incremental analysis of costs and consequences	Sensitivity analyses for uncertainty in estimates of costs or consequences	Results include all issues of concern to users	Results generalizable to setting of interest
Coronado Canada 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kawasaki Japan 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear
Khan South Africa 2013	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Unclear
Kim Korea 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Lian Hong Kong 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Nguyen Singapore 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Rachapelle India 2013	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Rein United States 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear

Scanlon United Kingdom 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Scotland United Kingdom 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Tufail United Kingdom 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Wu China 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Boodoo Canada 2018	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Srisubat Thailand 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear