

***HbA1c testing in the
diagnosis of diabetes
mellitus***

January 2014

MSAC application no. 1267

Assessment report

© Commonwealth of Australia 2014

ISBN (online) – 978-1-74186-142-6

ISSN (online) – 1443-7139

Publication Approval Number – 10785

Internet site <http://www.msac.gov.au/>

© Commonwealth of Australia 2014

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the *Copyright Act 1968*, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney-General's Department, Robert Garran Offices, National Circuit, Barton ACT 2600 or posted at <http://www.msac.gov.au/>

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's internet site at <http://www.msac.gov.au/>

This report was prepared for the Medical Services Advisory Committee (MSAC) by Jacqueline Parsons, Arlene Vogan, Judy Morona, Camille Schubert and Tracy Merlin from Adelaide Health Technology Assessment (AHTA), The University of Adelaide, with the assistance of Health Expert Standing Panel member Professor Stephen Colagiuri. The report was commissioned by the Department of Health on behalf of MSAC. It was edited by Jo Mason of MasonEdit, Adelaide.

MSAC is an independent committee that has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

This report should be referenced as follows:

Parsons J, Vogan A, Morona J, Schubert C & Merlin T 2014, *HbA1c testing in the diagnosis of diabetes mellitus*. MSAC Application 1267, Assessment Report, Commonwealth of Australia, Canberra, ACT.

Contents

Executive summary	xv
Assessment of HbA1c testing in the diagnosis of diabetes mellitus	xv
Glossary and abbreviations	24
Introduction	26
Rationale for the assessment of HbA1c testing	26
Process of technology assessment.....	26
Background	28
HbA1c testing	28
Intended purpose.....	28
Clinical need	30
Existing diagnostic tests.....	32
Current reimbursement arrangements	33
Consumer impact statement	34
Diagnostic criteria and terminology.....	34
Approach to assessment	36
Objective	36
Clinical pathway	36
Comparator.....	39
The reference standard	40
Research questions	40
Diagnostic assessment framework.....	41
Review of literature	44
Expert advice: Health Expert Standing Panel (HESP).....	53
Results of assessment	54
Is it safe?	54
Is it effective?	55
Is there an impact on clinical decision-making?	81
Other relevant considerations	83
Groups in whom the test may not be reliable	83
Ethical considerations	85
What are the economic considerations?	86

Economic evaluation.....	86
Financial impact	118
Discussion	137
Is it safe?	137
Is it effective?	137
Are there other relevant considerations?.....	140
What are the economic considerations?	141
Conclusions	143
Safety.....	143
Effectiveness.....	143
Other relevant considerations.....	144
Economic considerations.....	144
Appendix A Health Expert Standing Panel and Assessment Group.....	146
Appendix B Search strategies.....	147
Appendix C Study profiles of included studies	151
Appendix D Extra results	174
Appendix E Additional economic information	186
Appendix F Additional financial information.....	207
Appendix G Excluded studies.....	220
References	226

Tables

Table 1:	Summary of the economic evaluation.....	xix
Table 2:	Stepped incremental cost-effectiveness of the HbA1c_1 (base-case) scenario vs FPG with/without OGT testing	xx
Table 3:	Stepped incremental cost-effectiveness of the HbA1c_2 (alternative) scenario vs FPG with/without OGT testing	xx
Table 4:	Proposed MBS item descriptors for HbA1c testing in the diagnosis of diabetes	30
Table 5:	MBS item descriptors for current diagnostic tests (fees at 1 January 2014)	32
Table 6:	MBS item descriptors for associated consultations and HbA1c test for diabetes management (fees at 1 January 2014)	34
Table 7:	Diagnostic criteria used in the studies included in the review	35
Table 8:	Summary of PICO criteria to define research questions used to investigate HbA1c as a diagnostic tool.....	41
Table 9:	Electronic databases searched	44
Table 10:	Evidence dimensions	48
Table 11:	Designations of levels of evidence according to type of research question (including tablenotes).....	49
Table 12:	Body of evidence matrix.....	53
Table 13:	Summary of studies included in WHO review and DETECT-2 pooled analysis	56
Table 14:	Results from three studies comparing diagnostic accuracy of blood glucose measures against reference standard of retinopathy	58
Table 15:	Brief description of study design and quality of studies providing raw (2x2) data comparing HbA1c with FPG with or without 2hPG testing	62
Table 16:	Summary of diagnostic accuracy results for diabetes diagnosed by HbA1c vs OGT testing (additional studies).....	67
Table 17:	Summary of diagnostic accuracy results of diabetes diagnosed by HbA1c vs FPG testing	69
Table 18:	Summary of diagnostic accuracy results of diabetes diagnosed by HbA1c vs 2hPG testing	71

Table 19: Diagnostic accuracy of HbA1c testing for diabetes in subgroups of older adults	73
Table 20: Summary of the accuracy of HbA1c testing in the diagnosis of diabetes in ethnic minorities	76
Table 21: Estimated average cost per person associated with testing in the diagnosis of diabetes, per test strategy (assuming 100% compliance with testing).....	88
Table 22: Economic evaluations identified that investigate the cost-effectiveness of screening for pre-diabetes/diabetes using patient uptake and test accuracy parameters.....	89
Table 23: Summary of the economic evaluation.....	92
Table 24: Sensitivity and specificity parameters of HbA1c testing used in the economic model.....	96
Table 25: Proportion of positive results in diabetes range observed, compared with modelled estimates	97
Table 26: Patient uptake rates of the available testing options (by circumstance) used in the economic model.....	98
Table 27: Prevalence estimates observed in the general Australian population transformed to the high-risk population in the modelled economic evaluation	99
Table 28: Incidence estimates observed in the general Australian population transformed to the high-risk population (pre-diabetes only) in the modelled economic evaluation	100
Table 29: Mortality estimates used in the economic model	101
Table 30: Testing-related healthcare resources used in the economic model	103
Table 31: Annual Australian direct healthcare costs and modelled health state costs, reported by glucose tolerance status	104
Table 32: Health state utility weights used in the economic evaluation.....	105
Table 33: Implications for false positive and false negative tests and re-testing in the economic evaluation	106
Table 34: Stepped incremental cost-effectiveness of the base-case (HbA1c_1) scenario vs FPG/OGT testing.....	107
Table 35: Stepped incremental cost-effectiveness of the alternative (HbA1c_2) scenario vs FPG/OGT testing.....	108

Table 36: Five variables with the highest spread observed in the tornado analysis, base-case (HbA1c_1) scenario	112
Table 37: Five variables with the highest spread observed in the tornado analysis, alternative (HbA1c_2) scenario	114
Table 38: Additional sensitivity analyses.....	117
Table 39: Data sources used in the financial analysis	118
Table 40: MBS item fees and patient co-payments for tests in the financial analysis.....	120
Table 41: Total test costs used in financial analysis.....	120
Table 42: Estimated population projection of people with known diabetes or pre-diabetes, 2012–13	122
Table 43: Estimated number of people eligible for testing in the high-risk population, 2012–13	124
Table 44: Estimated number of people eligible for testing, 2012–13.....	125
Table 45: Test utilisation of current testing strategy, 2012–13.....	126
Table 46: Total number of tests under the base-case (HbA1c_1) scenario and cost implications.....	127
Table 47: Total number of tests under the alternative (HbA1c_2) scenario and cost implications.....	128
Table 48: Total number of tests under the current testing scenario and cost implications	130
Table 49: Net financial cost per year to the MBS for each test scenario	132
Table 50: Net financial cost per year to the MBS for each test scenario, excluding test accuracy parameters in analysis	133
Table 51: Sensitivity analyses around net financial implications to the MBS, base-case (HbA1c_1) scenario	134
Table 52: Sensitivity analyses around net financial implications to the MBS, alternative (HbA1c_2) scenario	135
Table 53: Net financial costs per year to private health insurers and/or patients for each test scenario, including safety net impacts.....	136
Table 54: Net financial costs per year to private health insurers and/or patients for each test scenario, including safety net impacts, excluding test accuracy parameters in analysis	136

Table 55: Body of evidence matrix for diagnostic accuracy of HbA1c testing against diabetic retinopathy.....	138
Table 56: Body of evidence matrix for diagnostic accuracy with no reference standard of retinopathy	139
Table 57: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes with retinopathy as the reference standard.....	151
Table 58: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes: studies included in meta-analysis.....	152
Table 59: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes: studies not included in meta-analysis but providing diagnostic accuracy data	159
Table 60: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in older adults	164
Table 61: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in ethnic minorities	165
Table 62: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in children.....	168
Table 63: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in people with CVD	171
Table 64: Summary of concordance results across categories of diabetes, pre-diabetes and no diabetes, for studies providing raw (3x3) data.....	174
Table 65: Summary of diagnostic accuracy results for HbA1c vs FPG and/or 2hPG testing for pre-diabetes	174
Table 66: Summary of diagnostic accuracy results for HbA1c vs FPG and/or 2hPG testing in people with conditions that increase the risk of developing diabetes	176
Table 67: Summary of data for comparison of HbA1c levels in patients with and without chronic renal disease	177
Table 68: Summary of data for comparison of HbA1c levels in patients with and without anaemia	177
Table 69: Summary of diagnostic accuracy for HbA1c testing vs WHO criteria (2006) for diagnosing diabetes and pre-diabetes in people with and without anaemia	178

Table 70: Summary of data for comparison of HbA1c levels in patients with and without haemoglobinopathies.....	179
Table 71: Summary of data for comparison of HbA1c levels using different methods in patients with haemoglobinopathies.....	181
Table 72: Testing-related healthcare resources used in the test cost analysis	186
Table 73: Range of test costs to reach each diagnostic conclusion for comparator and HbA1c testing.....	187
Table 74: Test accuracy estimates for pre-diabetes and diabetes (from studies identified in the systematic review, compiled for the economic evaluation)	190
Table 75: Weighted average patient episode initiation fee	195
Table 76: Resource use estimated for people with a false diagnosis of diabetes	196
Table 77: Stepped cost-effectiveness rankings, considering all scenarios.....	197
Table 78: Incremental costs and effectiveness outcomes, by model health state, HbA1c_1 scenario.....	197
Table 79: Incremental costs and effectiveness outcomes, by model health state, HbA1c_2 scenario.....	198
Table 80: Cost-effectiveness analysis, HbA1c_1 scenario vs HbA1c_2 scenario, step 3	198
Table 81: Tornado analysis of the base-case (HbA1c_1) scenario, tabulated.....	199
Table 82: Tornado analysis of the alternative (HbA1c_2) scenario, tabulated.....	200
Table 83: Tornado analysis of the base-case (HbA1c_1) scenario (Step 2), tabulated.....	203
Table 84: Tornado analysis of the alternative (HbA1c_2) scenario (Step 2), tabulated.....	205
Table 85: Additional sensitivity analyses.....	206
Table 86: Medicare statistics for items associated with tests listed in item 66500	207
Table 87: Estimated ordering of initial FPG test.....	207
Table 88: Diabetic and pre-diabetic population projections, 1999–00 to 2018–19 (some years omitted)	208

Table 89: Estimated population of women with a history of gestational diabetes or polycystic ovary syndrome eligible for OGT testing, 1999–00 to 2018–19 (some years omitted)	209
Table 90: Diagnostic conclusions of testing, current testing strategy, 2012–13.....	211
Table 91: Total number of tests under the base-case (HbA1c_1) testing scenario and cost implications	214
Table 92: Total number of tests under the alternative (HbA1c_2) scenario and cost implications.....	215
Table 93: Total number of tests under the current testing scenario and cost implications	215
Table 94: Sensitivity analyses of financial implications of base-case (HbA1c_1) scenario (including safety net implications).....	217
Table 95: Sensitivity analyses of financial implications of the alternative (HbA1c_2) scenario (including safety net implications).....	218

Boxes

Box 1: Criteria for selecting direct evidence on the safety and effectiveness of HbA1c testing	45
Box 2: Criteria for selecting studies relevant to assess the predictive accuracy of HbA1c testing	46
Box 3: Criteria for selecting studies relevant to assess a change in patient management as a result of HbA1c diagnostic testing.....	46

Figures

Figure 1: Age- and gender-specific prevalence (%) of diabetes among Australian residents.....	31
Figure 2: Current diagnostic algorithm according to NHMRC guidelines.....	38
Figure 3: Proposed diagnostic algorithm using HbA1c test for diagnosis	39
Figure 4: Ideal structure of comparative, direct diagnostic evidence.....	42
Figure 5: Decision framework to implement the linked evidence approach when evaluating medical tests	43

Figure 6: Summary of the process used to identify and select studies for the review (example).....	47
Figure 7: Results of diagnostic meta-analysis for diabetes diagnosed by FPG/2hPG vs HbA1c testing	64
Figure 8: Forest plot of studies comparing diagnostic accuracy of HbA1c and FPG/2hPG testing, grouped.....	65
Figure 9: Results of diagnostic meta-analysis for diabetes diagnosed using HbA1c vs FPG testing	66
Figure 10: Forest plot of studies comparing diagnostic accuracy of HbA1c and FPG testing.....	68
Figure 11: Results of diagnostic meta-analysis for diabetes diagnosed by HbA1c vs 2hPG testing	70
Figure 12: Forest plot of studies comparing diagnostic accuracy of HbA1c and 2hPG testing.....	70
Figure 13: Forest plot of the accuracy of HbA1c testing in the diagnosis of diabetes in people with cystic fibrosis.....	73
Figure 14: Forest plot of the accuracy of HbA1c testing in the diagnosis of diabetes in ethnic minorities	74
Figure 15: Results of meta-analysis for diagnosis of diabetes in people with CVD using HbA1c vs FPG/OGT testing	78
Figure 16: Forest plot of studies comparing the accuracy of HbA1c testing vs blood glucose measures in the diagnosis of diabetes in people with CVD	79
Figure 17: Markov state-transition model and allowable health state transitions	91
Figure 18: Outcomes for each testing strategy included in the economic evaluation	94
Figure 19: Tornado analysis of the base-case (HbA1c_1) scenario	110
Figure 20: Tornado analysis of the alternative (HbA1c_2) scenario.....	111
Figure 21: Test cost per person tested for current and proposed testing strategies (Analysis 1).....	188
Figure 22: Test cost per person tested for current and proposed testing strategies (Analysis 2).....	189

Figure 23: Testing parameters in the comparator testing strategy decision tree.....	191
Figure 24: Testing parameters in the HbA1c_1 testing strategy decision tree.....	193
Figure 25: Testing parameters in the HbA1c_2 testing strategy decision tree.....	194
Figure 26: Hazard ratios for diabetes-related complications associated with HbA1c concentration	195
Figure 27: The cost-effectiveness plane.....	196
Figure 28: Tornado analysis of the base-case (HbA1c_1) scenario (Step 2)	202

Executive summary

Assessment of HbA1c testing in the diagnosis of diabetes mellitus

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of HbA1c testing for diagnosis of diabetes in people at risk for diabetes was received from the Australian Diabetes Society, the Royal College of Pathologists of Australasia and the Australasian College of Clinical Biochemists by the Department of Health and Ageing in May 2012.

A team from Adelaide Health Technology Assessment (AHTA), University of Adelaide, was contracted to conduct a systematic review of the literature and an economic evaluation of the HbA1c test in the diagnosis of diabetes. A decision analytic protocol (DAP) was developed before commencement of the assessment and was approved by the Protocol Advisory Sub-Committee (PASC) of the Medical Services Advisory Committee (MSAC).

The purpose of DAPs is to describe in detail a limited set of decision option(s) associated with the possible public funding of proposed new medical technologies and procedures. DAPs also accurately capture current clinical practice and reflect likely future practice with the proposed new medical technologies and procedures, and provide a description of all potentially impacted healthcare resources. The guiding framework of the DAP was used throughout this assessment, with some changes to reflect truncated timelines.

Description of proposed intervention

The HbA1c test is a biochemical test that reflects the average level of glucose in the blood over a 2–3-month period by measuring the proportion of haemoglobin that has become glycosylated. The test is currently used in Australian clinical practice to monitor blood glucose in people with diabetes. It uses a venous blood sample and does not require any preparation or specific time of the day for testing. The proposal is to use the same test to diagnose diabetes. The test would replace the fasting plasma glucose (FPG) and oral glucose tolerance (OGT) tests in many, but not all, people deemed to be at risk for diabetes and tested for the condition (it is unreliable for use in people with certain conditions, such as haemoglobinopathies). Australian Clinical Practice Guidelines outline a risk assessment tool for medical practitioners to use to identify subjects who may be risk for diabetes.

The intervention would be used in the same settings as the current testing strategy, and would use the same (or fewer) resources in terms of attendance items. There is not expected to be any change to management once diabetes is diagnosed. The proposed items

have suggested limits of one test per year with confirmatory tests, allowing for an additional test in symptomatic patients with a negative first result.

Proposal for public funding

The proposed items are listed below:

Category 6 – Pathology Services Group P2 – Chemical
<p>MBS xxxxx</p> <p>Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in patients at high risk, as determined by the AUSDRISK screening tool or according to NHMRC guidelines</p> <p>Fee: \$16.80</p> <p>Limit: one per person, per year, if the patient is asymptomatic, but would allow a repeat test if the patient is symptomatic and the first test result is negative</p>
Category 6 – Pathology Services Group P2 – Chemical
<p>MBS xxxxx</p> <p>Confirmation of HbA1c (glycated haemoglobin) quantitation performed for the diagnosis of diabetes in patients at high risk, as determined by the AUSDRISK screening tool or according to NHMRC guidelines</p> <p>Fee: \$16.80</p> <p>Limit: one per person, per year, upon an initial positive test</p>

Current arrangements for public reimbursement

This is a new item. However, the test is already widely used and available for monitoring of diabetes, which is listed on the MBS (item 66551).

Consumer impact statement

Feedback received during the DAP public consultation period strongly supported considering HbA1c testing at the point of care in the assessment. This aspect of the review was initially included in the DAP but then, due to truncated timelines, was removed.

Clinical need

The test is designed to replace the current diagnostic tests, although in some people the current tests would still be appropriate, so it is not possible to remove them from the MBS. The management algorithms that show the current and intended pathways can be found in the body of the report (Figure 2, Figure 3).

Comparator to the proposed intervention

The comparator for the intervention is two blood glucose measures: the fasting plasma glucose (FPG) test and the oral glucose tolerance (OGT) test (OGTT). Both are done routinely in Australia, are listed on the MBS (FPG = item number 66500; OGTT = item number 66542) and are recommended for use by Australian guidelines. The HbA1c test is intended to replace these tests in the diagnostic pathway.

The comparators both also involve a blood test but with a preparatory overnight fast. An OGT test further requires the patient to ingest a 75g glucose load, after which another blood test is performed.

Scientific basis of comparison

A linked analysis examining the safety, accuracy and impact on clinical management was undertaken. Three level III-2 studies compared the diagnostic accuracy. A supplementary analysis compared diagnostic accuracy between tests without a reference standard.

Comparative safety

Key results

No studies were identified that could inform an assessment of the safety of HbA1c testing compared with FPG and/or OGT testing in the diagnosis of diabetes. There is some risk associated with venepuncture, but it is the same for all three tests. There are also risks associated with OGT testing that are unique to that test, but these are not deemed particularly serious.

Overall conclusion with respect to comparative safety

Given that the test is already available and widely used in Australia for monitoring of diabetes, and that it attracts the same or less risk than the comparators, safety is not a concern for this issue.

Comparative effectiveness

Three studies were identified to inform the comparison of diagnostic accuracy between HbA1c and the comparators, with retinopathy as the reference standard. The body of evidence was of poor quality, the studies were dated and there was considerable variability between studies in the accuracy of results. However, there was consistency within the studies in that there was no difference in the discriminatory power of the tests used. A further paper, which did not meet the inclusion criteria for the review due to population, pooled analyses from nine studies around the world. This paper was the basis for Australian recommendations to use HbA1c for diagnosis and was included in the systematic review that informed the World Health Organization's recommendations for using HbA1c for diagnosis.

This paper found equivalent and good discriminatory power of the three blood glucose measures.

As a supplementary analysis, diagnostic accuracy was compared in studies that did not have a retinopathy reference standard. There were 15 studies that provided raw data for meta-analysis. The level of bias in terms of participant selection and study flow and timing was unclear in many of these studies due to poor reporting; however, from the information provided, the studies were methodologically similar. The conduct of the tests themselves was unlikely to introduce bias. Overall, the body of evidence was of satisfactory quality. The results were characterised by considerable heterogeneity and it was difficult to draw any conclusions from them.

Key results

Although the evidence was poor, it was consistent in showing that the HbA1c test is equivalent to both FPG and OGT tests at predicting retinopathy. Where a reference standard was not used, the results were very heterogeneous, concordance between the tests was poor and it was difficult to draw any conclusions.

Key uncertainties

The studies included in the assessment of diagnostic accuracy with retinopathy as the reference standard were of poor quality and dated. It is clear that the three blood glucose tests measure different things, and thus it is difficult to compare them in a diagnostic meta-analysis.

Overall conclusion with respect to comparative clinical effectiveness

There is little difference between the discriminatory powers of FPG, 2hPG and HbA1c testing to predict retinopathy, despite there being considerable discordance when the tests are compared with one another for diagnosis. Three major international organisations have already recommended HbA1c for diagnosis on the basis of the strength of the relationship between it and retinopathy.

Economic evaluation

A modelled economic evaluation in the form of a cost–utility analysis is presented to assess the comparative costs and benefits associated with HbA1c testing in the diagnosis of diabetes, compared with FPG and OGT testing, in the Australian healthcare setting. The modelled benefits from testing for diabetes include:

1. the diagnosis of diabetes prior to symptom development, so as to enable control of blood glucose levels to prevent the occurrence of complications; and
2. the identification of pre-diabetes, to introduce annual re-testing for diabetes.

The structure of the economic model, based on previously published economic evaluations (Gillies et al. 2008; Mortaz et al. 2012), is a Markov model that includes seven health states: normal glucose tolerance (NGT), pre-diabetes (undiagnosed and diagnosed), diabetes (undiagnosed and diagnosed), diabetes with complications and dead. Transitioning to a diagnosed pre-diabetes/diabetes health state is dependent on not only the accuracy of the testing strategy, but also the estimated patient uptake of testing. A summary of the structure of the mechanics of the economic model is presented in Table 1.

Table 1: Summary of the economic evaluation

Time horizon	50 years
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov model (with half-cycle correction)
Cycle length	1 year
Discount rate	5% for both costs and outcomes
Software package	TreeAge Pro

The economic evaluation considers two testing scenarios, denoted as:

- HbA1c_1 (the base-case scenario), where a single HbA1c cut-off is applied for the diagnosis of diabetes only; and
- HbA1c_2 (the alternative scenario), where two diagnostic cut-offs are applied to enable a diagnosis of pre-diabetes and diabetes, respectively.

The results (Table 2, Table 3) are presented in a stepped manner, based on the stepped inclusion of inputs regarding patient uptake of testing and test accuracy:

- Step 1 Assuming 100% uptake in each of the testing strategies for all prescribed tests and 100% accuracy of all tests, such that the only difference modelled is the cost of the test and current/proposed testing algorithms.
- Step 2 Applying patient uptake rates, as described in the literature and based on expert opinion¹.
- Step 3 Incorporating sensitivity and specificity parameters of the HbA1c test, as identified in the systematic review and meta-analysis conducted in this report.

¹ Health Expert Standing Panel (HESP) Member advice provided to Assessment Group

Table 2: Stepped incremental cost-effectiveness of the HbA1c_1 (base-case) scenario vs FPG with/without OGT testing

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
<i>Step 1</i>					
Comparator	\$8,439	-	16.2420	-	-
HbA1c_1	\$8,084	-\$355 (cost saving)	16.2267	-0.0153 (less effective)	\$23,217 (SW quadrant of CE plane)
<i>Step 2</i>					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_1	\$8,049	-\$298 (cost saving)	16.2175	-0.0178 (less effective)	\$16,762 (SW quadrant of CE plane)
<i>Step 3</i>					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_1	\$8,224	-\$200 (cost saving)	16.2015	-0.0326 (less effective)	\$6,133 (SW quadrant of CE plane)

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; CE = cost-effectiveness plane (as depicted in Figure 27, Appendix E); FPG = fasting plasma glucose; ICER = incremental cost-effectiveness ratio; OGT = oral glucose tolerance; SW = south-west
 Note: Numbers may not be exact due to rounding.

Table 3: Stepped incremental cost-effectiveness of the HbA1c_2 (alternative) scenario vs FPG with/without OGT testing

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
<i>Step 1</i>					
Comparator	\$8,439	-	16.2420	-	-
HbA1c_2	\$8,185	-\$254 (cost saving)	16.2420	0.0000 (equivalent)	Dominant (SE quadrant of CE plane)
<i>Step 2</i>					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_2	\$8,143	-\$205 (cost saving)	16.2387	0.0034 (more effective)	Dominant (SE quadrant of CE plane)
<i>Step 3</i>					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_2	\$8,503	\$79 (more costly)	16.2139	-0.0202 (less effective)	Dominated (NW quadrant of CE plane)

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; CE = cost-effectiveness plane (as depicted in Figure 27, Appendix E); FPG = fasting plasma glucose; ICER = incremental cost-effectiveness ratio; NW = north-west; OGT = oral glucose tolerance; SE = south-east
 Note: Numbers may not be exact due to rounding.

In Step 1 of the analysis the incremental cost-effectiveness ratio (ICER) for the base-case HbA1c_1 analysis (\$23,217/QALY) exists in the south-west (SW) quadrant of the cost effectiveness (CE) plane, in that it is less costly and less effective than the comparator. The alternative analysis (HbA1c_2) is dominant to the comparator testing strategy, as it is less

costly for equivalent effectiveness. These differences are due to the ability (or inability) of the respective HbA1c testing strategies to identify pre-diabetes.

In Step 2 patient uptake rates are included in the analysis, and improvements in favour of the HbA1c testing strategies are observed, as HbA1c testing is likely to be acceptable to patients and have more favourable uptake. However, the overall conclusions as observed in Step 1 are maintained (base-case less costly but less effective, while the alternative scenario is dominant in that it is less costly and more effective).

On the inclusion of test accuracy parameters (Step 3), the current testing strategy is assumed to be 100% accurate, even though it is known that it imperfectly predicts diabetes. However, as retinopathy (the 'gold' reference standard) is not a practical testing alternative in clinical practice, the current test strategy of FPG with/without OGT has to be assumed to be perfect. The inclusion of test accuracy parameters for HbA1c in the base-case scenario (HbA1c_1), relative to FPG with/without OGT testing, results in increased incremental costs of HbA1c testing and reduced incremental gains. However, as the overall cost of HbA1c testing does not exceed that of current testing, the ICER remains in the SW quadrant of the CE plane. In the alternative scenario (HbA1c_2) HbA1c testing switches from a dominant testing strategy to being dominated by the current diabetes testing regimen, in that:

- it is more expensive—due to false positive patients inappropriately receiving diabetes treatment, and false negative patients who do not receive a diagnosis until symptoms of their disease present, thus incurring the high costs of treating diabetes complications; and
- it is less effective—due to the poorer quality of life associated with increased numbers of patients having symptomatic disease.

The results of the Step 3 analysis are likely to underestimate the cost-effectiveness of HbA1c testing, given the issues described in obtaining robust diagnostic accuracy measures. As HbA1c testing appears to be equally predictive of retinopathy as FPG or OGT testing, and the latter two are known to be imperfect reference standards, the best estimate of the real cost-effectiveness of HbA1c testing is likely to lie between the modelled estimates that do and do not include the available but uncertain test accuracy of HbA1c referenced against FPG with/without OGT testing.

When sensitivity analyses around the base-case ICERs at Step 3 were performed (including test accuracy data), the overall conclusions of HbA1c testing essentially did not change (less costly and less effective for HbA1c_1 scenario, and dominated in HbA1c_2 scenario). No analyses were identified for either scenario in which HbA1c testing was associated with improved effectiveness outcomes (i.e. all ICERs exist in western quadrants of the CE plane).

Overall, the model is most sensitive to the inclusion of HbA1c accuracy data, variations in health state costs and patient uptake rates of testing.

Key uncertainties

The quantitative results derived from the model-based economic evaluation are highly uncertain. Diagnostic accuracy inputs of sensitivity and specificity were based on findings from the 'Effectiveness' section of the report. Given the high degree of variability and comparisons made to imperfect reference standards, a high degree of uncertainty is present in these results, and the inclusion of these estimates in the stepped model has a substantial impact on the results of the economic evaluation.

Overall conclusion with respect to comparative cost-effectiveness

Conclusions regarding the cost-effectiveness of HbA1c testing for the diagnosis of diabetes are difficult to draw, given the uncertainties around inputs, particularly regarding test accuracy. Irrespective of the inclusion of test accuracy data, the base-case scenario (which does not identify pre-diabetes) appears consistently less costly and less effective than the comparator (i.e. the ICERs lie in the SW quadrant of the CE plane). The inclusion of these estimates in the alternative scenario alters the cost-effectiveness of the intervention substantially, from being likely to be relatively cost-effective to being dominated. Sensitivity analyses conducted were fairly robust around the base-case ICERs in that the overall conclusion of cost-effectiveness did not often change (e.g. where the base-case ICER existed in the SW plane, so too did the ICERs in the majority of sensitivity analyses tested).

The true measure of cost-effectiveness of HbA1c testing is likely to lie between estimates that either include (i.e. ICERs in the vicinity of \$6,133/QALY in the SW quadrant of the CE plane for the HbA1c _1 scenario or dominated for the HbA1c_2 scenario) or do not include test accuracy data (i.e. ICERs in the vicinity of \$16,762/QALY in the SW quadrant of the CE plane for the HbA1c _1 scenario or dominant for the HbA1c_2 scenario). However, it should be noted that when test accuracy data were not included in the analyses, 100% test performance was assumed, and this is likely to overestimate the performance of HbA1c as well as the currently available tests.

The limited clinical data suggests that HbA1c testing may have similar (poor) performance to the current testing strategies at predicting diabetic retinopathy (the appropriate reference standard)—and thus, by definition, diabetes. If these data are accurate, overall test accuracy is likely to be similar between the HbA1c_2 test strategy (which includes pre-diabetes) and FPG with/without OGT testing. However, the test accuracy in each testing strategy would be considerably lower than 100%, and it is likely that different groups of patients within the spectrum of diabetes presentation would be identified by each of the strategies. If this is the case, the most economically efficient scenario from an economics perspective would be that which identifies pre-diabetes and diabetes (the alternative

scenario, HbA1c_2). However, the clinical uncertainty associated with this conclusion is significant.

Financial/budgetary impacts

While HbA1c testing is proposed to replace currently available tests, accurate MBS utilisation data could not be retrieved for the FPG test, as the relevant item number also lists a number of other tests. In consequence, an epidemiological approach has been undertaken for estimation of the pre-diabetic and 'high-risk' population (who are recommended for FPG and OGT testing, if indicated). As women with a history of gestational diabetes or polycystic ovary syndrome are recommended for regular testing with the OGT test (Australian Diabetes Society & Australasian Diabetes in Pregnancy Society 2009; Jean Hailes Foundation for Women's Health 2011), a market-share approach is used to estimate this population.

The total cost savings to the MBS for the proposed use of diagnostic HbA1c testing, using a base-case set of assumptions, averages \$39 million per year for the HbA1c_1 scenario and \$25 million per year for HbA1c_2, when estimates include test accuracy data. When accuracy data is not included in the estimates, the average annual net cost savings to the MBS is \$39 million for the HbA1c_1 and \$37 million for the HbA1c_2 scenarios. However, a number of issues are present that contribute to uncertainty in the results of the financial analysis. Uncertainties relating to the estimated population likely to be tested include the proportion of pre-diabetic patients that are undiagnosed, the uptake rates of diabetes risk assessment (given that screening is recommended opportunistically), the patient uptake of testing, and the accuracy of the comparator and intervention tests. These issues are further compounded by recommendations for repeat testing in subsequent years. Additionally, the cost of the initial FPG test is uncertain (it varies depending on whether the test is ordered alone or with other tests listed in the same item number), leading to overall uncertainty in the costs that would be offset with the introduction of HbA1c testing.

When financial impact estimates are varied from the base-case in sensitivity analyses (using plausible variable limits), the *estimates range widely between annual cost savings of \$40 million to net costs of \$11 million*. Given the multiple uncertainties in the estimated population eligible for testing and other testing parameters, the financial implications to the MBS cannot be confidently estimated.

Glossary and abbreviations

2hPG	2-hour postprandial glucose
ABS	Australian Bureau of Statistics
ADA	American Diabetes Association
AHTA	Adelaide Health Technology Assessment
AusDiab	Australian Diabetes, Obesity and Lifestyle study
AUSDRISK	questionnaire used to determine diabetes risk in Australian general practice
BMI	body mass index
CE	cost-effectiveness
CI	confidence interval
CVD	cardiovascular disease
DAP	decision analytic protocol
DOR	diagnostic odds ratio
FPG (T)	fasting plasma glucose (test)
GP	general practitioner
HbA1c	glycated haemoglobin
HESP	Health Expert Standing Panel
HSROC	hierarchical summary receiver–operator characteristic curve
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IVD	in-vitro diagnostic medical device
IFG	impaired fasting glucose
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
LMP	lifestyle modification program
LR	likelihood ratio

MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NATA	National Association of Testing Authorities, Australia
NGT	normal glucose tolerance
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
NPV	negative predictive value
OGT (T)	oral glucose tolerance (test)
PASC	Protocol Advisory Sub-Committee
POCS	polycystic ovary syndrome
PoCT	point-of-care testing
PPV	positive predictive value
PRISMA	Preferred Reporting in Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
QAAMS	Quality Assurance for Aboriginal and Torres Strait Islander Medical Services
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies, version 2
ROC	receiver–operator characteristic curve
TGA	Therapeutic Goods Administration
UK	United Kingdom
WHO	World Health Organization

Introduction

Rationale for the assessment of HbA1c testing

An application requesting Medicare Benefits Schedule (MBS) listing of HbA1c testing in the diagnosis of diabetes mellitus was received by the Department of Health and Ageing ('the Department') in May 2012. The application was submitted by the Australian Diabetes Society, the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists ('the Applicant'). HbA1c testing for the *management* of established diabetes is currently reimbursed through the MBS (item 66551, and 66554 in pregnant patients). However, the proposal requests two new items on the MBS for use of the same test in the *diagnosis* of diabetes mellitus ('diabetes').

Process of technology assessment

A team from Adelaide Health Technology Assessment (AHTA), School of Population Health, University of Adelaide, was commissioned to review the safety, effectiveness and cost-effectiveness of HbA1c testing in the diagnosis of diabetes. AHTA sought clinical input and advice from an appropriately constituted Health Expert Standing Panel (HESP; see Appendix A).

The findings of this review are intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the MBS in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach in its decision-making, based on reviews of the scientific literature and economic modelling (such as the health technology assessment (HTA) presented here), as well as other information sources including clinical expertise and consumer views.

A decision analytic protocol (DAP) was developed prior to commencement of this assessment of HbA1c testing. The purpose of the DAP was to describe in detail a limited set of decision options associated with the possible public funding of HbA1c testing in the diagnosis of diabetes. The DAP describes current clinical practice in the diagnosis of diabetes, reflects the likely future practice should HbA1c testing be used in the diagnosis of diabetes, and describes all potentially affected healthcare resources.

Public comment was sought during development of the final DAP. The DAP was released for public comment on 3 October 2012 and closed for comments on 9 November 2012. This

public comment was incorporated into the Final DAP and was approved by the Protocol Advisory Sub-Committee (PASC) of MSAC in December 2012.

The framework of the DAP was used to guide this assessment. However, the assessment does not completely reflect the DAP agreed upon by PASC. In order to meet the Department's request for an expedited assessment process—for completion of the review in time for the February 2014 Evaluation Sub-Committee (ESC) meeting rather than the June 2014 meeting—several restrictions were placed on the systematic literature review so that it could be achieved in the restricted time frame but without sacrificing methodological rigour. The restrictions were:

- Studies with fewer than 500 people were not considered for the review. Smaller studies were acceptable if they provided information on specific population subgroups (population groups of interest, groups with haemoglobinopathies etc.) for whom data was not available elsewhere in the review; and
- The comparison of point-of-care testing versus laboratory testing, which was included in the DAP in response to public consultation, was not undertaken. The review was restricted to assessment of HbA1c testing as performed in accredited laboratories. This reflects the original application for MBS funding submitted by the Applicant.

Background

HbA1c testing

The HbA1c test is a biochemical test that reflects the average level of glucose in the blood over a 2–3-month period by measuring the proportion of haemoglobin that has become glycosylated. The test is already widely used in people with established diabetes to monitor glycaemic control and guide treatment. The test can be undertaken using several methods, including high-performance liquid chromatography, ion-exchange chromatography and immunoturbidimetric assay. In the past the test has been criticised for a lack of standardisation across laboratories and countries; however, there have been significant global efforts to standardise the assay (such as the National Glycohemoglobin Standardization Program in the US), leading to improvement in test accuracy (d'Emden et al. 2012). In Australia it is believed that the variability in HbA1c values is acceptably low (d'Emden et al. 2012).

The World Health Organization (WHO 2011), an International Expert Committee (Nathan & The International Expert Committee 2009) and the American Diabetes Association (American Diabetes Association 2010) have all now recommended HbA1c testing in the diagnosis of diabetes. The rationale for using the test in diagnosing diabetes is that it is a better index of overall glycaemic status and a good predictor of hyperglycaemia-related complications, and is relatively unaffected by acute fluctuations in blood glucose (such as those due to stress or illness) (Nathan & The International Expert Committee 2009). The test also has substantially less biologic variability and pre-analytic instability, and is more acceptable to the patient in that it requires no preparation such as fasting, or the inconvenience and possible discomfort of the OGT test (Nathan & The International Expert Committee 2009).

The Applicant published a position statement in the *Medical Journal of Australia* in 2012 supporting the use of HbA1c testing in the diagnosis of diabetes (d'Emden et al. 2012).

Intended purpose

The HbA1c test would be used as part of the case detection pathway for diabetes. The test would be performed in Australian National Association of Testing Authorities (NATA)-accredited laboratories, consistent with MBS item 66551. There are NHMRC guidelines (Colagiuri et al. 2009a) for case detection of type 2 diabetes, and the HbA1c test would be used in place of the random blood glucose or fasting blood glucose (FBG) test and the oral glucose tolerance (OGT) test (where required) in the case detection pathway. Medical practitioners would order the HbA1c test under the same circumstances that they would order the existing diabetes diagnostic tests. There are certain population groups, such as

people with haemoglobinopathies or red cell turnover disorders (among others), in whom the HbA1c test may not be as reliable (Nathan & The International Expert Committee 2009; World Health Organisation 2011), and so it is proposed that for these people the existing test strategies would remain in place.²

The Applicant proposed that HbA1c re-testing in people without diabetes would occur at relevant time points and in accordance with NHMRC guidelines. Should diabetes be diagnosed, subsequent HbA1c tests would be conducted as part of the usual management of the disease and billed under item 66551 (Colagiuri et al. 2009b).

While the HbA1c test is proposed to replace the FPG and OGT tests in the diagnosis of diabetes, it cannot diagnose related conditions such as glucose intolerance and impaired fasting glucose. However, the identification of a pre-diabetic state is important and PASC asked the assessors to consider the consequences of not being able to identify a pre-diabetic state.

Proposed MBS items

The Applicant proposes an MBS listing of two new items for quantitation of HbA1c (glycated haemoglobin) performed in the diagnosis of diabetes (Table 4). These tests, conducted in an NATA-accredited pathology laboratory, are proposed to sit alongside the HbA1c test for management of diabetes (Category 6: Pathology Services), MBS item 66551. PASC preferred two items be defined within each category:

- initial testing, which would be limited to one test per year for an asymptomatic patient, with repeat testing allowed if the patient is symptomatic and the first test result is negative; and
- confirmatory testing, which would be limited to patients in which the initial test is positive.

PASC noted that it is important to limit the frequency of diagnostic testing because there are potential perverse incentives to more frequently order the HbA1c test. Practitioners would be eligible for diabetes service incentive payments for every patient identified and managed with established diabetes. PASC asked that the assessment provide evidence of the suitability of the nominated frequency of testing, and of the nominated HbA1c threshold of $\geq 6.5\%$ as being positive for diabetes; these assessments are considered in the research questions.

² PASC requested that population subgroups in whom HbA1c testing is unsuitable be explicitly considered in the assessment of evidence. This has been undertaken in an abbreviated manner given the restricted time frames (see section 'Other relevant considerations', commencing on page 81).

The Applicant also proposed that, in the existing MBS item for HbA1c, the term 'glycosylated' be replaced with 'glycated', to better reflect current terminology.

Table 4: Proposed MBS item descriptors for HbA1c testing in the diagnosis of diabetes

Category 6 – Pathology Services Group P2 – Chemical
<p>MBS xxxxx</p> <p>Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in patients at high risk, as determined by the AUSDRISK screening tool or according to NHMRC guidelines</p> <p>Fee: \$16.80</p> <p>Limit: one per person, per year, if the patient is asymptomatic, but would allow a repeat test if the patient is symptomatic and the first test result is negative.</p>
Category 6 – Pathology Services Group P2 – Chemical
<p>MBS xxxxx</p> <p>Confirmation of HbA1c (glycated haemoglobin) quantitation performed for the diagnosis of diabetes in patients at high risk, as determined by the AUSDRISK screening tool or according to NHMRC guidelines</p> <p>Fee: \$16.80</p> <p>Limit: one per person, per year, upon an initial positive test</p>

Clinical need

The proposed intervention is for the diagnosis of diabetes mellitus, essentially type 2 diabetes. Diabetes is a common chronic disease in Australia and contributes to mortality and morbidity through microvascular (e.g. retinopathy, neuropathy) and macrovascular (e.g. stroke, heart disease) complications, and can result in blindness, kidney failure and limb amputation. Effective therapy can reduce the complications associated with diabetes, and the earlier this therapy is initiated, the better the outcomes for the patient (Holman et al. 2008). Thus, case detection of diabetes at the earliest stage is recommended (Colagiuri, S et al. 2009).

NHMRC guidelines suggest that case detection should be done on an opportunistic basis (most commonly during general practitioner (GP) consultations) (Colagiuri, S et al. 2009). Individuals who are judged to be at risk are recommended to be tested for diabetes (Colagiuri, S et al. 2009). Risk assessment is done on the basis of a score ≥ 12 on the AUSDRISK assessment tool, or eligibility for one of the following population groups with a known higher risk:

- people with impaired glucose tolerance or impaired fasting glucose;
- women with a history of gestational diabetes mellitus;
- women with a history of polycystic ovary syndrome;

- people presenting with a history of a cardiovascular disease event (e.g. myocardial infarction, stroke); and
- people on antipsychotic medication.

Prevalence of diabetes, using the diagnostic criteria outlined in the NHMRC case detection guidelines (Colagiuri et al. 2009a), was reported in the baseline Australian Diabetes, Obesity and Lifestyle (AusDiab) study in 2001 (Dunstan et al. 2001). During 1999–00 more than 11,000 adults (aged 25 years and older) across Australia participated in this longitudinal population-based study that observed an overall prevalence of diabetes of 7.6%, of which half were previously undiagnosed. The prevalence of diabetes was observed to increase with age, with the highest prevalence identified in people aged 75 years and older (23.6%) (Figure 1), and with prevalence higher in males between the ages of 35 and 74 years.

As diabetes case detection guidelines (Colagiuri et al. 2009a) recommend that diabetes risk assessment begin from age 40 years, the estimated prevalence of diabetes in this population is calculated to be 11.2%—derived from the age-specific prevalence of diabetes reported in AusDiab (Dunstan et al. 2001) applied to the estimated resident population for 1999–00 reported by the ABS (Australian Bureau of Statistics (ABS) 2013b).

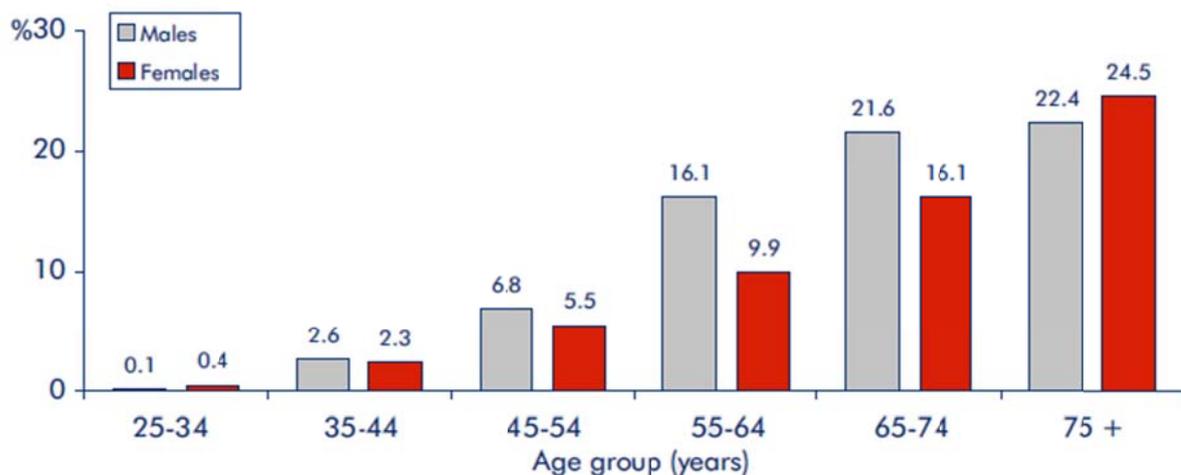


Figure 1: Age- and gender-specific prevalence (%) of diabetes among Australian residents

Source: (Dunstan et al. 2001)

The total prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (collectively termed pre-diabetes) was observed to be 16.3%. Similar to diabetes, the prevalence of pre-diabetes was observed to increase with age, with the highest prevalence identified in people aged 75 years and older (29.3%). The estimated prevalence of pre-diabetes in the population older than 40 years was calculated to be 21%—similarly derived from the age-specific prevalence of diabetes reported in AusDiab (Dunstan et al. 2001) applied to the estimated resident population for 1999–00 reported by the ABS (Australian Bureau of Statistics (ABS) 2013b).

Subsequent follow-up studies, conducted at 5 and 12 years after the baseline AusDiab study, reported that the overall annual incidence of diabetes was 0.7%; however, it varied according to baseline glucose tolerance status. The highest incidence rate (3.0%) was reported in those with IGT at baseline, with 2.2% in those who were IFG and 0.3% in those with normal glucose tolerance. The overall annual incidence of IGT was 0.9% and of IFG 0.4%.

MBS data for the OGT test (item 66542) indicate a slight increase in the number of claims over the past 5 years, from 294,000 in 2008–09 to 305,000 in 2012–13. Similar data could not be retrieved for the FPG test (the test recommended initially) as the item number additionally lists a number of other tests.

Existing diagnostic tests

In Australia cases of diabetes are detected through a three-stage process: risk assessment followed by two blood tests (one FPG test followed by confirmatory tests—either another FPG on a separate occasion or an OGT test) (Colagiuri, S et al. 2009). In some patients a third test may be required—if the initial FPG test suggests diabetes, and the follow-up FPG is equivocal, then the patient should have an OGT test. The FPG test requires venepuncture following an overnight fast, and is reimbursable under MBS item 66500 (see Table 5). The OGT test, reimbursable under item 66542 (see Table 5) is more taxing on the patient, requiring dietary preparation for the prior 3 days, an overnight fast, venepuncture and then ingestion of a 75-g glucose load. The patient then needs to wait for 2 hours before venepuncture is performed again. Both of these tests require some degree of preparation by the patient and, in the case of the OGT test, a considerable time commitment and the possibility of adverse effects from the glucose load (e.g. vomiting). The diagnostic criteria are described in the methodology section (page 34).

Table 5: MBS item descriptors for current diagnostic tests (fees at 1 January 2014)

Category 6 – Pathology Services Group P2 – Chemical
<p>MBS 66500</p> <p>Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea - 1 test</p> <p>Fee: \$9.70</p>
<p>MBS 66542</p> <p>Oral glucose tolerance test for the diagnosis of diabetes mellitus that includes:</p> <p>(a) administration of glucose; and</p> <p>(b) at least 2 measurements of blood glucose; and</p>

(c) (if performed) any test described in item 66695

Fee: \$18.95

As the diabetes risk assessment and test ordering is done during a patient consult with a GP, there are also MBS consultation items associated with diabetes case detection and items for monitoring blood glucose control.

Regulatory status

An assay designed for HbA1c testing is classified as an in-vitro diagnostic medical device (IVD). IVDs are pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2011).

The Therapeutic Goods Administration (TGA) regulatory framework for IVDs changed in July 2010. All IVDs now require pre-market approval by the TGA (unless they were offered prior to July 1 2010 in Australia, where a transition period up to 2014 applies). As the test was available before July 1 2010, it is exempt from registration on the register of therapeutic goods in Australia; however, it will be required to be registered by 2014. The test may be a Class 2 or Class 3 IVD. Laboratories that manufacture Classes 1–3 in-house IVD medical devices must comply with the requirements of Part 6A, Schedule 3, of the Regulations (Therapeutic Goods Administration 2012).

To meet these requirements, the laboratory must be accredited as a medical testing laboratory by either NATA or a conformity assessment body determined suitable by the TGA, and meet the National Pathology Accreditation Advisory Council (NPAAC) performance standard requirements for the development and use of in-house IVDs (Therapeutic Goods Administration 2012).

Current reimbursement arrangements

Currently, patients who are diagnosed as having diabetes are required to undertake an HbA1c test to assess the severity of diabetes as part of management of the disease. MBS item 66551 can be claimed for tests performed in a NATA-accredited laboratory (66554 in pregnant patients), or MBS item 73840 if performed in a Quality Assurance for Aboriginal and Torres Strait Islander Medical Services (QAAMS)-accredited Aboriginal and Torres Strait Islander health and medical centre (Table 6). There is currently no reimbursement for determining a diagnosis of diabetes using HbA1c laboratory tests.

Table 6: MBS item descriptors for associated consultations and HbA1c test for diabetes management (fees at 1 January 2014)

Category 1 – Professional Attendances
<p>MBS 23 Consultation at consulting rooms Fee: \$36.30</p>
Category 6 – Pathology Services
<p>MBS 66551 Quantitation of glycosylated haemoglobin performed in the management of established diabetes - (Item is subject to rule 25) Fee: \$16.80</p>
(QAAMS project participants only)
<p>MBS 73840 Quantitation of glycosylated haemoglobin performed in the management of established diabetes - each test to a maximum of 4 tests in a 12-month period. Fee: \$14.55 Note: this is not listed in the MBS; this information is from QAAMS.</p>

Consumer impact statement

The primary response from the public consultation was to strongly suggest inclusion of an assessment of HbA1c point-of-care testing (PoCT) within the scope of the review. This recommendation was accepted by PASC, and PoCT was included in the DAP approved by PASC in December 2012. However, subsequently, in order to expedite the conduct of the review, the Department and the Applicant agreed that the assessment of HbA1c PoCT should be removed from the DAP and thus not be assessed as part of this review.

Diagnostic criteria and terminology

The thresholds for diagnosis of diabetes and pre-diabetes vary in the studies included in this review according to the criteria used. These have changed over time. There are two sources of diagnostic criteria—WHO and the American Diabetes Association (ADA)—and these are shown in Table 7. The FPG test is a single fasting blood test that can diagnose diabetes. The OGT test involves blood tests both before (FPG) and after (2hPG) the glucose load. When an OGT test is conducted, diabetes can be diagnosed using either just the FPG result (if the 2hPG result is below the threshold) or just the 2hPG result (if the FPG result is below the threshold) or both. This demonstrates how the tests identify different glycaemic states. For simplicity, reference to 'diabetes diagnosed by OGT test' means a diagnosis using either of

the two measures taken in an OGT test. This is to distinguish it from studies using the FPG test alone.

Where pre-diabetes is diagnosed using only the FPG test, it is referred to as impaired fasting glucose (IFG). Where pre-diabetes is diagnosed using only the 2hPG test, it is referred to as impaired glucose tolerance (IGT). Either or both of these may be used to diagnose pre-diabetes. People with IFG, IGT or both are often combined in a group called impaired glucose regulation (IGR).

Where the results of the FPG test are reported, the designation FPG is used. For the results of the OGT test, the designation 2hPG is used as per convention. All values for FPG and 2hPG are given in mmol/L; the equivalent measures in mg/dL are shown in Table 7.

Table 7: Diagnostic criteria used in the studies included in the review

	Diabetes	Pre-diabetes	Normal
1985 WHO	FPG \geq 7.8 (140) 2hPG \geq 11.1 (200)	FPG <7.8 (140) 2hPG 7.8–11.0 (140–199)	FPG <7.8 (140) 2hPG \leq 7.7 (139)
1999 WHO	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200)	FPG 6.1–6.9 (110–125) 2hPG 7.8–11.0 (140–199)	FPG \leq 6.0 (109) 2hPG \leq 7.7 (139)
2003 WHO	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200)	FPG 6.1–6.9 (110–125) 2hPG 7.8–11.0 (140–199)	FPG \leq 6.0 (109) 2hPG \leq 7.7 (139)
2006 WHO	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200)	FPG 6.1–6.9 (110–125) 2hPG 7.8–11.0 (140–199)	FPG \leq 6.0 (109) 2hPG \leq 7.7 (139)
2011 WHO	HbA1c \geq 6.5% (48)	No recommendation	
American Diabetes Association			
1997 ADA	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200)	FPG 6.1–6.9 (110–125) 2hPG 7.8–11.0 (140–199)	FPG \leq 6.0 (109) 2hPG \leq 7.7 (139)
2003 ADA	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200)	FPG 5.6–6.9 (100–125) 2hPG 7.8–11.0 (140–199)	FPG \leq 5.5 (100) 2hPG \leq 7.7 (139)
2010 ADA	FPG \geq 7.0 (126) 2hPG \geq 11.1 (200) HbA1c \geq 6.5%	FPG 5.6–6.9 (100–125) 2hPG 7.8–11.0 (140–199) HbA1c 5.7–6.4%	FPG \leq 5.5 (100) 2hPG \leq 7.7 (139) HbA1c <5.7%

2hPG units = mmol/L (mg/dL); HbA1c units = % (mmol/L)

Approach to assessment

Objective

The objective of this assessment was to determine whether there is sufficient evidence of clinical need, safety, effectiveness and cost-effectiveness to recommend the public funding of HbA1c testing in the diagnosis of diabetes in patients deemed at high risk. Risk status would be determined by the AUSDRISK screening tool or according to NHMRC guidelines, and those found to be at risk would receive an initial HbA1c test, followed by a confirmatory test (if eligible), conducted by a pathology service in an accredited laboratory.

Clinical pathway

The clinical pathway for diabetes case detection in current Australian practice is based on recommendations in the NHMRC case detection guidelines (Colagiuri, S et al. 2009), as described in Figure 2. The addition of HbA1c testing to monitor disease severity in patients with confirmed diabetes is not part of the NHMRC case detection guidelines, but it is recommended in the NHMRC blood glucose control guidelines that HbA1c measurements should be used to assess long-term blood glucose control (Colagiuri, S et al. 2009).

The proposed use of HbA1c tests in the diagnosis of diabetes would replace the use of FPG and OGT tests in Figure 1, for all people in whom HbA1c testing is not contraindicated (i.e., in whom the HbA1c test is known to be unreliable, such as people with red cell turnover disorders). It is also likely that the initial HbA1c test performed in those patients diagnosed by the current case detection methods to obtain a baseline glycated haemoglobin level for monitoring purposes would not be required if the patient had undergone an HbA1c test during the diagnostic process. Figure 3 shows the clinical pathway as proposed by the Applicant for using HbA1c testing in the diagnosis of diabetes. A cut-off of 6.5% has been used as this is the level recommended by an International Expert Committee (Nathan & The International Expert Committee 2009), the World Health Organization (World Health Organisation 2011) and the American Diabetes Association (American Diabetes Association 2010).

This pathway would need to be communicated to GPs by groups such as the Australian Diabetes Society (or through updated NHMRC clinical practice guidelines) should the HbA1c test be publicly funded for use in the diagnosis of diabetes. This would be particularly important if a patient had one HbA1c result in the diagnostic range and a confirmatory result in the 'no diabetes' range. The Applicant has suggested a 'two out of three' rule (i.e. two tests positive for diabetes out of three) to overcome this issue. This would have cost ramifications and thus has been included in the base-case economic analysis. This also

applies to the current diagnostic regimen and is dealt with within the guidelines (Colagiuri et al. 2009a). The HbA1c test diagnoses different people compared with the FPG and OGT tests and, given that all glucose measures are a continuum, there may be some impact on the timing of diagnosis and subsequent treatment initiation. However, management is not expected to be different with the proposed change in diagnostic method.

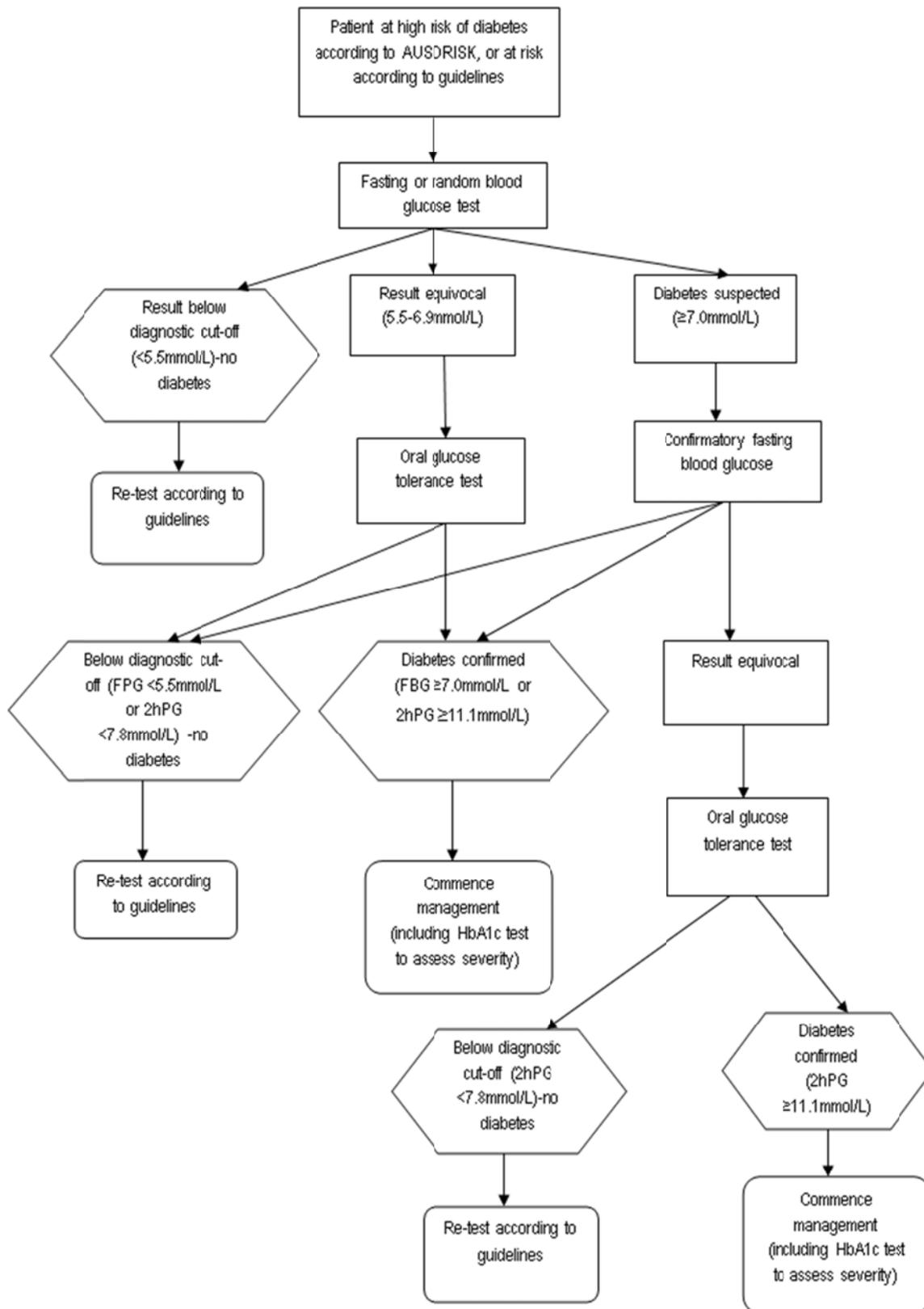


Figure 2: Current diagnostic algorithm according to NHMRC guidelines

Source: Colagiuri, et al. 2009a

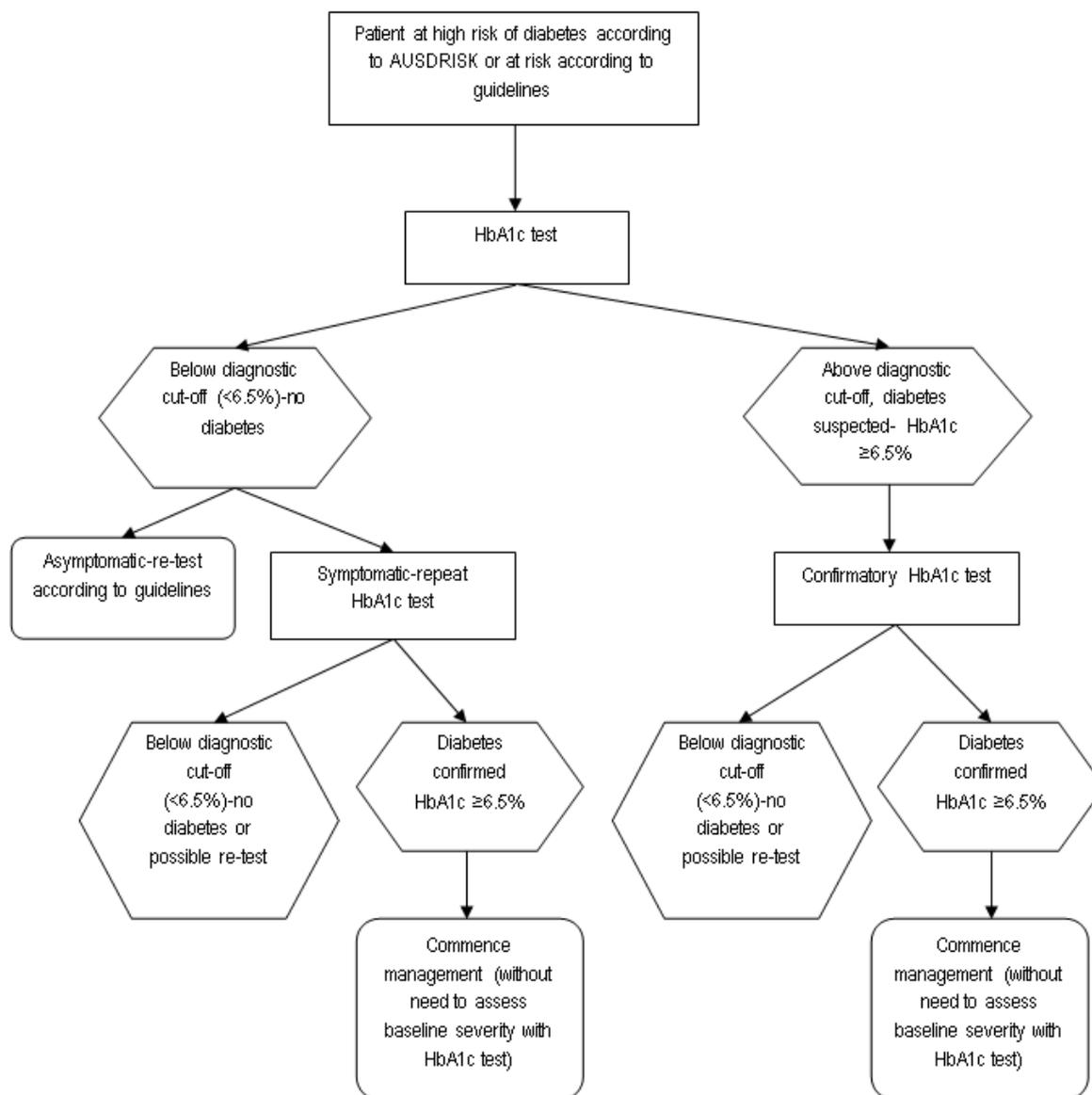


Figure 3: Proposed diagnostic algorithm using HbA1c test for diagnosis

Comparator

The correct comparators against which the safety, effectiveness and cost-effectiveness of HbA1c testing should be measured are fasting or random plasma glucose (FPG) and (in some circumstances) oral glucose tolerance (OGT) tests. MBS item descriptors for the comparators are listed in Table 5. According to the pathway given in Figure 2, once a patient has been screened for diabetes risk using the AUSDRISK instrument and has scored ≥ 12 , or is otherwise considered to fall into a high-risk group, they should undergo an FPG test. If the results of this test indicate a diagnosis of diabetes, the test is repeated on another day to confirm the diagnosis. If the results of the first and second tests are equivocal, the patient should undergo an OGT test to confirm the diagnosis.

The reference standard

The DAP designated that the 'gold' reference standard to determine diagnostic test accuracy was the development of microvascular disease in the form of diabetic retinopathy. The evaluation also compared the accuracy and concordance of the proposed test with the current testing regime, despite the current testing strategy being considered an imperfect diagnostic reference standard.

Research questions

Research questions were formulated to determine the place of HbA1c testing in the diagnosis of diabetes and thus address whether public funding is warranted:

1. Does HbA1c testing in an accredited laboratory have similar accuracy to the current testing strategy for diagnosis of diabetes mellitus?
2. Given that HbA1c testing detects different cases of diabetes than other tests using the same diagnostic range, what are the ramifications for diabetes management?
3. Is there any health benefit to patients in being diagnosed by HbA1c testing compared with the current diagnostic strategy for diabetes mellitus?
4. How suitable is the nominated frequency of HbA1c testing proposed by the Applicant? Is the nominated HbA1c threshold of $\geq 6.5\%$ appropriate to determine a diabetes diagnosis?

The PICO (population, intervention, comparator, outcomes) criteria that guided this assessment are presented in Table 8.

Table 8: Summary of PICO criteria to define research questions used to investigate HbA1c as a diagnostic tool

Patients	Intervention	Comparator	Reference standard ^a	Outcomes to be assessed
People at high risk of diabetes or suspected of having diabetes	HbA1c test followed by confirmatory HbA1c test if first result indicated diabetes, or repeated if symptomatic patient has negative result; tests conducted in accredited laboratory	Fasting blood glucose or random blood glucose test, followed by a confirmatory fasting blood glucose test if diabetes suspected; or an oral glucose tolerance test if first result indefinite	Clinical diagnosis of diabetic retinopathy after long term follow-up ^a	Safety Diagnostic accuracy ^a Change in patient management Cost-effectiveness Patient-relevant health outcomes (including retinopathy and other diabetes complications) Patient satisfaction and acceptance Patient convenience Test turnaround times Number of patients tested Characteristics of patients tested Number of patients tested per case of diabetes detected Number of patients tested per case of diabetes treated Cost of testing per case of diabetes detected Cost of testing per case of diabetes treated

^a NB: In the absence of good-quality evidence comparing the HbA1c testing strategy and the comparative testing strategy in terms of their diagnostic accuracy relative to the reference standard, PASC determined that concordance between the two testing strategies should be determined.

Diagnostic assessment framework

This assessment of HbA1c testing is based on the framework outlined in the *MSAC guidelines for the assessment of diagnostic technologies* (MSAC 2005).

The effectiveness of a diagnostic or predictive test depends on whether it improves patient health outcomes. The clinical benefit can be assessed by studies that directly investigate the impact of the test on health outcomes or, alternatively, in some situations by linking evidence from different studies within the diagnostic or predictive pathway.

Direct evidence

In a very simplified manner, comparative **direct evidence** would present data on patients suspected (due to signs/symptoms) or at risk (as determined by the AUSDRISK screening tool or according to NHMRC guidelines) of having diabetes. These people would be tested using either HbA1c or FPG and/or OGT tests, in addition to long-term clinical screening for retinopathy. In both study arms patients would receive treatment for diabetes if the test results were positive (Figure 4). If one study arm was better at identifying patients who had diabetes (as determined by the development of diabetic retinopathy) and appropriately targeted treatment compared with the other study arm, this would be reflected in a difference in the health outcomes between the patient groups.

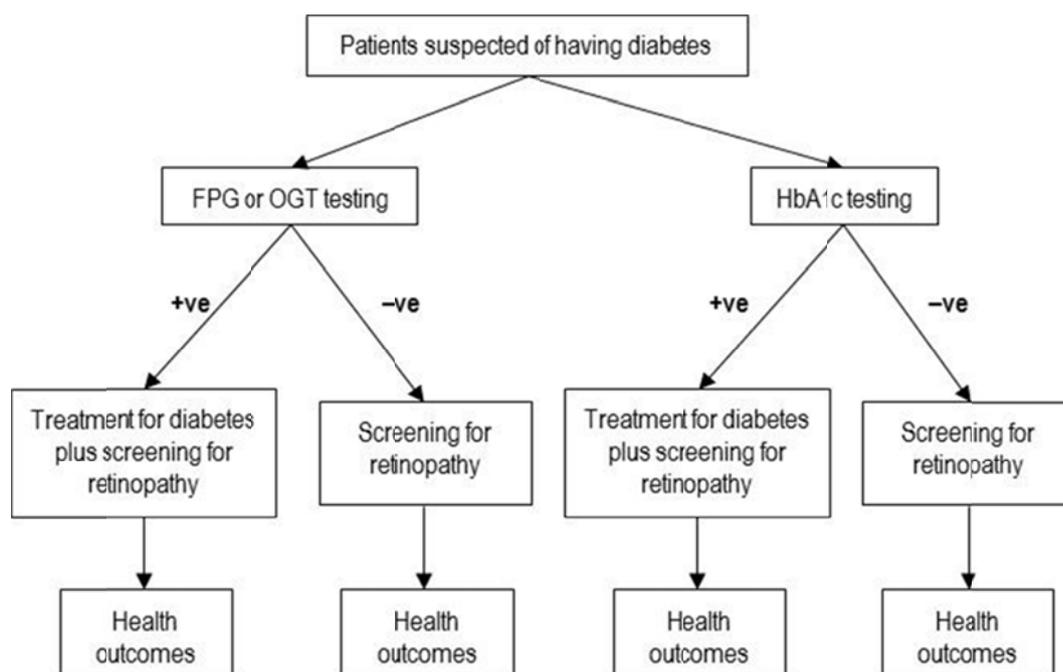


Figure 4: Ideal structure of comparative, direct diagnostic evidence

Note: +ve = positive, -ve = negative

Linked evidence

Scoping literature searches indicated that the available direct evidence was limited, so a **linked evidence** approach was used to supplement the evidence-base.

Literature was identified on the:

- diagnostic performance of HbA1c testing (i.e. test accuracy)
- impact of HbA1c testing on clinical decision-making—do treatment options change as a result of the test?
- impact of the treatment on the health outcomes of diagnosed patients—is it likely that patients who would receive the test would benefit from any subsequent change in management?

The linked evidence approach is undertaken in three steps, with subsequent steps relying on the findings of the previous steps, as per the framework given in Merlin et al (Merlin et al. 2013). and shown in Figure 5. Depending on the results of the diagnostic accuracy review (evidence linkage 1), evidence linkage 2 is undertaken to assess change in patient management; and depending on the results of that, evidence linkage 3, which looks at treatment effectiveness, may need to be addressed.

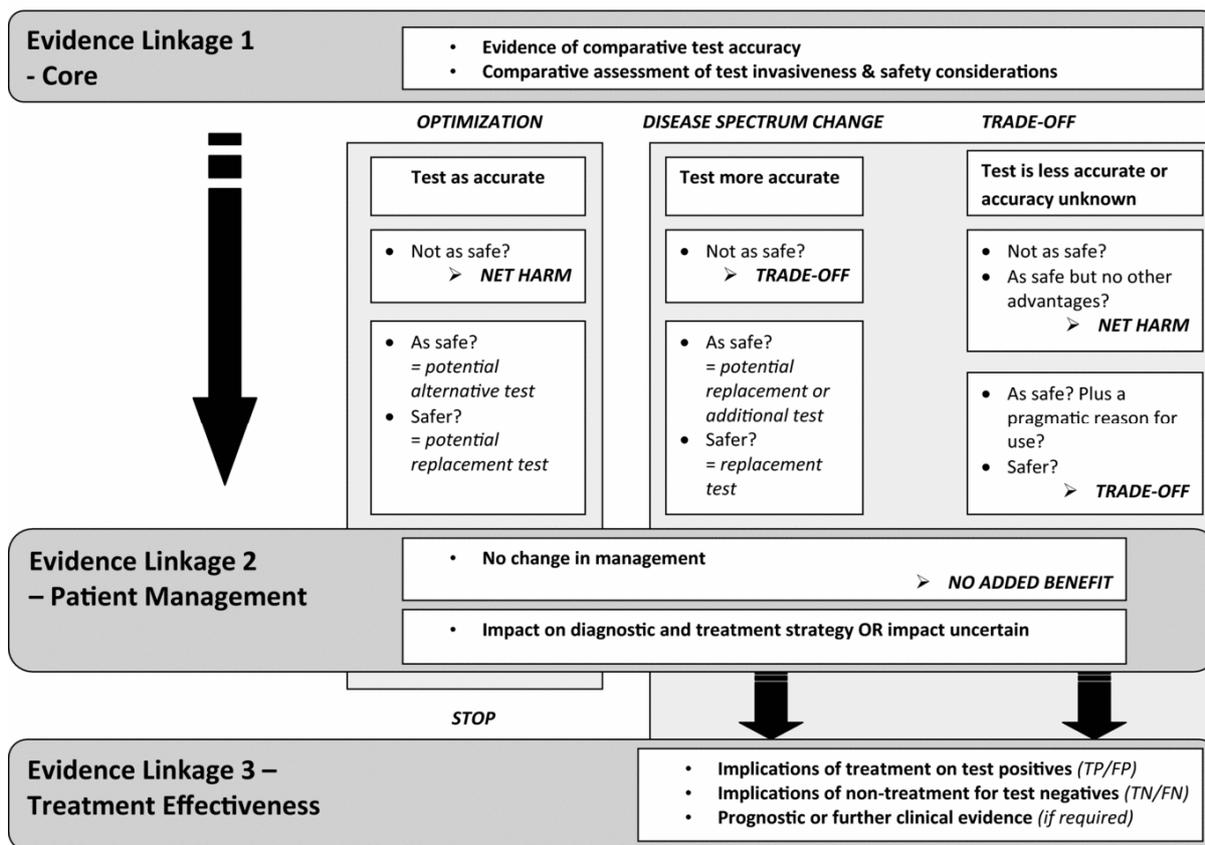


Figure 5: Decision framework to implement the linked evidence approach when evaluating medical tests

Source: (Merlin et al. 2013)

The questions addressed through the evidence linkage are:

Diagnostic accuracy:

1. Does HbA1c testing in an accredited laboratory have similar accuracy to the current testing strategy for diagnosis of diabetes?
2. What proportion of individuals have discordant diabetes diagnoses when tested with both the proposed and current testing strategies; that is, diagnosed using FPG but not HbA1c testing, or diagnosed using HbA1c but not FPG testing?
3. How suitable is the nominated frequency of HbA1c testing proposed by the Applicant? Is the nominated HbA1c threshold of $\geq 6.5\%$ appropriate to determine a diabetes diagnosis?

Impact on clinical decision-making:

4. What are the potential ramifications for the management and follow-up of individuals who are unable to be definitively diagnosed by either method?
5. What are the potential ramifications for the follow-up of individuals who would have been diagnosed with pre-diabetes (falling in the impaired fasting glucose or impaired glucose tolerance range) if tested using the current test strategy, but when tested using HbA1c

would not be identified? Is there a comparable pre-diabetes HbA1c range to identify at-risk individuals?

Cost-effectiveness:

6. What is the cost of HbA1c testing per case of diabetes detected?

7. What is the cost of HbA1c testing per case of diabetes treated?

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews between 1960 and September 2013. Searches were conducted via the electronic databases listed in Table 9.

Table 9: Electronic databases searched

Database	Period covered
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1960 – Sept 2013
PubMed	1960 – Sept 2013
Embase.com	1960 – Sept 2013
Scopus	1960 – Sept 2013
Web of Science – Science Citation Index Expanded	1960 – Sept 2013
Current Contents	1998 – Sept 2013
CINAHL	1981 – Sept 2013
EconLit	1987 – Sept 2013

The search strategy used for the PubMed database was as follows:

((Diabetes Mellitus, Type 2[MeSH Subheading] OR diabet*) OR (impaired AND glucose) AND ((Hemoglobin A, Glycosylated[MeSH Subheading] OR glycated hemoglobin OR glycated haemoglobin OR glycosylated hemoglobin OR glycosylated haemoglobin OR HbA1c OR Hb A1c) AND (test* OR monitor* OR diagnos* OR manage*)) AND ("humans"[MeSH Terms] AND English[lang]))

The other databases were searched with similar text words and the indexing terms relevant to the database.

Selection criteria

Direct evidence

The PICO criteria for selecting direct evidence on the safety and effectiveness of HbA1c testing is shown in Box 1.

Box 1: Criteria for selecting direct evidence on the safety and effectiveness of HbA1c testing

Characteristic	Criteria
Population	People at high risk of diabetes, or suspected of having diabetes
Intervention	HbA1c testing to diagnose diabetes AND clinical screening for retinopathy
Comparator(s)	FPG and/or OGT testing to diagnose diabetes AND clinical screening for retinopathy
Outcomes	Safety—psychological and physical harms from HbA1c, FPG or OGT testing and clinical screening for retinopathy Effectiveness— Primary outcomes: mortality/survival, quality of life, incidence and severity of life-threatening events arising from diabetes complications including retinopathy Secondary outcomes: incidence and severity of diabetes symptoms, patient satisfaction, acceptance and convenience of testing
Search period	1960 – September 2013
Language	Non-English language articles were excluded

HbA1c = glycated haemoglobin; FPG = fasting plasma glucose; OGT = oral glucose tolerance

Linked evidence

In the absence of comparative direct evidence, a supplementary linked evidence approach was used to assess the effectiveness of HbA1c testing to diagnose people at high risk of diabetes, as determined by the AUSDRISK screening tool or according to NHMRC guidelines. The abridged linked evidence approach used in this assessment used the criteria for selecting studies that are outlined in Box 2 and Box 3.

Box 2: Criteria for selecting studies relevant to assess the predictive accuracy of HbA1c testing

Research questions

Does HbA1c testing in an accredited laboratory have similar accuracy to the current testing strategy for diagnosis of diabetes mellitus?

What proportion of individuals have discordant diabetes diagnoses when tested with both the proposed and current testing strategies; that is, diagnosed using FPG or 2hPG but not HbA1c testing, or diagnosed using HbA1c but not FPG or 2hPG testing?

How suitable is the nominated frequency of HbA1c testing proposed by the Applicant? Is the nominated HbA1c threshold of $\geq 6.5\%$ appropriate to determine a diabetes diagnosis?

Selection criteria

Inclusion criteria

Population	People at high risk of diabetes, or suspected of having diabetes
Intervention	HbA1c testing to diagnose diabetes
Comparator(s)	FPG and/or OGT testing to diagnose diabetes
Reference standard	Clinical screening for diabetic retinopathy ^a
Outcomes	Test accuracy measures including sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, negative likelihood ratio, receiver–operator characteristic curve data
Search period	1960 – September 2013
Language	Non-English language articles were excluded

^a There were no test performance studies identified during the review that compared HbA1c testing accuracy against the ‘gold’ reference standard of clinical screening for retinopathy; thus, use of FPG and/or OGT testing to confirm a diabetes diagnosis was considered the reference standard for the analysis—noting that this is an imperfect reference standard. HbA1c = glycated haemoglobin; FPG = fasting plasma glucose; OGT = oral glucose tolerance

Box 3: Criteria for selecting studies relevant to assess a change in patient management as a result of HbA1c diagnostic testing

Research questions

What are the potential ramifications for the management and follow-up of individuals who are unable to be definitively diagnosed by either method?

What are the potential ramifications for the follow-up of individuals who would have been diagnosed with pre-diabetes (falling in the impaired fasting glucose or impaired glucose tolerance range) if tested using the current test strategy, but when tested using HbA1c would not be identified? Is there a comparable pre-diabetes HbA1c range to identify at-risk individuals?

Selection criteria

Inclusion criteria

Population	People at high risk of diabetes, or suspected of having diabetes
Intervention	HbA1c testing to diagnose diabetes
Comparator(s)	FPG and/or OGT testing to diagnose diabetes
Outcomes	Change in patient management including changes in treatment options and timing and follow-up testing
Search period	1960 – September 2013
Language	Non-English language articles were excluded

HbA1c = glycated haemoglobin; FPG = fasting plasma glucose; OGT = oral glucose tolerance

Search results

The PRISMA flowchart detailing the search results for this assessment is shown in Figure 6.

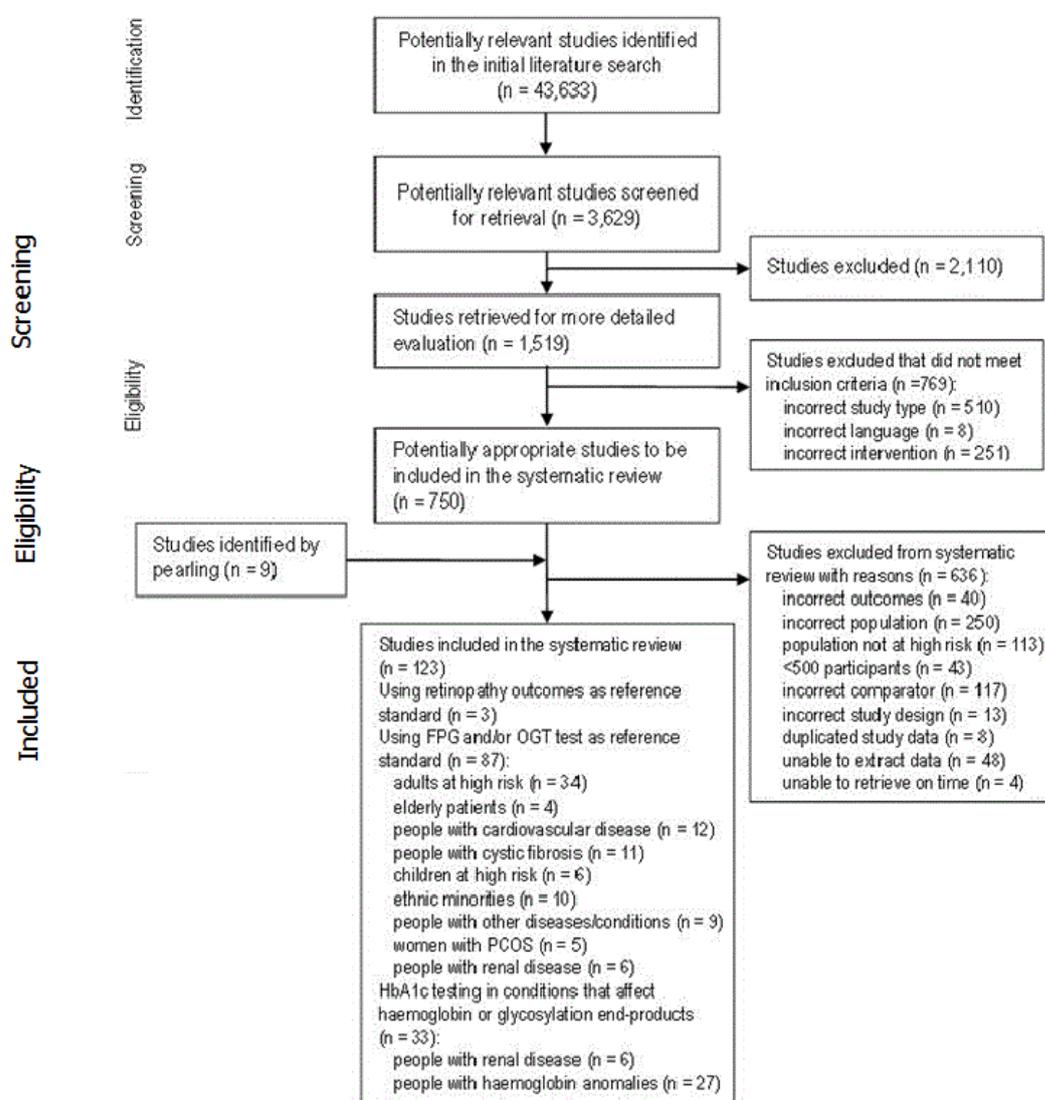


Figure 6: Summary of the process used to identify and select studies for the review (example)

Source: adapted from Liberati et al (Liberati et al. 2009)

The study profiles of all included studies are shown in Appendix C. Full text articles that did not meet the inclusion criteria are provided in Appendix G, where the studies are listed according to the reason for exclusion.

Data extraction and analysis

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

These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence (Table 10). The first domain is derived directly from the literature identified as informing a particular intervention; the last two require expert clinical input as part of the determination.

Table 10: Evidence dimensions

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

^a See Table 11

Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the systematic review—used to determine whether the findings obtained from the literature are likely to be trustworthy (strength of the evidence).

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

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

Stage 1: strength of the evidence

Three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results. The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see abridged version in Table 11).

Table 11: Designations of levels of evidence according to type of research question (including tablenotes)

Level	Intervention ^a	Diagnostic accuracy ^b
I ^c	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard ^d , among consecutive persons with a defined clinical presentation ^e
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard ^d , among non-consecutive persons with a defined clinical presentation ^e
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ non-randomised, experimental trial^f ▪ cohort study ▪ case-control study ▪ interrupted time series with a control group 	A comparison with a reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ historical control study ▪ two or more single-arm studies^g ▪ interrupted time series without a parallel control group 	Diagnostic case-control study ^e
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ^h

Sources: Merlin, Weston & Toohar (Merlin, Weston & Toohar 2009; National Health and Medical Research Council 1999)

Explanatory notes:

^a Definitions of these study designs are provided in National Health and Medical Research Council (2000), pp. 7–8, and in the Glossary accompanying Merlin, Weston and Toohar (2009).

^b These levels of evidence apply only to studies assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test, there also needs to be a consideration of the impact of the test on patient management and health outcomes (MSAC 2005; Sackett & Haynes 2002). The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis or comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or alternative screening methods.

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

^d The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al. 2003).

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

- ^f This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. using A vs B and B vs C to determine A vs C, with statistical adjustment for B).
- ^g Comparing single-arm studies, i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. using A vs B and B vs C to determine A vs C, but where there is no statistical adjustment for B).
- ^h Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

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

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

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

In terms of assessing the quality of the identified studies, those assessing test performance (diagnostic accuracy) were graded according to pre-specified quality and applicability criteria using the QUADAS-2 tool (Whiting et al. 2011). There were no test performance studies identified that compared HbA1c testing accuracy against the 'gold' reference standard of clinical screening for retinopathy; thus, use of FPG and/or OGT testing to confirm a diabetes diagnosis was considered the reference standard for this analysis—noting that this reference standard is imperfect. The appraisal of uncontrolled before-and-after case series was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al. 2001). The six questions were scored 0–1 and summed to give an estimate of study quality within the limitations of this study design: ≤ 2 = poor quality; >2 & ≤ 4 = moderate quality; >4 = high quality.

Stage 2: precision, size of effect and clinical importance

To assess the diagnostic accuracy of each of the included studies, data were extracted, where possible, into a classic 2x2 table in which the results of the index diagnostic test were cross-classified against the results of the reference standard (Armitage, Berry & Matthews 2002); (Deeks 2001), and Bayes' Theorem was applied:

	<i>Reference test +ve</i>	<i>Reference test -ve</i>	
<i>Index test +ve</i>	true positive	false positive	Total test positive
<i>Index test -ve</i>	false negative	true negative	Total test negative
	Total with diabetes	Total without diabetes	

Primary measures

The sensitivity, specificity, negative and positive predictive values (NPV, PPV) and likelihood ratios (LR) of the tests (as defined below) were calculated with corresponding 95% confidence intervals (95% CIs). Small confidence intervals give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). The results from included studies that did not provide the raw data have been summarised in the text.

Sensitivity (true positive rate) = true positives / total with diabetes

Specificity (true negative rate) = true negatives / total without diabetes

PPV (proportion of positive results that are true positives) = true positives / true + false positives

NPV (proportion of negative results that are true negatives) = true negatives / true + false negatives

Positive LR (LR+) = sensitivity/1–specificity

Negative LR (LR–) = 1–sensitivity/specificity

Meta-analysis

Diagnostic test accuracy (DTA) meta-analysis was undertaken to assess the accuracy of HbA1c testing in the diagnosis of diabetes, relative to FPG and/or OGT testing, using Stata version 12 (Stata Corporation 2011). Only studies that provided raw (2x2) data could be included in a meta-analysis. Hierarchical summary receiver–operator characteristic (HSROC) curves were generated using the metandi command that fits the model (based on (Rutter & Gatsonis 2001)) by using xtmelogit (multi-level mixed-effects logistic regression model). Estimates for the summary points sensitivity, specificity, diagnostic odds ratio (DOR), LR+ and LR– were also calculated. Confidence intervals were computed assuming asymptotic normality after a log transformation for variance parameters and for DOR, LR+ and LR–. Forest plots were generated using the midas command, which requires a minimum of four studies for analysis and calculates summary operating sensitivity and specificity (with confidence and prediction contours in SROC space), also using xtmelogit. Heterogeneity was calculated using the formula $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom (Higgins 2003). In the presence of heterogeneity, however, pooled sensitivities and specificities do not give a reliable summary estimate and a pooled DOR is a more appropriate summary measure.

DOR = (true positive / true negative) / (false positive / false negative)

The DOR describes the odds of a positive test in those with the disease compared with those without the disease. Values larger than 1 indicate the strength of the test to discriminate between the presence and absence of abnormal blood sugar levels—a value equal to 1 indicates that the test does not provide any useful diagnostic information, and values below 1 indicate that the test identifies more positives among those with normal blood sugar levels than with abnormal levels.

Stage 3: Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008). Five components are considered essential by the NHMRC when judging the body of evidence:

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

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 12) (NHMRC 2008).

Table 12: Body of evidence matrix

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

Source: adapted from(NHMRC 2008).

^a Level of evidence determined from the NHMRC evidence hierarchy—Table 11

^b If there is only one study, rank this component as ‘not applicable’.

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

SR = systematic review; several = more than two studies

Expert advice: Health Expert Standing Panel (HESP)

HESP has been established as a panel of the Medical Services Advisory Committee (MSAC) and is a pool of experts collated from various medical fields who are nominated by their associated professional body or by applicants. HESP members are engaged to provide practical, professional advice to evaluators that directly relates to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees (ESC and PASC). Their role is limited to providing input and guidance to the assessment groups to ensure that the proposed use of the medical service (pathway) is clinically relevant and that consumer interests are taken into account. HESP members’ advice is also used to inform the deliberations that MSAC presents to the Minister.

Results of assessment

Is it safe?

Summary of safety

No studies were identified that could inform an assessment of the safety of HbA1c testing compared with FPG and/or OGT testing in the diagnosis of diabetes. There is some risk associated with venepuncture but it is the same for all three tests. There are also risks associated with OGT testing that are unique to that test, but these are not deemed to be particularly serious.

Primary safety outcomes

None of the included studies reported on any safety outcomes. In only one reviewed study were adverse events mentioned as a reason for missing data (vomiting during the OGT test), but no numbers were provided (Rathmann et al. 2012). In most studies the population was insufficiently described to ascertain whether any participants did not receive or complete the tests, for any reason. It is assumed that, because the tests are so common and not particularly invasive, safety and adverse events were not really considered in the included studies.

However, HbA1c, FPG and OGT testing require sampling of the patient's blood, generally from veins in the upper limbs. Phlebotomy is considered to be a safe procedure even though venepuncture may be associated with minor physical harms such as bruising and haematoma (12.3% of venepunctures in one study; Galena 1992). Rarely, more serious events can also occur, including pain, nerve damage, arterial puncture or infection of the puncture site(Lavery & Ingram 2005; Scales 2008)(Lavery & Ingram 2005; Scales 2008), fear and phobia, syncope and fainting, excessive bleeding, oedema and thrombus (Buowari 2013; Galena 1992). These risks are the same for the three tests under consideration. It should be noted that all three tests are also already in use in Australia.

The *Oral Glucose Tolerance Test (OGTT) Procedures Manual* used in the US National Health and Nutrition Examination Survey (Centers for Disease Control 2007) reported that rare adverse reactions associated with the OGT testing procedure are also known to occur, including nausea, vomiting, abdominal bloating and headache. In addition, there is a rare incidence of hypoglycaemia.

Is it effective?

Direct evidence

No direct evidence comparing HbA1c testing with FPG or OGT testing was identified.

Evidence linkage 1: is the test accurate?

Studies with retinopathy as the reference standard

Summary of the evidence—studies with diabetic retinopathy reference standard

There is little difference between the discriminatory powers of FPG, 2hPG and HbA1c measures to predict retinopathy. Only three papers were identified that fulfilled the inclusion criteria, two of which were nearly two decades old, raising concerns about the current applicability of the tests used in the studies, and both were in unique populations (Pima Indians in the USA and Egyptians). The third study was from France and more recent, with a low risk of bias, although it included people with diabetes; therefore, there would be confounding by treatment, which may account for the poor accuracy of the blood glucose measures.

Although there was variation in the studies' findings in terms of test accuracy (e.g. sensitivity as low as 9% and as high as 87.5%), within each study there was little difference between the tests considered. A pooled analysis of data from a variety of studies, many that did not meet the inclusion criteria because they were population-based rather than high-risk populations, was also considered due to its use as the primary evidence-base for Australian recommendations about using HbA1c for diagnosis. The analysis found each of the three blood glucose measures (FPG, 2hPG and HbA1c) to be equally good at predicting retinopathy. A review undertaken by WHO did not report the detail on the findings but was used as the basis for WHO recommending HbA1c testing in the diagnosis of diabetes.

There are two major papers that investigate the accuracy of blood glucose measures against the reference standard of diabetic retinopathy; the first is a systematic review undertaken on behalf of WHO, which informed their recommendations for the use of HbA1c testing in the diagnosis of diabetes (WHO 2011). The second is a paper on the DETECT-2 collaboration, which is an analysis of a pooled dataset of studies that measured blood glucose (any combination of FPG, 2hPG and HbA1c) and retinopathy, both from published and unpublished data (Colagiuri et al. 2011). This paper is also included in the WHO review, and is the basis for the recommendations of the Australian Diabetes Society, the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists to use HbA1c for a diabetes diagnosis (d'Emden et al. 2012). These two papers were examined in detail during the current review and it was found that not all the studies included in the WHO review or the pooled analysis were eligible for this assessment, predominantly because of incorrect populations or because data were not provided in the referenced papers. Table 13 shows the studies from the pooled analysis and the WHO

review that measured HbA1c and another blood glucose measure, and notes whether they were eligible for this assessment (i.e. if they met the pre-specified inclusion criteria).

Table 13: Summary of studies included in WHO review and DETECT-2 pooled analysis

Study	Source	Measures	Eligibility	Included
Pima Indian study: USA, 1994 (McCance et al. 1994)	WHO review	FPG, 2hPG, HbA1c	Eligible: high-risk population	Yes
Diabetes in Egypt study: Egypt, 1997 (Engelgau et al. 1997)	WHO review	FPG, 2hPG, HbA1c	Eligible: high-risk population	Yes
French DESIR study: France, 2011 (Massin et al. 2011)	WHO review	FPG, HbA1c	Eligible: some subjects with diabetes, some with impaired fasting glucose and some with normal glucose	Yes
AusDiab: Australian Diabetes Obesity and Lifestyle study: Australia, 2008 (Tapp et al. 2008)	DETECT-2 and WHO review	FPG, 2hPG, HbA1c	Eligible: mostly at-risk population	No: diagnostic accuracy data not presented
Hiroshima study: Japan, 2000 (Ito et al. 2000)	DETECT-2 and WHO review		Ineligible: population-based study	No
Hisayama study: Japan, 2004 (Miyazaki et al. 2004)	WHO	FPG, 2hPG, HbA1c	Ineligible: population-based study	No
CURES: Chennai Urban Rural Epidemiology study: India, 2007 (Mohan et al. 2007)	DETECT-2	FPG, 2hPG, HbA1c	Ineligible: population-based study; data not available separately	No
MESA Multi-ethnic Study of Atherosclerosis: USA, 2006 (Wong, TY et al. 2006)	DETECT-2	FPG, HbA1c	Ineligible: population-based study	No
NHANES III, National Health and Nutritional Examination Survey: USA, 1998 (Harris et al. 1998)	DETECT-2	FPG, HbA1c	Ineligible: population-based study	No

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; 2hPG = 2-hour postprandial glucose

Of the three eligible and included studies, two were conducted in the 1980s and 1990s (Engelgau et al. 1997; McCance et al. 1994) prior to the standardisation of the HbA1c assay and, in all likelihood, with poorer ophthalmological examination. There were numerous issues with the quality of the Pima Indian study (McCance et al. 1994), not least the tests themselves, in which HbA1 (an earlier measure of glycated haemoglobin) was measured in

many of the subjects and HbA1c in the remainder, and retinopathy was diagnosed by ophthalmological examination without photography. Although this study was nested within a large longitudinal study, participation rates and population characteristics were not reported, which makes it difficult to assess methodological quality and applicability; however, the population included in the analysis did not have previously diagnosed diabetes or retinopathy.

The Egyptian study (Engelgau et al. 1997), also conducted in the 1990s, had a sound methodology where randomly sampled Egyptian adults from Cairo and surrounding areas were invited to participate in further testing if they had a random plasma glucose ≥ 5.6 mmol/L in the baseline examination. All subjects with random plasma glucose ≥ 5.6 mmol/L, plus a random sample of subjects below that level, were asked to have an OGT test and a retinal photograph. This study included people with known diabetes, although the analysis was conducted separately for the groups with and without known diabetes. There was limited description of the population provided. The type and conduct of the test was of low concern; however, it should be noted that both these studies were conducted prior to the standardisation of the HbA1c assay, which is likely to have some impact on the reported accuracy of the test.

The third eligible study is more recent, conducted in France in the early 2000s and published in 2011 (Massin et al. 2011). This study included participants in a cohort located in central western France, who were aged 30–65 years at recruitment in 1994–96. At the 9-year follow-up one group of participants who had all been treated for diabetes or had at least one FPG level of ≥ 126 mg/dL; another group matched for age, sex and examination centre who had an impaired fasting glucose level at any time during the study; and a further group matched for age, sex and examination centre with glucose levels within normal range were invited for a special exam about microvascular complications. Subjects included in the analysis had an FPG and HbA1c from baseline and a retinal photograph from the 10-year follow up, which was graded according to the Wisconsin protocol. The risk of bias in the conduct of this study is low, although results are likely to be confounded by treatment as the study included some subjects who had received treatment for diabetes; this could explain the poor accuracy of both the blood glucose measures in the study. The tests were appropriate (baseline HbA1c was measured prior to assay standardisation; the study standardised the HbA1c and glucose tests between the four participating laboratories) and the study is applicable to the Australian setting, given that it included people in a risk range for diabetes.

The results from these three studies are presented in Table 14.

Table 14: Results from three studies comparing diagnostic accuracy of blood glucose measures against reference standard of retinopathy

Study	ROC cut-off points	Sensitivity	Specificity	Other data
Pima Indians (McCance et al. 1994)	Optimal: FPG 7.2 mmol/L 2hPG 13.0 mmol/L HbA1c 7.0% WHO diagnostic: FPG 6.8 mmol/L 2hPG 11.1 mmol/L HbA1c 6.1%	81.3% 87.5% 78.1% 81.2% 87.5% 81.3%	81.4% 80.4% 84.7% 77.1% 75.8% 76.8%	
Diabetes in Egypt (Engelgau et al. 1997)	FPG 125 mg/dL 2hPG 200 mg/dL HbA1c 6.5%	57% 51% 51%	88% 89% 86%	
French DESIR (Massin et al. 2011)	FPG 108 mg/dL HbA1c 6.0% FPG 116 mg/dL HbA1c 6.5% Area under ROC: FPG 0.64 HbA1c 0.64	27% 19% 19% 9% 	88% 92% 97% 98% 	PPV 8.4%, NPV 97% PPV 6.0%, NPV 92% PPV 14.0%, NPV 96% PPV 14.8%, NPV 97%

ROC = receiver–operator characteristic curve; FPG = fasting plasma glucose; 2hPG = 2-hour postprandial glucose; HbA1c = glycated haemoglobin; PPV = positive predictive value; NPV = negative predictive value;

It can be seen that, even when the ability of the blood glucose measures to predict retinopathy is not particularly good, there is not a major difference between the three tests. The best quality and most recent of these studies, the French study (Massin et al. 2011), found very poor sensitivity of both FPG and HbA1c for predicting retinopathy (potentially confounded by treatment of cases), but the PPV was about the same for each test and the area under the ROC curve was identical, indicating that both tests have similar accuracy.

Although the pooled analysis of the DETECT-2 collaboration included studies that did not fit our inclusion criteria (because they were population-based or did not have HbA1c measures), it was deemed informative to include the results of the analysis as this paper is the basis for the Australian consensus recommendations for using HbA1c in the diagnosis of diabetes (d'Emden et al. 2012), and it is also included in the WHO review. Moreover, data from Australia is included in this pooled analysis and the individual data was not available separately. The study used data from nine studies, some of which had only one blood glucose measurement and looked at each measure separately against retinopathy. In total the analysis looked at n=44,623 participants with at least one blood glucose measure and a gradable retinal photograph. The participants were from a range of countries and cultural backgrounds. The analysis found that the overall discriminatory power for predicting retinopathy (measured by the area under the curve in a ROC analysis) for each of the glucose measures was uniformly high (HbA1c 0.90, 95%CI 0.88,0.92; FPG 0.87, 95%CI 0.85,0.89; 2hPG 0.89, 95%CI 0.87,0.91) and not statistically significantly different from one

another. Moreover, the study reported threshold ranges for diabetes-specific retinopathy from ROC curve analysis of 6.6 mmol/L for FPG, 13.0 mmol/L for 2hPG and 6.4% for HbA1c.

The WHO review is very limited in detail and does not report any specific findings; however, it recommends using HbA1c testing for diagnosis, stating that 'HbA1c gives equal or almost equal sensitivity and specificity to glucose measurement as a predictor of prevalent retinopathy', but acknowledging that 'it is not known which is the better for predicting microvascular complications' .

Evidence linkage 1, supplementary: is the test accurate?

Studies without the diabetic retinopathy reference standard

Summary of the evidence—studies without retinopathy reference standard

The risk of bias in terms of participant selection and study flow and timing was unclear in many of these studies due to poor reporting; however, from the information provided, the studies were methodologically similar. The conduct of the tests themselves was unlikely to introduce bias. The results were characterised by considerable variability and, in addition, the diagnostic accuracy varied according to the cut-off points chosen. Concordance between HbA1c tests and the different (imperfect) reference standards was generally poor, but with a large range (kappa from as low as 0.221 and as high as 0.751). Where studies comparing diabetes diagnosed by either HbA1c or OGT testing were able to be combined, the pooled sensitivity increased from 53.5% to 90.1% as the HbA1c cut-off decreased from 6.5% to 6.0% or 6.1%. The results were reversed for specificity, decreasing from 94.7% to 67.7% when the HbA1c cut-off decreased from 6.5% to 6.0 or 6.1%.

It is difficult to draw conclusions about the accuracy of HbA1c testing when compared with an imperfect reference standard, but it is apparent that a lower threshold may be more conservative at identifying diabetes cases and that there are differences in the test results that are unrelated to test threshold (which may be due to the fact that the tests are measuring different markers of diabetes, i.e. circulating blood glucose levels versus the ability of the body to break down glucose).

To supplement the information about diagnostic accuracy with diabetic retinopathy as the reference standard, studies that compared test accuracy between HbA1c and either or both FPG and OGT testing were considered.

Overall, the test accuracy studies identified for inclusion in the review were characterised by heterogeneity in their results and a lack of detail in the reporting of the methodology, meaning that it was difficult to assess the risk of bias in each study. All studies were designated level III-2 according to the NHMRC levels of evidence, primarily due to the lack of a valid reference standard. All studies were cross-classification studies, in which each subject had an HbA1c measurement and one or both of FPG and OGT measurements. Some studies retrospectively analysed administrative datasets (laboratory results) and others used the diabetes tests as part of a battery of tests in intervention, cross-sectional or cohort studies; in many it seemed that the comparison of HbA1c test results with other glucose

measures was a post-hoc analysis, although this was often not made explicit. In most studies it was unclear how and from where the tested population was sourced; however, we were confident that all the studies included high-risk (or predominantly high-risk) populations. The studies used a variety of cut-off points in the tests to determine diabetes, thus limiting the ability to summarise their results in a meta-analysis.

Diabetes in high-risk adults

A total of 15 studies were identified that fulfilled the inclusion criteria and provided adequate data for the diagnostic meta-analysis (Alqahtani et al. 2013; Baral et al. 2000; Cavagnoli et al. 2011; Cosson et al. 2011; Du et al. 2013; Hutchinson et al. 2013; Ko, GT et al. 1998; Lee, H et al. 2013; Lu et al. 2010; Manley, SE et al. 2009; Marini, Succurro, Arturi, et al. 2012; Mostafa, Davies, et al. 2010; Peter et al. 2011; Saiedullah, Rahman & Khan 2011). The study profiles can be found at Appendix C.

In these studies HbA1c was compared against diabetes diagnosed using FPG with or without OGT testing as the (imperfect) reference standard. Several different thresholds for diagnosis were used, and the findings of studies using the same (or very similar) cut-offs were pooled.

The studies were undertaken in a variety of settings, some with more applicability to the Australian context and the proposed use of the test than others. Two of the included studies were undertaken in Australia (Lu et al. 2010; Manley et al. 2009). A number of other studies were undertaken in European countries (UK, Italy, Norway, France and Germany), one was from Brazil, one from Saudi Arabia and several from Asia (Nepal, China, South Korea and Bangladesh). The tests used were 'in-house' laboratory-developed diagnostic tests for fasting plasma glucose (FPG), oral glucose tolerance (2hPG) and glycated haemoglobin (HbA1c).

The study quality overall was difficult to ascertain, due to the lack of detail in the reporting. This was particularly true of the description of the referral and recruitment of the participants in the study, and of any exclusions after recruitment, including who actually received the tests and in whom the tests were incomplete. It is possible that the 'high-risk' determination in the studies was less or more stringent than would be applied in Australia, and this could impact on the diagnostic accuracy outcomes (if, e.g., there is likely to be more concordance between blood glucose measures and HbA1c at higher levels of blood glucose). However, as a wide range of tests, test settings and interpretations have been sampled in the evidence-base, it is likely that the range of presented results would be reflective to some extent of the likely impact of testing 'high-risk' people in Australia. It is unlikely that the conduct of the tests themselves would introduce bias. Although none of the studies reported if the HbA1c results had been interpreted without knowledge of the other test results, in instances where the results are reported by the laboratory as a number and there is a pre-specified and accepted cut-off or threshold for a diabetes diagnosis, there is

probably limited scope for misclassification bias. A summary of the studies and their quality appraisal can be found in Table 15. Studies are ranked by quality. Below the table, results are reported separately for diabetes diagnosed by HbA1c versus OGT, HbA1c versus FPG and HbA1c versus 2hPG, as each of these comparators measures something different.

Table 15: Brief description of study design and quality of studies providing raw (2x2) data comparing HbA1c with FPG with or without 2hPG testing

Study name	Design	Population	Quality appraisal and applicability
Algahtani (2013)	Administrative data review of patients tested for diabetes in Khamis Mushayt, Saudi Arabia	N=1,814 records of subjects were tested in outpatient clinic of armed forces hospital because of suspicion of diabetes; mean age = 54.3 years, 34.3% male	Low risk of bias. Applicability unclear as review of administrative database, and included and excluded populations not well described; unclear if 'armed forces hospital' setting affects population selection.
Du (2013)	Cross-sectional study in Wuhan, China	N=2,318 patients referred to diabetes outpatient clinic of hospital; mean age = 47.5 years	Low risk of bias. Limited applicability to Australian setting as Chinese population.
Lee, H (2013)	Cross-sectional study in 10 sites in South Korea	N=4,616 patients referred or voluntarily attended hospital outpatient clinic; mean age = 50 years, 55% male	Low risk of bias. Limited applicability to Australian setting as Korean population.
Bianchi (2012)	Population-based cross-sectional study in Italy	N=844 subjects recruited from referrals to diabetes clinic because of suspected diabetes; mean age = 49.5 years, 44% male	Low risk of bias. Applicable to Australian setting.
Cavagnolli (2011)	Cross-sectional study of high-risk subjects referred to hospital clinical pathology department for OGT testing in Porto Alegre, Brazil	N=498 patients with high-risk of diabetes referred (unclear where from) for OGT testing; all Brazilians, 84% white, 39% male	Low risk of bias. Few applicability concerns; Brazilian study but majority of subjects of European descent.
Cosson (2011)	Cross-sectional study in Bondy, France	N=1157 subjects referred to hospital clinic for weight management; mean age = 41 years, 17% male	Low risk of bias. Applicable to Australian setting.
Lu (2010)	Administrative dataset review of tests conducted by private pathology service in Victoria, Australia	N=2,494 patients referred by GPs for tests, no description of population	Low risk of bias although no description of population; however, likely to be exactly the population of interest in this assessment.
Mostafa (2010a) (also reported in Mostafa (2013) and Mostafa ((2010b))	Population-based cross-sectional study in Leicestershire, UK	N=9,494 subjects recruited from primary care; 75% had a risk factor, mean age = 57.3 years, 47.7% male	Low risk of bias. Applicable to Australian setting.
Hutchinson (2013)	Cross-sectional analysis of longitudinal study in Tromso, Norway	N=3,476 subjects recruited from larger population-based study, most with HbA1c in pre-diabetes range; 65% of participants 60 years of age or older, 51% male	Risk of bias unclear due to poor reporting and possible concerns about time lag between two tests. Probably applicable to Australian setting but limited information.
Marini (2012a) (also reported in Marini (2012b))	Cross-sectional study of patients in Rome and Cantanzaro, Italy	N=1,091 patients assessed for cardiometabolic risk factors but source of population unclear; two papers presented different	Risk of bias unclear due to poor reporting of population source and differences in reported numbers. Probably applicable to

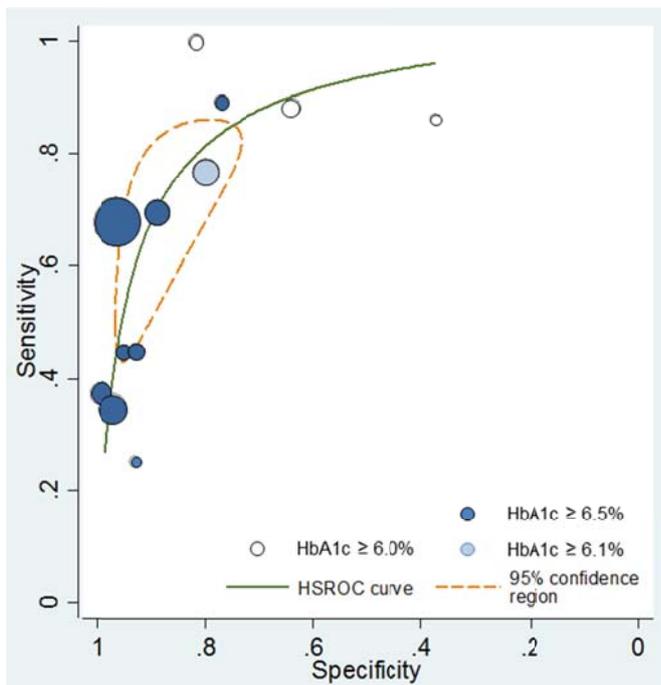
Study name	Design	Population	Quality appraisal and applicability
		parts of the same study but mean age and gender not consistent; mean age around 45 years, between 33% and 42% male	Australian setting but limited information.
Peter (2011)	Cross-sectional analysis of patients in ongoing cohort studies in Tübingen, Germany	N=2,036 patients at risk of diabetes involved in ongoing studies of pathogenesis of diabetes; mean age = 40.3 years, 35% male	Risk of bias unclear due to poor reporting. Probably applicable to Australian setting but limited information.
Manley (2009) (also reported in Manley (2010))	Cross-sectional study of patients in Australia and UK (reported separately in this analysis)	N=1,682 patients referred for OGT testing but no further description of source or recruitment of patients; UK mean age = 62 years, 52% male; Australian mean age = 57 years, 54% male	Risk of bias unclear due to poor reporting. Applicable to Australian setting.
Baral (2000)	Cross-sectional study in Dharan, Nepal	N=920 subjects referred to hospital clinic for OGT testing; age range = 30–65 years	Unclear risk of bias due to poor reporting. Applicability unclear due to poor reporting; Nepalese setting, so possible limited applicability.
Ko (1998a) (also reported in Ko (1998b))	Cross-sectional study of patients in Hong Kong, China	N=2,877 patients referred to hospital diabetes clinic for testing; mean age = 36.6 years, 19% males	Risk of bias unclear due to poor reporting. Limited applicability to Australian setting as Chinese population.
Saiedullah (2011)	Cross-sectional study of patients in Dhaka, Bangladesh	N=800 patients who underwent diabetes tests at Institute of Health Sciences; mean age = 43 years, 40% male	High risk of bias due to very limited reporting of population and methods. Limited applicability to Australian setting as Bangladeshi population.

Note: Australian studies in bold

HbA1c test relative to OGT test

There were 11 studies that compared diabetes diagnosed using HbA1c testing with diabetes diagnosed using OGT testing (diagnostic threshold FPG ≥ 7.0 mmol/L and/or 2hPG ≥ 11.1 mmol/L). With an HbA1c cut-off of $\geq 6.5\%$, eight studies contributed data (Cavagnoli et al. 2011; Cosson et al. 2011; Hutchinson et al. 2013; Lu et al. 2010; Marini, Succurro, Arturi, et al. 2012; Mostafa, Davies, et al. 2010; Peter et al. 2011; Saiedullah, Rahman & Khan 2011). A further two studies, contributing three sets of data, used an HbA1c cut-off of 6.0% (Baral et al. 2000; Manley, SE et al. 2009), and these results were combined with one additional study using a cut-off of 6.1% (Ko, GT et al. 1998). Results from the meta-analysis are presented in Figure 7 as the HSROC curve and in Figure 8 as a forest plot showing the sensitivity, specificity and concordance results. As expected, sensitivity and specificity varied by HbA1c cut-off and there was considerable heterogeneity in the findings (meta-analysis of all 12 datasets resulted in I^2 values of 98.1% for sensitivity

and 99.5% for specificity; data not shown). However, this does not appear to be the only factor contributing to variation in the results between studies, as stratification of results by HbA1c threshold did not reduce the heterogeneity substantively (I^2 values varied from 92.7% to 99.98%; Figure 8). As mentioned previously, the three tests detect different physiological conditions and diagnose a different subpopulation of affected individuals. Thus, it is not surprising that the overall concordance between the tests was low, with kappa statistics ranging from 0.221 to 0.661. However, the DOR for both HbA1c cut-offs (19.1 at 6.0% and 20.6 at 6.5%) indicate that the HbA1c test discriminates between the presence and absence of diabetes (DOR value of 1 provides no useful information).



HbA1c ≥ 6.5% (8 studies)	HbA1c ≥ 6.0% or 6.1% (4 studies)
Sensitivity 53.5% (95% CI 36.9, 69.3)	90.1% (95% CI 73.9, 96.7)
Specificity 94.7% (95% CI 89.9, 97.3)	67.7% (95% CI 48.9, 82.2)
Diagnostic Odds Ratio 20.6 (95% CI 11.5, 37.1)	19.1 (95% CI 4.0, 91.7)
Positive Likelihood Ratio 10.1 (95% CI 6.0, 17.1)	2.8 (95% CI 1.6, 5.0)
Negative Likelihood Ratio 0.49 (95% CI 0.35, 0.69)	0.15 (95% CI 0.05, 0.46)

Figure 7: Results of diagnostic meta-analysis for diabetes diagnosed by FPG/2hPG vs HbA1c testing

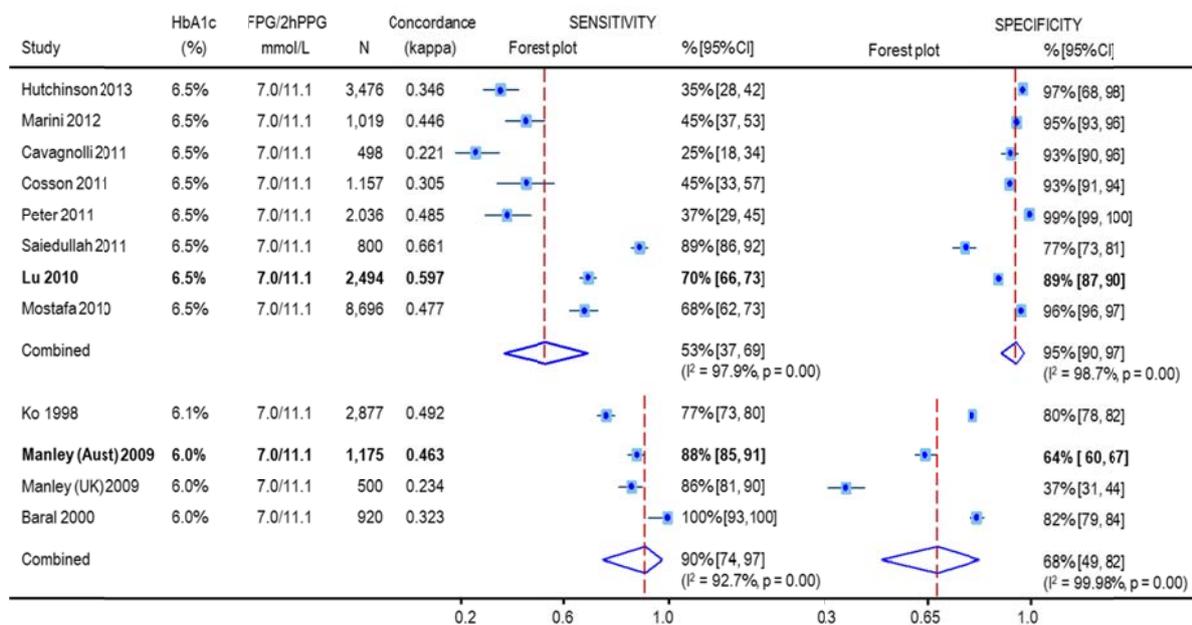


Figure 8: Forest plot of studies comparing diagnostic accuracy of HbA1c and FPG/2hPG testing, grouped

Note: Studies are ranked according to HbA1c cut-off value, year and quality; **Australian data in bold.**

There were an additional eight studies that fulfilled the criteria for inclusion in the review but did not provide data for the meta-analysis (Bianchi et al. 2012; Colagiuri et al. 2004; Hajat, Harrison & Al Siksek 2011; Hu et al. 2010; Jesudason et al. 2003; Khoo et al. 2012; Lee, H et al. 2013; Tankova et al. 2012). The study profiles can be found in Appendix C. These studies provided results in a variety of ways, mostly ROC analyses results with corresponding sensitivity and specificity statistics. Some of the studies included in the meta-analysis also provided additional results from other analyses (Cavagnolli et al. 2011; Cosson et al. 2011; Ko, GT et al. 1998; Manley, S et al. 2010; Marini, Succurro, Arturi, et al. 2012; Mostafa et al. 2013; Peter et al. 2011), which are also reported here.

The studies were of very similar methodology to those included in the meta-analysis and had the same flaws; namely, poor reporting of study population referral, recruitment and exclusions. Again, the studies were from around the world, with two from Australia among others from Europe (UK, Bulgaria and Spain), Asia (Japan, China, Singapore and India) and the Middle East (United Arab Emirates).

When diabetes diagnosed by HbA1c testing was compared with diabetes diagnosed by OGT testing (diagnostic threshold FPG ≥ 7.0 mmol/L and/or 2hPG ≥ 11.1 mmol/L), the results showed that, for an HbA1c cut-off of 6.5%, sensitivity was in the range 43.2–72.3%, with a corresponding specificity of 82.7–94.4%. For studies that reported on the optimal HbA1c diagnostic threshold, the cut-off ranged from 5.9% to 6.5%. Area under the curve statistics ranged from 0.74 (at HbA1c = 6.1%) to 0.958 (at HbA1c = 6.1%). The results are summarised in Table 13.

HbA1c test compared with FPG test

There were five studies that compared the diagnostic accuracy of HbA1c testing against FPG testing alone (Alqahtani et al. 2013; Du et al. 2013; Lee, H et al. 2013; Manley, SE et al. 2009; Marini, Succurro, Arturi, et al. 2012), and four of these used the same diagnostic thresholds and were combined in meta-analysis (Alqahtani et al. 2013; Du et al. 2013; Lee, H et al. 2013; Marini, Succurro, Arturi, et al. 2012). The results were similar to the first analysis, although the concordance was a little higher (up to $\kappa=0.751$ in one study). The results of the HSROC analysis are shown in Figure 9, and the forest plots for the five studies are shown in

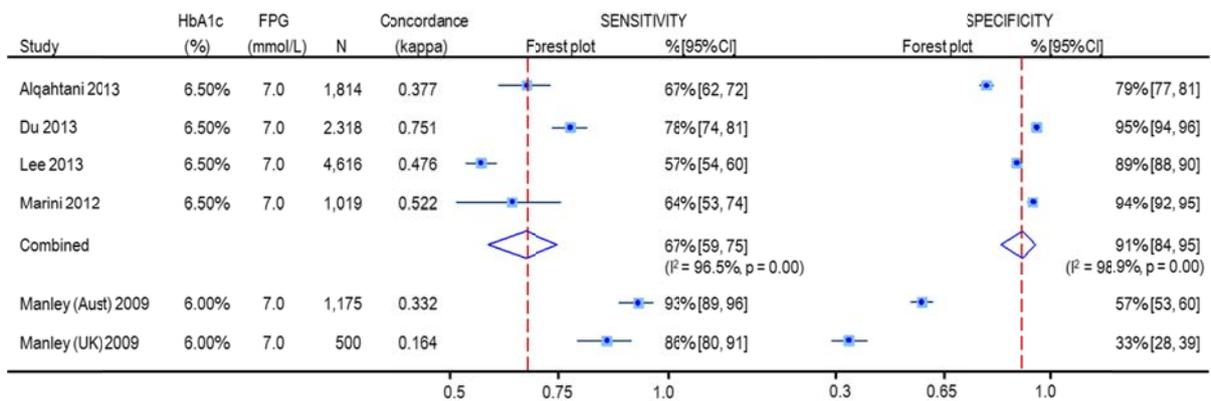


Figure 10.

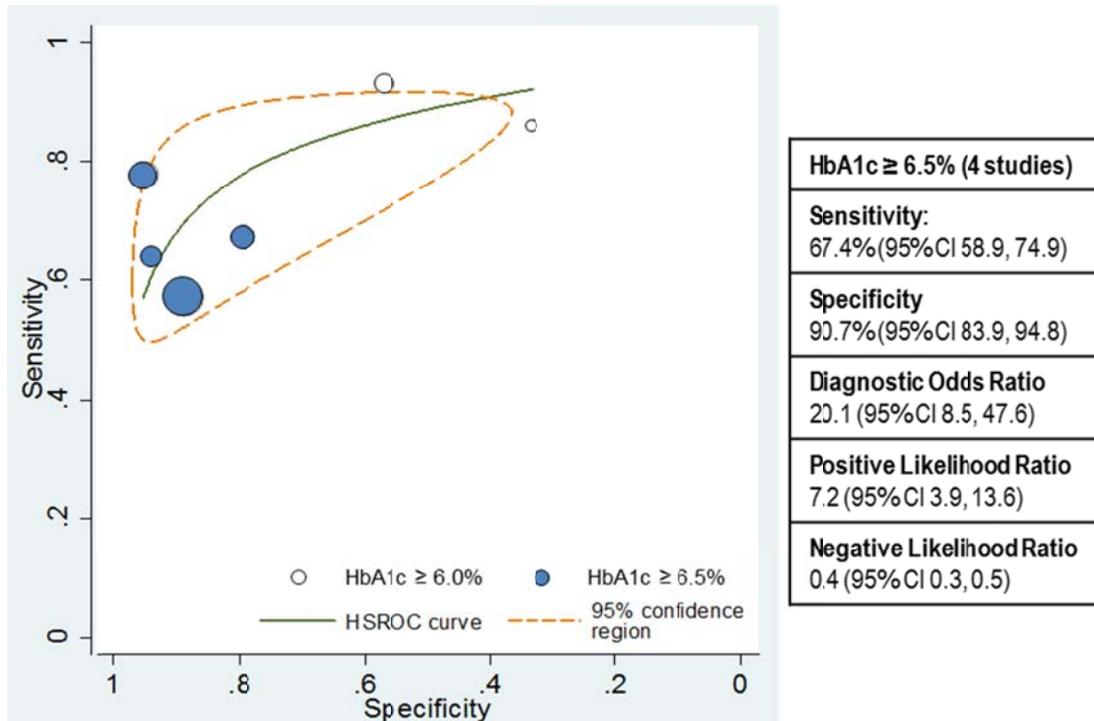


Figure 9: Results of diagnostic meta-analysis for diabetes diagnosed using HbA1c vs FPG testing

Table 16: Summary of diagnostic accuracy results for diabetes diagnosed by HbA1c vs OGT testing (additional studies)

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
Manley (2009) Australia, UK (Australian pop.)	FPG ≥7.0 2hPG ≥11.1	ROC	nr	5.0% 5.5% 6.0% 6.5%	100.0% 98.5% 88.3% 68.9%	3.7% 25.9% 63.8% 89.8%		
Manley (2009) Australia, UK (UK pop.)	FPG ≥7.0 2hPG ≥11.1	ROC	nr	5.0% 5.5% 6.0% 6.5%	100.0% 97.5% 86.3% 61.4%	2.0% 8.3% 37.4% 68.9%		
Colagiuri (2004) Australia	FPG ≥7.0 2hPG ≥11.1	ROC	nr	5.3%	78.7%	82.8%	15.5%	
Jesudason (2003) Australia	FPG ≥7.0 2hPG ≥11.1	ROC	0.893	5.7%	80.0%	86.3%		
Cavagnoli (2011) Brazil	FPG ≥7.0 2hPG ≥11.1	ROC	nr	5.9% ^a	63.5%	66.1%		
Hajat (2011) UAE	FPG ≥7.0 2hPG ≥ 1.1	ROC	0.74 [0.71, 0.78] 0.78 [0.75, 0.82] 0.77 [0.74, 0.81]	6.1% 6.4% ^a 6.5%	82.5% [76.4, 87.7] 72.0% [65.0, 78.2] 65.6% [58.4, 72.4]	66.2% [62.9, 69.4] 84.3% [81.6, 86.7] 89.1% [86.8, 91.1]	42.8% [40, 45.6] 47.9% [43.4, 52.4] 52.3% [46.8, 57.7]	92.5% [90, 94.4] 93.7% [92.2, 95] 93.4% [92.1, 94.5]
Hu (2010) China	FPG ≥7.0 2hPG ≥11.1	ROC	0.899 [0.88, 0.91]	6.1% ^a	81.0% [79.4, 82.6]	81.0% [79.4, 82.6]	PLR=4.26	NLR=0.23
Ko (1998a) China	FPG ≥7.0 2hPG ≥11.1	ROC		6.1%	77.5%	78.8%		
Lee, H (2013) Korea	FPG ≥7.0 2hPG ≥11.1	ROC	0.810	6.1% ^a 6.5%	63.8% 50.5%	88.1% 95.0%	72.4% 87.1%	79.5% 74.2%
Mostafa (2010a) (also reported in Mostafa (2013) and Mostafa (2010b))	FPG ≥7.0 2hPG ≥11.1 (white European population)	ROC	0.92 [0.89, 0.94]	6.1% ^a 6.5% 7.0%	83.0% [76.8, 87.7] 62.1% [54.8, 68.8] 41.8% [34.8, 49.0]	87.8% [87.0, 88.6] 97.7% [97.3, 98.1] 99.6% [99.4, 99.7]	16.8% [14.3, 19.2] 44.8% [38.7, 51.0] 76.0% [67.6, 84.4]	99.4% [99.2, 99.6] 98.9% [98.6, 99.1] 98.3% [98.0, 98.6]
Peter (2011) Germany	FPG ≥7.0 2hPG ≥11.1	2x2		6.1% 6.5% 7.1%	70.6% 46.8% 20.6%	91.5% 98.7% 99.9%	43.8% 84.0% 98.4%	97.9% 96.6% 95.0%
Tankova (2012) Bulgaria	FPG ≥7.0 2hPG ≥11.1	ROC	0.958 [0.95, 0.97]	6.1%	86% [82, 89]	92% [88, 95]		
Cosson	FPG ≥7.0	ROC	0.767	6.4%	52.6%	90.3%	-	-

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
(2011) France	2hPG \geq 11.1		[0.70, 0.83]	6.5% ^a	44.7%	92.7%		
Bianchi (2012) Italy	FPG \geq 7.0 2hPG \geq 11.1	ROC	0.80 [0.73, 0.85]	6.5%		74%		
Khoo (2012) China	FPG \geq 7.0 2hPG \geq 11.1	ROC	nr	6.5%	72.3% [69.2, 75.0]	82.7% [77.8, 87.1]		
Marini (2012) Italy	FPG \geq 7.0 2hPG \geq 11.1	ROC	0.778	6.5%	43.2%	94.4%	58.3%	93.9%

^a Optimal cut-off point

AUC = area under the curve; NA = not applicable; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver-operator characteristic

Note: Table ordered by HbA1c cut-off point; **Australian studies in bold**.

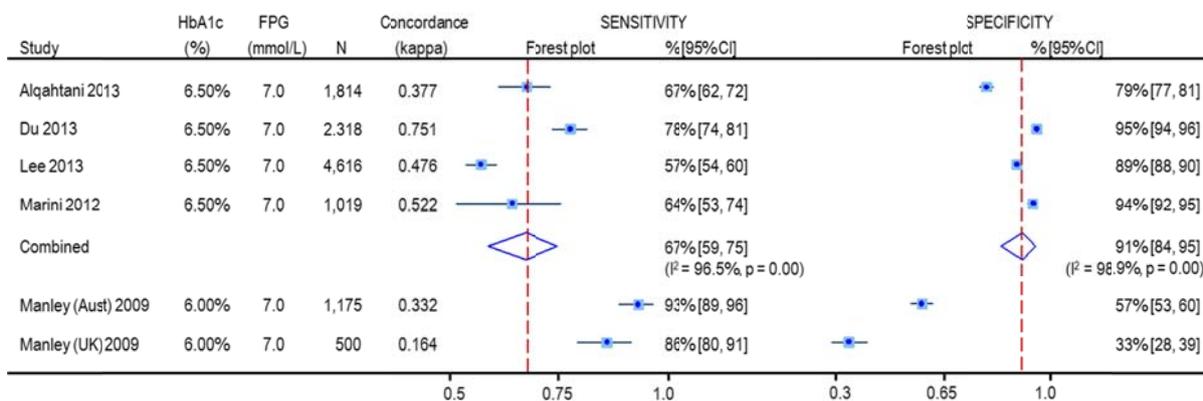


Figure 10: Forest plot of studies comparing diagnostic accuracy of HbA1c and FPG testing

Five studies provided additional diagnostic accuracy analyses comparing HbA1c testing against FPG testing (Cavagnoli et al. 2011; Du et al. 2013; Kumaravel et al. 2012; Marini, Succurro, Arturi, et al. 2012; Snehalatha et al. 2000). Four reported ROC analyses and the fifth conducted a logistic regression. Using an HbA1c cut-off of 6.5%, sensitivity was in the range 60.5–76.6% with specificity 96.0–98.0%. Only one study investigated an optimal HbA1c diagnostic threshold; this was 6.0% with a sensitivity of 74.2% and specificity of 72.0%. A summary of results from these studies is in Table 17.

Table 17: Summary of diagnostic accuracy results of diabetes diagnosed by HbA1c vs FPG testing

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
Cavagnoli (2011) Brazil	FPG ≥7.0	ROC	nr	6.0% ^a 7.0% 8.0%	74.2%	72.0% 99.5% 99.8%	-	-
Kumaravel (2012) UK	FPG ≥7.0	Logistic regression	NA	6.0% 6.5% 7.0%	88.9% 60.5% 42.0%	92.4% 98.0% 99.7%	PLR = 11.8 PLR = 56.4 PLR = 160	NLR = 0.12 NLR = 0.40 NLR = 0.58
Snehalatha (2000) India	FPG ≥7.0	ROC		6.0%	85.2%	61.2%		
Du (2013) China	FPG ≥7.0	ROC	nr	6.5%	76.6%	96.0%	87.7%	91.8%
Marini (2012) Italy	FPG ≥7.0	ROC	0.856	6.5%	64.1%	94.0%	51.3%	96.3%

^a Optimal cut-off point

AUC = area under the curve; NA = not applicable; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver–operator characteristic

Note: Table ordered by HbA1c cut-off point.

HbA1c test relative to OGT (2hPG) test

Four studies provided useable data to compare the diagnostic accuracy of HbA1c testing with 2hPG testing (using only the 2hPG measure) in a meta-analysis, three using the HbA1c cut-off of 6.5% (Alqahtani et al. 2013; Lee, H et al. 2013; Marini, Succurro, Arturi, et al. 2012) and one using a cut-off of 6.1% (Ko, GT et al. 1998). These studies were all also included in the HbA1c versus FPG comparison above, with the 2hPG and FPG results reported separately. Again, the results show considerable variation, as indicated in Figure 11 and Figure 12.

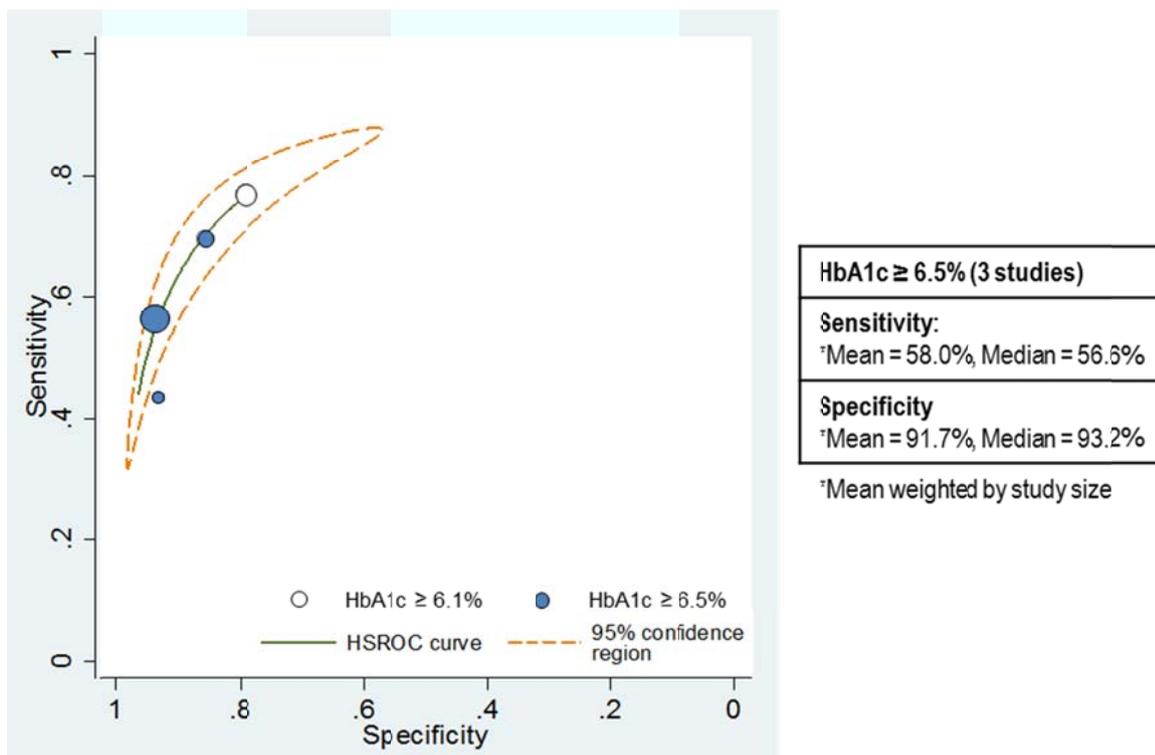


Figure 11: Results of diagnostic meta-analysis for diabetes diagnosed by HbA1c vs 2hPG testing

Study	HbA1c (%)	2hPPG (mmol/L)	N	Concordance (kappa)	SENSITIVITY		SPECIFICITY	
					Forest plot	% [95%CI]	Forest plot	% [95%CI]
Alqantani 2013	6.5%	11.1	1,814	0.540		70% [65, 74]		88% [84, 88]
Lee 2013	6.5%	11.1	4,616	0.546		57% [54, 59]		94% [93, 95]
Marini 2012	6.5%	11.1	1,019	0.379		44% [35, 53]		93% [91, 95]
Ko 1998	6.1%	11.1	2,877	0.472		77% [73, 80]		79% [77, 81]

Figure 12: Forest plot of studies comparing diagnostic accuracy of HbA1c and 2hPG testing

Other test accuracy measures were reported in the comparison of HbA1c versus 2hPG testing in five included studies (Cavagnoli et al. 2011; Gomyo et al. 2004; Marini, Succurro, Arturi, et al. 2012; Snehalatha et al. 2000; Tanaka et al. 2001). Four of these studies did an ROC analysis and one reported sensitivity and specificity without presenting the data for the 2x2 table. Again, the results were variable. Only two studies presented results at an HbA1c diagnostic threshold of 6.5%, and these had low sensitivity (46.6% and 49.0%) and relatively high specificity (93.9% and 98%), respectively. The results are summarised in Table 18.

Table 18: Summary of diagnostic accuracy results of diabetes diagnosed by HbA1c vs 2hPG testing

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
Gomyo (2004) Japan	2hPG ≥11.1	ROC	nr	5.5% ^a	72.7%	79.8%		
Cavagnoli (2011) Brazil	2hPG ≥11.1	ROC	nr	5.9% ^a	62.9%	64.1%		
Tanaka (2001) Japan	2hPG ≥11.1	2x2 table	NA	5.9% 6.5%	76% 49%	86% 98%		
Snehalatha (2000) India	2hPG ≥11.1	ROC	nr	6.0%	88.5%	62.8%		
Marini (2012a) Italy	2hPG ≥11.1	ROC	0.794	6.5%	46.6%	93.9%	53.0%	92.3%

^a Optimal cut-off point

AUC = area under the curve; NA = not applicable; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver–operator characteristic

Note: Table ordered by HbA1c cut-off point.

Overall, as with the meta-analyses, it is difficult to draw conclusions about the diagnostic accuracy of HbA1c testing relative to these imperfect reference standards given such heterogeneous results; however, each of them appears to have some discriminative ability in detecting the presence and absence of diabetes.

Pre-diabetes in high-risk adults

Pre-diabetes is considered important due to the high risk associated with progression to diabetes. The current testing strategy of FPG or OGT can identify people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), and there was concern from PASC that HbA1c results would not have an equivalent pre-diabetes range. ADA has a stated HbA1c range for pre-diabetes (5.7–6.4%) and many of the studies included in this review used 6.0–6.4% as a pre-diabetes range. Should HbA1c be approved in the diagnosis of diabetes in Australia, appropriate guidelines would need to be developed to standardise a pre-diabetic range for HbA1c tests.

Some of the studies included in the review considered pre-diabetes and used either or both the IFG and IGT definitions of pre-diabetes, with varying thresholds, to define them. The data were very difficult to interpret due to the considerable differences in thresholds used, and thus the findings about accuracy in pre-diabetes are difficult to summarise and draw any conclusions from. As a result, these findings do not add anything to the interpretation of the HbA1c accuracy results presented for determining diabetes, and are not considered any further here; however, some concordance data is provided and the studies are described in Appendix D.

Although defining a pre-diabetes range for HbA1c would be the responsibility of guidelines developers, the identification of pre-diabetes does have an impact on the economic considerations for the utilisation of this test. This is described in the 'Economic Considerations' chapter of the report (page 82).

HbA1c testing in specific population subgroups

Summary of evidence—HbA1c testing in population subgroups

As with the evidence for adults at high risk, the results for the subgroups considered (older adults, people with cystic fibrosis, ethnic minorities, children, people with cardiovascular disease and women with PCOS) were subject to considerable heterogeneity, and it is difficult to draw any conclusions from the analysis. There is too little evidence from older adults to make any claim about the HbA1c test and its performance with increasing patient age. No conclusions could be drawn about the performance of HbA1c testing in people with cystic fibrosis or women with PCOS. The accuracy of the HbA1c test seemed to be worse in people with cardiovascular disease, perhaps due to the impact of acute illness or medication on the blood glucose measures. There were no consistent findings among the studies considering ethnic minorities although, in one study of Aboriginal and Torres Strait Islanders in Australia, the sensitivity and specificity of HbA1c were high and the area under the curve large; this may indicate that the test is appropriate in this group in Australia.

Several studies provided useful information of specific population subgroups that would fall into the 'high-risk' category for diabetes/pre-diabetes. The study profiles can be found in Appendix C.

Older adults

Studies in older adults were of interest as there is some evidence that HbA1c levels increase with age, but it is unclear how this relates to the development of complications (Nathan & The International Expert Committee 2009). Two studies were identified that considered older adults specifically (Kramer, Araneta & Barrett-Connor 2010; Rathmann et al. 2012). Both studies looked at elderly subgroups of population-based studies, one conducted in Germany and the other in the United States, and both performed an ROC analysis with diabetes diagnosed by FPG ≥ 7.0 mmol/L and/or 2hPG ≥ 11.1 mmol/L. The Rathmann. (2012) study also looked at concordance and sensitivity and specificity based on a 2x2 table. Concordance was low, at 0.279, and the sensitivity of the test was only 21.1% with a corresponding specificity of 98.7%. Both studies had very similar optimal HbA1c cut-off points—Rathmann (2012) at 6.0% and Kramer (2010) at 6.15%. The results from the ROC analysis are presented in Table 19.

There is too little evidence from older adults to make any claim about the HbA1c test and its performance with increasing patient age.

Table 19: Diagnostic accuracy of HbA1c testing for diabetes in subgroups of older adults

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off point	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
Rathman (2012) Germany	FPG ≥7.0 2hPG ≥11.1	ROC	0.82	6.0% ^a	68%	86%	30%	97%
Kramer (2010) USA	FPG ≥7.0 2hPG ≥11.1	ROC	0.65	6.15% ^a	63%	60%		

^a Optimal cut-off point

AUC = area under the curve; NA = not applicable; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver-operator characteristic

Note: Table ordered by HbA1c cut-off point.

People with cystic fibrosis

Cystic fibrosis-related diabetes is common and diabetes presents differently in this group. There is some unpredictability in the measurement of HbA1c in people with cystic fibrosis, so the accuracy of HbA1c testing was also assessed in this subgroup.

A systematic review (Waugh et al. 2012) provided data, including four studies that looked at the accuracy of HbA1c testing to predict diabetes in people with cystic fibrosis, and the results were mixed (De Luca et al. 1991; Kinnaird & Sauerwein 2010; Magni et al. 1996; Stutchfield, O'Halloran & Teale 1987). As each of these studies used a different cut-off point, it is difficult to compare them. Three studies using diagnostic thresholds of 5.7%, 6.0% and 9.0%, respectively, each had sensitivity rates of 100%; the corresponding specificity rates were 33%, 89% and 42%. A forest plot is presented in Figure 13 that suggests that the sensitivity and specificity results may have been affected by the small sample sizes in the studies, as the confidence intervals are wide. A further study (Yung et al. 1999) with n=122 participants that did not present raw data (able to populate a 2x2 table) found a sensitivity of 83% (95%CI 62%,100%) and a specificity of 89% (95%CI 82%, 96%) at an HbA1c cut-off of 6.1%. Overall, there were no conclusions that could be drawn from this data.

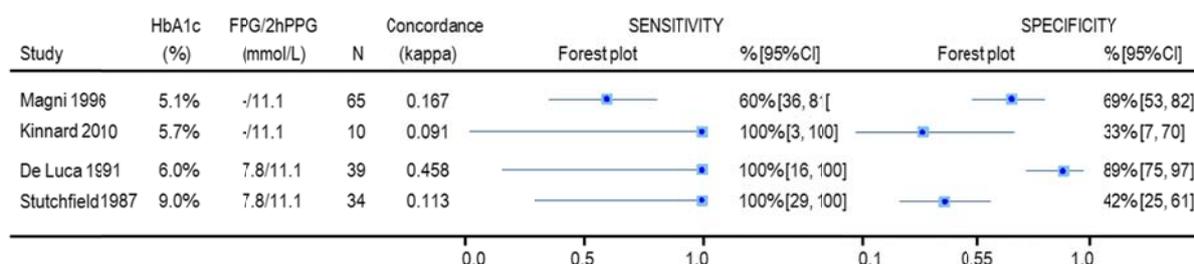


Figure 13: Forest plot of the accuracy of HbA1c testing in the diagnosis of diabetes in people with cystic fibrosis

Ethnic minorities

Studies that evaluated the accuracy of HbA1c testing in diagnosing diabetes in ethnic minorities were also assessed. These studies included ethnic minorities within the greater population from which they came. Two studies, one at two time points, provided data from which concordance, sensitivity and specificity results could be obtained (Araneta, Grandinetti & Chang 2010; Wang, H et al. 2011) (also reported in (Wang, W et al. 2011)). The Wang. (2011) study investigated American Indians at baseline and follow-up who were recruited into a cohort study. The risk of biased findings is unclear due to poor reporting of population recruitment, inclusions and exclusions, except that people with existing heart conditions were excluded. The Araneta (2010) study included Filipino-American women in San Diego; and native Hawaiians, Japanese-Americans and Filipino-Americans from rural Hawaii. The risk of bias in this study was also unclear as the population recruitment and selection, and study flow and timing, were not well described. The results from these studies are shown in

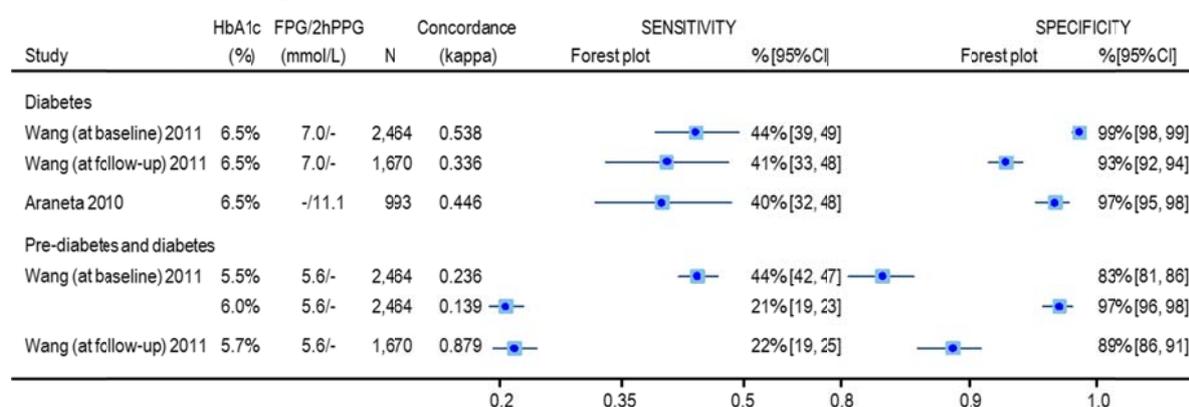


Figure 14.

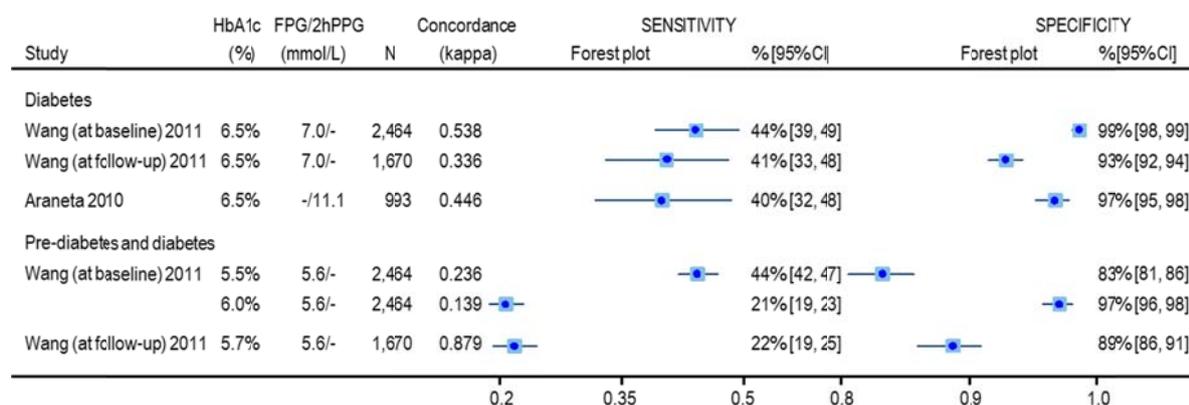


Figure 14: Forest plot of the accuracy of HbA1c testing in the diagnosis of diabetes in ethnic minorities

The results show a uniformly low sensitivity and high specificity, and relatively poor concordance. A further six studies provided additional diagnostic accuracy data, which are summarised in Table 20 (Exebio et al. 2012; Lin et al. 2012; Rowley, Daniel & O'Dea 2005; Vlaar et al. 2013; Young & Krahn 1988). The ethnic minorities of interest in most of these studies are not applicable to Australia; only one study was identified that provided some

diagnostic accuracy data of Aboriginal and Torres Strait Islander people in Australia (Rowley, Daniel & O'Dea 2005), and the sensitivity and specificity of HbA1c versus FPG testing was considerably higher than most of the studies of high-risk adults. It is difficult to draw conclusions about the accuracy of HbA1c in ethnic minorities, particularly when most studies did not consider minorities relevant to Australia.

Table 20: Summary of the accuracy of HbA1c testing in the diagnosis of diabetes in ethnic minorities

Study	Ethnicity	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off point	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]
Mostafa (2010b) UK	South Asians	2hPG ≥11.1	ROC	0.92 [0.89, 0.94]	5.5%	98.9% [93.6, 100]	21.4% [19.5, 23.3]	6.1% [4.9, 7.3]	99.7% [99.3, 100]
					5.7%	98.9% [93.6, 100]	38.4% [36.2, 40.6]	99.8% [99.4, 100]	
					6.0%	94.7% [87.9, 98.0]	66.6% [64.4, 68.7]	99.6% [99.2, 99.9]	
					6.3% ^a	85.3% [76.6, 91.1]	86.5% [84.9, 88.0]	99.1% [98.7, 99.6]	
					6.5%	78.9% [69.6, 86.0]	92.8% [91.6, 93.9]	98.8% [98.3, 99.3]	
Araneta (2010) USA	Filipino-Americans, Japanese-Americans and native Hawaiians	2hPG ≥11.1	ROC	0.78 0.68	5.8% 6.5% ^a	75.9% 40.0%	80.0% 96.8%	nr 69.9%	nr 89.8%
		FPG ≥7.0	ROC	0.82	6.5%	68.9%	95.3%	50.6%	97.8%
Young (1988) Canada	American Indians	FPG ≥7.8	ROC	nr	6.0%	97.8%	13.4%	nr	nr
					6.5%	97.8%	40.9%		
					7.0%	97.8%	64.8%		
					8.0%	95.6%	91.9%		
Exebio (2012) USA	Patients of Haitian origin (2 Haitian parents)	FPG ≥7.0	ROC	0.86	6.26%	80%	74%	nr	nr
					6.5%	73%	89%		
					6.72%	60%	97%		
					7.1.8%	47%	100%		
					7.64%	33%	100%		
Vlaar (2013) The Netherlands	Hindustani Surinamese people	2hPG ≥11.1	ROC	0.86 [0.79, 0.93]	6.3% ^a 6.5%	63% [49, 77] 46% [29, 63]	96% [95, 97] 98% [98, 99]	37% [25, 49] 52% [35, 69]	nr
Lin (2012) China	She ethnic group in Fujian province of China	FPG ≥7.0 2hPG ≥11.1	ROC	0.654	6.9%	35.3%	94.0%	LR+ = 5.88	LR- = 0.69
Rowley (2005) Australia and Canada	Aboriginal people	FPG ≥7.0	ROC	0.982 [0.95, 1.00] 0.927 [0.85, 1.00] 0.793 [0.61, 0.98]	7.0%	88.9% 76.2% 42.9%	96.9% 100% 96.3%	nr	nr
	Torres Strait Islanders								
	First Nations people								

^a Optimal cut-off point

AUC = area under the curve; NA = not applicable; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver-operator characteristic

Note: Table ordered by HbA1c cut-off point; **Australian studies in bold.**

Type 2 diabetes in children

According to Diabetes Australia (Diabetes Australia 2008), type 2 diabetes is being increasingly diagnosed in children and adolescents, primarily due to the rise of overweight and obesity. The accuracy of HbA1c testing in the diagnosis of diabetes in children and adolescents was therefore considered in this assessment. Six studies were identified, of which five were in overweight and obese children (Lee, Park & Hwang 2012; Lee, JM et al. 2011; Nowicka et al. 2011; Sharma & Fleming 2012; Yesiltepe Mutlu et al. 2013) and one was in children with glucosuria (Ogawa et al. 2012). Two studies were chart reviews (Lee, Park & Hwang 2012; Yesiltepe Mutlu et al. 2013). Most of these studies had some risk of bias, or an unclear risk of bias, associated with their design due to either a long time frame (with some of the tests being undertaken as long ago as the 1990s, when the quality of the tests was not as high), subject selection or because the population and methodology were not well described. In Sharma (2011), Lee (2012) and Yesiltepe Mutlu (2013), data for diabetes diagnoses could not be separated from data for pre-diabetes diagnoses, which has ramifications for the diagnostic accuracy statistics. The results of these studies have not been considered further.

In the two studies that provided raw (2x2) data for diabetes diagnoses at an HbA1c of 6.5%, compared with FPG \geq 7.0 mmol/L or 2hPG \geq 11.1 mmol/L, the Nowicka (2011) study had a sensitivity of 32% and a specificity of 99%, while the Ogawa (2012) study had a sensitivity of 96% and a specificity of 96%. These results are so widely varying that it is likely that the two populations differed in other aspects. In the studies that did not provide 2x2 data, Lee (2011) found a sensitivity of 75.0% and a specificity of 99.9% at an HbA1c cut-off of 6.5% and FPG \geq 7.0 mmol/L, while Nowicka (2011) found a sensitivity of 67.7% and a specificity of 87.6% at the optimal HbA1c cut-off of 5.8% in an ROC analysis. Given the different diagnostic thresholds used and the varying results from a limited number of studies, conclusions are unable to be drawn with regard to the diagnostic accuracy of HbA1c testing in children.

Women with polycystic ovary syndrome (PCOS)

Women with PCOS are considered an at-risk group for the development of diabetes in Australia, and thus were considered in this assessment. Considering diabetes, two studies provided test accuracy data (Lerchbaum et al. 2013; Magnussen et al. 2011) with an HbA1c test cut-off of 6.5% and FPG \geq 7.0 mmol/L or 2hPG \geq 11.1 mmol/L. In both these studies concordance (measured by kappa) was poor (0.122 and 0.039), with Lerchbaum (2013) reporting a sensitivity of 67% with wide confidence intervals (95%CI 30%, 93%) and a specificity of 100% (95%CI 99%, 100%), while Magnussen (2011) found a sensitivity of 35% (95%CI 15%, 59%) and specificity of 99% (95%CI 97%, 100%). In the Lerchbaum (2013) study, women with a body mass index (BMI) $>$ 25 kg/m² were considered separately;

in these women concordance was much higher, at 0.656, with a sensitivity of 85% (95%CI 42%, 100%) and specificity of 99% (95%CI 97%, 100%). This could suggest that BMI is an effect modifier.

People with cardiovascular disease

As with women with PCOS, people with pre-existing cardiovascular disease (CVD) are at a higher risk of diabetes. There were six studies that compared test performance and provided data for a meta-analysis comparing HbA1c with FPG and/or 2hPG testing in this population group (Doerr et al. 2011; Gianchandani et al. 2011; Hanna et al. 2012; Hjeltestad et al. 2013; Somani et al. 2013; Wang et al. 2013). These studies mostly had a low risk of bias, with any bias concerns related to poor reporting of methodology. The results of the meta-analysis are shown in Figure 15.

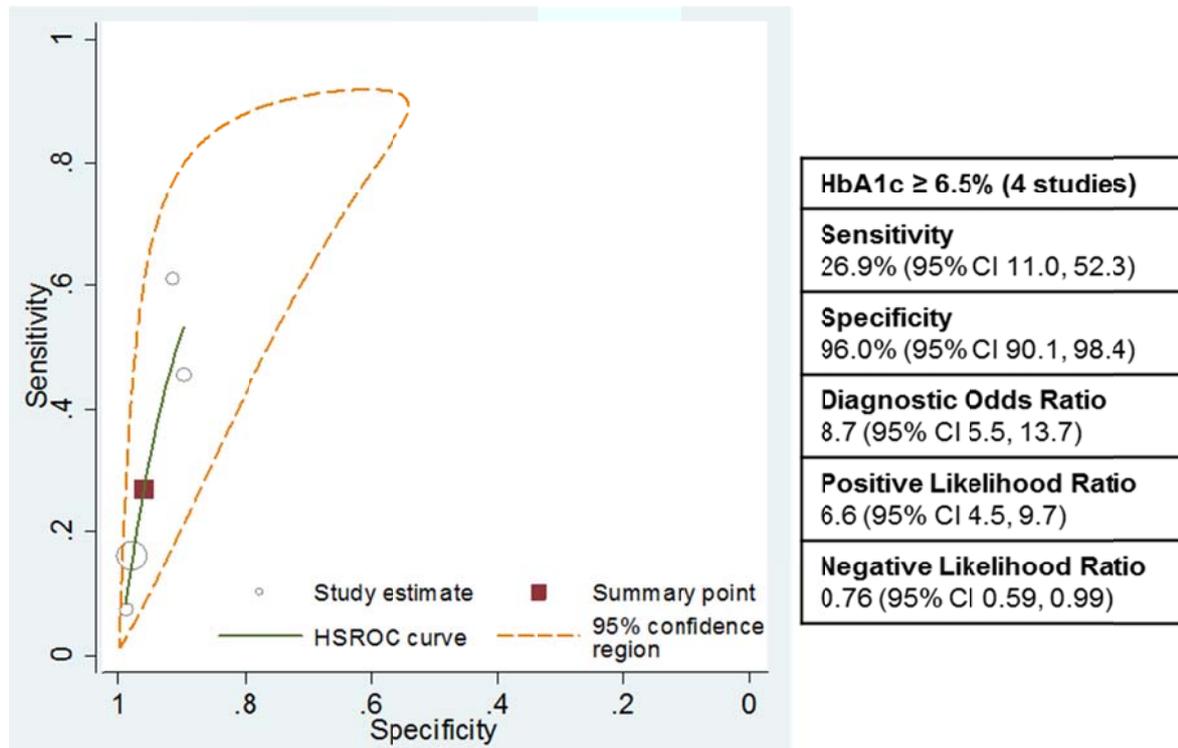


Figure 15: Results of meta-analysis for diagnosis of diabetes in people with CVD using HbA1c vs FPG/OGT testing

A forest plot including the above studies in addition to two studies that used different blood glucose measures is shown in

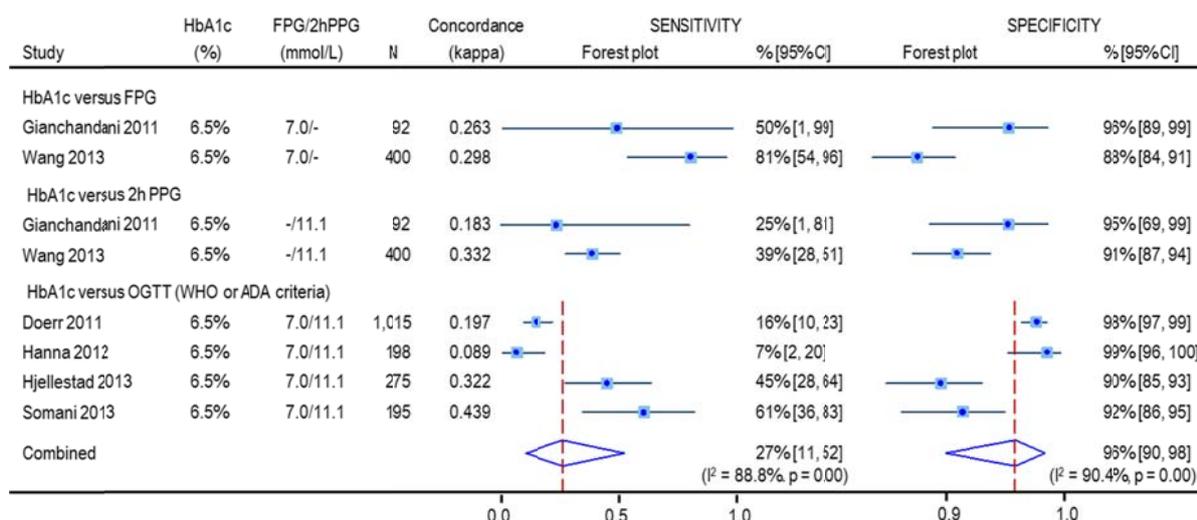


Figure 16.

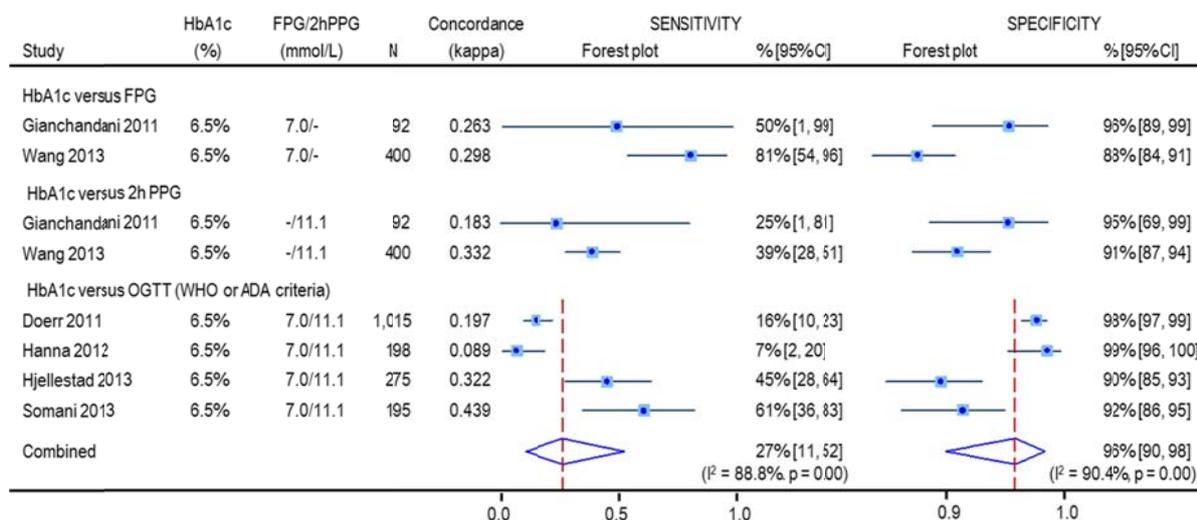


Figure 16: Forest plot of studies comparing the accuracy of HbA1c testing vs blood glucose measures in the diagnosis of diabetes in people with CVD

The diagnostic accuracy of HbA1c testing versus the other blood glucose measures appears worse in people with CVD than in high-risk adults, with both concordance and sensitivity low (although with correspondingly high specificity). Without a test for interaction comparing the CVD subgroup with a non-CVD subgroup, however, it cannot be certain that CVD itself is the effect modifier. It might be expected that a population with CVD is more likely to have dysglycaemia using any method of measurement. It could be that the blood glucose in the populations in the studies included in this analysis, who were all undergoing or had recently undergone cardiac procedures, was not particularly stable because of acute disease or concomitant medication (e.g. beta blockers), and therefore the reference standards may be even less reliable in this population subgroup.

Other groups

Some studies were identified that considered groups in whom the risk of developing diabetes is greater. These are summarised in Appendix D.

Is there an impact on clinical decision-making?

The findings from the diagnostic accuracy assessment are limited and it is difficult to ascertain if accuracy is comparable between the index and comparator tests. Thus, a trade-off scenario is the most conservative approach to take for the evidence linkage. The test is as safe and there are pragmatic reasons for using it (i.e. no preparation for the patient, no unpalatable glucose drink, more stability in vitro). The second evidence linkage requires a consideration of whether there is a change in management or any impact on diagnostic and treatment strategy. While none of the included studies considered change in management, it is likely that diagnosing diabetes with the HbA1c test will not impact considerably on treatment options and their impact on health outcomes (effectiveness). It is clear that the three tests in question all identify different components of blood glucose and will therefore vary in the people actually diagnosed; however, the choice of diagnostic tool will not affect treatment decisions and thus will not impact on the effectiveness of the treatments selected. That is, the effectiveness of the currently available treatment options for diabetes and pre-diabetes will be the same irrespective of whether the patient is diagnosed via HbA1c, or FPG with/without OGT testing. Thus, the evidence linkage stops at this point without needing to investigate evidence linkage 3, as per the diagnostic framework used for this assessment (Merlin et al. 2013).

Other relevant considerations

Groups in whom the test may not be reliable

Diagnosing diabetes in patients with chronic renal disease

Six case series studies reported on HbA1c levels in patients with chronic renal failure compared with people with normal renal function (Table 67 in Appendix D Extra results). (De Boer, Miedema & Casparie 1980) reported that the mean HbA1c level was higher in patients with impaired renal function and that there was no correlation between HbA1c and FPG levels in these patients, concluding that renal failure itself causes an increase in HbA1c levels. Sabatar et al. (Sabatar et al. 1991) found that patients with end-stage renal disease had the highest HbA1c levels of all studied groups, and suggested that abnormal non-enzymatic glycosylation of proteins is elevated in uraemia. Lindholm and Karlander (Lindholm & Karlander 1986) also reported that the mean HbA1c level was higher in patients with chronic renal failure than in normal controls, and that HbA1c levels remained elevated even after receiving continuous ambulatory peritoneal dialysis for 12 months. De Marchi et al. (De Marchi et al. 1983) also found no significant difference in HbA1c levels between dialysed and non-dialysed patients with chronic renal failure, and reported that there was no significant difference in HbA1c levels between NGT and IGT patients with chronic renal failure, unlike the significant difference seen between NGT and IGT patients with normal renal function. Thus, De Marchi et al. (De Marchi et al. 1983) concluded that blood sugar levels do not play a major role in increasing HbA1c levels in patients with chronic renal failure. Both Nakao et al. (Nakao et al. 1998) and Ng et al. (Ng et al. 2008) reported that treatment of renal anaemia with erythropoietin significantly decreased HbA1c levels. Additionally, Nakao (Nakao et al. 1998) reported that this effect was independent of blood glucose levels as there were no significant changes in FPG during the study period.

Diagnosing diabetes in patients with anaemia

Five studies, including a systematic review of case series, three case series and a comparative study, reported on the reliability and accuracy of HbA1c testing in the diagnosis of diabetes in patients with anaemia (Table 68 and Table 69 in Appendix D Extra results). The results of these studies suggest that blood loss, haemolytic anaemia and sickle cell anaemia (which affect the life span of red blood cells) result in underestimated HbA1c values, compared with iron and B12 vitamin deficiency anaemia, which have been reported to overestimate HbA1c results independent of blood sugar levels. One study provided diagnostic accuracy data comparing the sensitivity and specificity of HbA1c testing ($\geq 5.7\%$) compared with the WHO criteria (2006; FPG ≥ 6.1 and/or 2hPG ≥ 7.8) for diagnosing pre-diabetes and diabetes in patients with or without anaemia (Hardikar et al. 2012). However,

only 37% of the anaemic patients were iron deficient. The authors found that HbA1c testing had higher sensitivity (75.0% vs 37.5%) and lower specificity (62.9% vs 84.1%) in patients with anaemia compared with non-anaemic patients; the results are shown in Table 69 in Appendix D Extra results.

Diagnosing diabetes in patients with haemoglobinopathies

Comparison of HbA1c levels in patients with and without haemoglobinopathies

Ten studies reported on the difference in HbA1c levels in patients with haemoglobinopathies compared with those with normal haemoglobin (HbAA; Table 70 in Appendix D Extra results). Al-Fadhli et al. (Al-Fadhli, Ahmad & Al-Jafer 2001) and Reid et al. (Reid et al. 1992) reported that HbA1c levels were elevated in patients with β -thalassemia (minor and major, respectively) compared with people with HbAA. Four studies reported on HbA1c levels in patients with haemoglobin C trait (HbAC) compared with people with HbAA (Bleyer et al. 2010; Camargo & Gross 2004); (Koethe, Zielinski & Perry 1999; Weykamp et al. 1994). Two of these studies reported that HbAC patients may have lower HbA1c values than those with HbAA (Camargo & Gross 2004); (Koethe, Zielinski & Perry 1999), whereas the other two studies found no difference between the two groups (Bleyer et al. 2010; Weykamp et al. 1994).

Eight studies reported on the difference in HbA1c levels in patients with sickle cell trait (HbAS) compared with people with HbAA (Table 70 in Appendix D Extra results). Four of these studies reported that patients with HbAS had lower HbA1c levels compared with those with HbAA (Camargo & Gross 2004; Koethe, Zielinski & Perry 1999; Moutet et al. 1988; Reid et al. 1992), and the other four reported no difference in HbA1c levels between HbAS and HbAA patients (Al-Fadhli, Ahmad & Al-Jafer 2001; Ama et al. 2012; Bleyer et al. 2010; Weykamp et al. 1994).

One additional study (Robertson et al. 1992) reported that patients with elevated levels of foetal haemoglobin (HbF; >2%) had higher levels of HbA1c compared with those with normal levels of HbF (<2%).

Comparison of HbA1c levels using different HbA1c assays in patients with haemoglobinopathies

Fifteen studies looked at the HbA1c levels detected by different assay methods, and the results are summarised in Table 71 (Appendix D Extra results). These studies looked at 14 ion-exchange HPLC analysers, 9 borate-affinity HPLC analysers, 11 immunoassays, 2 enzymatic assays, 1 micro-chromatography method and a colorimetric thiobarbituric acid assay. The HbA1c values obtained varied considerably, both among different methodologies and among different analysers using the same methodology in many of the studies for all Hb

variants tested. Most authors recommended that HbA1c results be interpreted with caution when the patient is suspected of having a haemoglobinopathy.

Ethical considerations

There are no ethical considerations for this assessment. The proposed test is already in use for monitoring diabetes in Australia and there is no reason to believe that it is any less safe than the comparators; it is also widely available and the quality is acceptable (d'Emden et al. 2012).

What are the economic considerations?

Economic evaluation

Overview

The evaluation of the clinical evidence considered that, due to considerable heterogeneity in the results and the use of an imperfect reference standard, robust conclusions regarding the diagnostic accuracy of HbA1c testing could not be made. Nevertheless, an estimate of the cost-effectiveness of HbA1c testing in the diagnosis of diabetes, compared with FPG and OGT testing, in the Australian healthcare setting has been attempted using the best data available.

Given that the HbA1c test (compared with FPG or OGT testing) is equally predictive of retinopathy and that the test is associated with advantages regarding patient compliance, the modelled economic evaluation initially assumes equivalent diagnostic accuracy to assess the comparative costs and outcomes. A further optional step in the model incorporates the relatively uncertain point estimates of diagnostic accuracy as identified in the meta-analysis during the clinical evaluation (Figure 7, Figure 9 and Table 74).

The type of modelled evaluation is a cost–utility analysis, consistent with similar previously published Markov models (further detail is given below) that presents seven health states: normal glucose tolerance (NGT), pre-diabetes (undiagnosed and diagnosed), diabetes (undiagnosed and diagnosed), diabetes with complications and dead. In both the comparator and intervention arms of the model, the benefits from testing include:

1. the diagnosis of diabetes prior to symptom development, so as to enable control of glucose levels to prevent the occurrence of complications; and
2. the identification of pre-diabetes, to introduce annual re-testing for diabetes.

Model inputs were predominantly derived from the population-based Australian diabetes study AusDiab, with outputs measured in terms of quality-adjusted life years (QALYs), based on utility weights reported in the Australian DiabCo\$t report (Colagiuri et al. 2003).

Population and setting for the economic evaluation

The NHMRC guidelines (Colagiuri et al. 2009a) recommend that all Australians undergo diabetes risk assessment from age 40 years, using the AUSDRISK screening tool. In those considered at high risk of developing diabetes (score ≥ 12), blood glucose testing for diabetes is currently recommended. Testing for diabetes without AUSDRISK assessment is

also recommended in those with known pre-diabetes, a history of CVD, gestational diabetes or POCS.

HbA1c testing is proposed to replace FPG and/or OGT testing in these populations. Therefore, in this economic evaluation the population modelled includes people with a known history of pre-diabetes or gestational diabetes, CVD, POCS and/or an AUSDRISK score ≥ 12 .

The population enters the economic model at age 40 years. Prevalence and incidence estimates of undiagnosed diabetes and pre-diabetes have not been specifically identified for the population recommended for testing; therefore, the available general Australian population estimates (reported in the population-based Australian diabetes study AusDiab) have been transformed. The transformation is based on estimates reported in the AUSDRISK validation study on the prevalence of undiagnosed diabetes in a high-risk, compared with a general, population (Chen et al. 2010). This is detailed in the section below on 'Inputs to the economic evaluation' (page 98).

Periodic re-testing for undiagnosed diabetes is recommended by the NHMRC, annually in people with pre-diabetes and every 3 years in all others. Re-testing according to these recommendations has been incorporated into the economic evaluation. All testing is assumed to occur in a laboratory setting.

Structure and rationale of the economic evaluation

Test cost per person tested

Based on the clinical evidence presented in this report, the economic analysis will compare HbA1c testing with the current strategy of FPG with/without OGT testing for the diagnosis of diabetes and pre-diabetes in two scenarios:

- where a single HbA1c cut-off is applied for the diagnosis of diabetes (or no diabetes) only (base-case scenario, as proposed in the Final DAP); and
- where two diagnostic cut-offs are applied to enable a diagnosis of either pre-diabetes or diabetes (or neither) (alternative scenario).

PASC noted in the Final DAP that, should the cost of the HbA1c test strategy per person tested exceed that of the current strategy, health outcomes for the population tested would need to be estimated to calculate an ICER to enable MSAC to consider whether the increase in cost is justified.

The average total test costs to conclude or exclude a diagnosis of diabetes, per person per testing strategy and assuming a 100% uptake of each testing strategy, are presented in Table 21. These cost comparisons have been based on the current and proposed testing

algorithms presented in the 'Clinical pathway' section of the report (page 36), using inputs described in Appendix E. The first analysis presented assumes no difference in the performance of the testing strategies (i.e. 100% test accuracy for FPG, OGT and HbA1c tests). The second analysis incorporates the performance of the HbA1c test identified in the 'Effectiveness' section of this report (and further detailed in Appendix E).

Table 21: Estimated average cost per person associated with testing in the diagnosis of diabetes, per test strategy (assuming 100% compliance with testing)

Test strategy	Estimated total test cost per person ^a
<i>1. Assuming no difference in test accuracy</i>	
Comparator (FPG with/without OGT test) – for diabetes and pre-diabetes	\$81.96
Base-case – HbA1c testing for diabetes only	\$65.23
Alternative scenario – HbA1c testing for diabetes and pre-diabetes	\$65.23
<i>2. Incorporating test accuracy data for HbA1c</i>	
Comparator (FPG with/without OGT test) – for diabetes and pre-diabetes	\$88.98
Base-case – HbA1c testing for diabetes only	\$74.09
Alternative scenario – HbA1c testing for diabetes and pre-diabetes	\$68.41

^a Total test costs include MBS costs of tests, repeated tests, associated GP consultations and patient episode initiation fees; in the comparator it also includes one HbA1c test conducted on the diagnosis of diabetes (see page 186, Appendix E for more detail).

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance

Regardless of whether test performance is considered in the analysis, both HbA1c testing scenarios (with/without pre-diabetes diagnostic range) have a lower average cost to conclude or exclude a diagnosis of diabetes (or pre-diabetes in strategy 2) than the comparator. This is because confirmatory HbA1c re-testing is only required when the initial test results are in the diabetic range, whereas commonly identified equivocal results routinely require re-testing when using FPG/OGT strategies.

PASC noted that the economic evaluation would need to consider the consequences for people in whom a different diagnostic conclusion would be observed under the proposed strategies. The committee further noted that, given the progressive nature of diabetes and ongoing screening recommendations, the inability of HbA1c testing to identify these other conditions might only be expected to delay the correct diagnosis (as the patient will eventually become symptomatic) and so the change in treatment and treatment outcomes would be limited to those caused by the delay rather than an ongoing failure to diagnose.

In order to address these issues, a modelled economic evaluation is presented to compare the costs and outcomes of the HbA1c testing strategies with the current strategy, to capture the health outcomes associated with a delay in diagnosis as opposed to an ongoing failure to diagnose.

Modelled economic evaluation

Literature search

A literature search was conducted to identify published economic evaluations of HbA1c testing in the diagnosis of diabetes (Appendix E) and to inform the structure of and inputs to the economic model. No studies were identified that compared HbA1c testing in the diagnosis of diabetes with FPG with/without OGT testing. One study, Icks et al. (2004), compared a combined strategy of HbA1c (with confirmatory OGT) testing with strategies of FPG or OGT testing alone, as well as FPG confirmed with OGT testing, in the German setting. The HbA1c testing strategy was the most effective and most costly at detecting cases of diabetes, due to higher patient uptake with initial HbA1c screening.

PASC noted in the Final DAP that the output of the economic evaluation would need to assess the impact of HbA1c testing on health outcomes for people with pre-diabetes and diabetes (not just cost per case of diabetes identified). Thus, economic modelling of the costs and outcomes of introducing HbA1c testing, compared with the current strategy of FPG with/without OGT testing, in the proposed Australian population is required. This is presented below.

To inform the structure of the economic model, economic evaluations within the literature search were sought that investigated the cost-effectiveness of screening for pre-diabetes and diabetes (compared with no screening), enabling an evaluation of the testing strategy in terms of patient uptake, test accuracy and/or implications for falsely diagnosed or undiagnosed patients. Three studies were identified (Table 22).

Table 22: Economic evaluations identified that investigate the cost-effectiveness of screening for pre-diabetes/diabetes using patient uptake and test accuracy parameters

Study	Setting	Model and results
Mortaz et al. (2012)	Compares screening (for diabetes and pre-diabetes in Canadian patients at high risk) with no screening. Assumes repeated screening annually for those identified with pre-diabetes and every 3 years for those with normal glucose tolerance.	Markov model that includes undiagnosed and diagnosed pre-diabetes and diabetes health states. Model structure considers patient uptake and accuracy of the test. Outcomes were modelled to 10 years. Compared with no screening, screening was dominant in the base-case and in sensitivity analyses that varied the frequency of testing.
Schaufler & Wolff (2010)	Compares screening for diabetes and pre-diabetes in Germany with no screening. Assumes annual repeated screening.	Markov Monte Carlo micro-simulation model. Model structure considers patient uptake of the testing strategy (OGT only), with lifetime outcomes modelled. Screening for diabetes and pre-diabetes was observed to be cost-effective.

Study	Setting	Model and results
Gillies et al. (2008)	Compares scenarios of one-off screening for diabetes, and screening for diabetes and pre-diabetes in high-risk patients, in UK with no screening.	Markov model that includes undiagnosed and diagnosed pre-diabetes and diabetes health states. Model structure considers the accuracy of the testing strategy. Outcomes were modelled to 50 years. Screening for diabetes and pre-diabetes, followed by appropriate interventions, appeared to be cost-effective; however, the cost-effectiveness of screening for diabetes alone was uncertain.

Similar Markov models were presented in economic evaluations in Gillies et al. (2008) and Mortaz et al. (2012), which included seven health states. The model presented in Schaufler & Wolff (2010) was also similar but only considered five health states. All models were consistent in that transitions were not allowed from diabetes to pre-diabetes, or from pre-diabetes to NGT. The seven-health-state Markov model structure, which includes separate health states for people with undiagnosed pre-diabetes/diabetes, appeared most applicable to the current assessment.

Test accuracy data was included in the models presented by Gillies et al. (2008) and Mortaz et al. (2012). Neither study appeared to obtain estimates by a systematic review of the literature. Schaufler & Wolff (2010) assumed that OGT testing was the 'gold' standard and did not incorporate accuracy data into the model.

In each of the three economic evaluations the modelled benefit of identifying patients with pre-diabetes was to introduce lifestyle modification programs (LMPs) to reduce the risk of developing diabetes. The duration of the LMPs and their subsequent treatment effects were applied for the period spent in the diagnosed pre-diabetes health state. Such a benefit is difficult to apply in the Australian context, given that formal LMPs for people with pre-diabetes differ between the states in regard to the composition, length and level of patient participation in such programs, and consequently are likely to also differ in terms of treatment effect from those cited in the literature. As such, the base-case of this economic evaluation has not incorporated an LMP treatment effect for people with pre-diabetes. *This is a conservative approach* in that it is likely to underestimate the cost-effectiveness of identifying people with pre-diabetes, as effective management of pre-diabetes (e.g. with lifestyle modifications or medication) has been shown to reduce the progression to diabetes (Gillies et al. 2007). Sensitivity analyses have been presented that incorporate potential LMP costs and benefits into the economic model.

The three published models varied with regard to the modelled benefit of early diabetes identification. Gillies et al. (2008) assumed a reduced mortality risk, Schaufler & Wolff (2010) modelled a reduced risk in developing diabetes-related complications, and Mortaz et

al. (2012) did not appear to model a benefit. Given that the NHMRC guidelines recommend the identification and treatment of diabetes prior to clinical presentation to reduce morbidity from long-term complications, the approach taken by Schaufler & Wolff (2010) appears most reasonable for the current assessment.

Structure of the economic evaluation

The structure of the economic evaluation is based on the Markov models presented in Gillies et al. (2008) and Mortaz et al. (2012), and is presented in Figure 17. The model includes seven health states: NGT, pre-diabetes (undiagnosed and diagnosed), diabetes (undiagnosed and diagnosed), diabetes with complications and dead. The model has a 50-year time horizon (assumed to capture lifetime costs and outcomes for a population entering the model at age 40 years), with cycle lengths of 1 year.

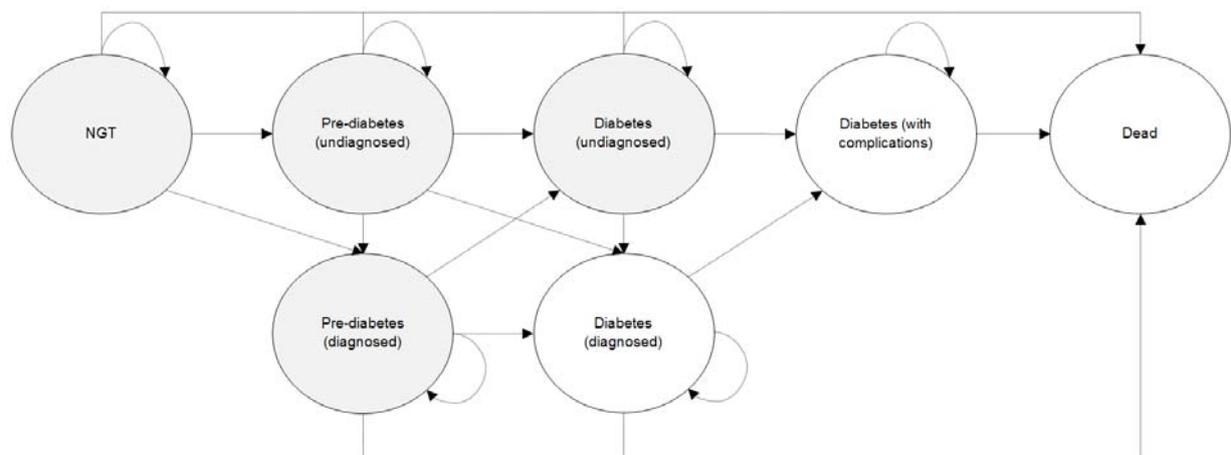


Figure 17: Markov state-transition model and allowable health state transitions

Source: adapted from Gillies et al. (2008) and Mortaz et al. (2012).

NGT = normal glucose tolerance

Note: Patients enter the model in one of the four shaded health states. Transitions to the pre-diabetes (diagnosed) health state are not allowed in the base-case (HbA1c_1) intervention scenario.

Each of the two previously identified scenarios of HbA1c test interpretation are considered relevant; therefore, results are generated under each scenario. For modelling purposes these are labelled as:

- HbA1c_1 (base-case scenario), where a single HbA1c cut-off is applied for the diagnosis of diabetes; and
- HbA1c_2 (alternative scenario), where two diagnostic cut-offs are applied to enable a diagnosis of pre-diabetes and diabetes, respectively.

The comparator is a combined testing strategy where FPG and OGT testing are available for the diagnosis of diabetes and pre-diabetes, according to cut-offs specified in the NHMRC guidelines.

Transitioning to a diagnosed pre-diabetes/diabetes health state is dependent on patient test uptake rates and accuracy of the testing strategy. For the comparator and both intervention scenarios the modelled benefit of a diagnosis of diabetes is to manage blood glucose levels in order to reduce the likelihood of developing diabetes complications. In the comparator and the HbA1c_2 scenario the modelled benefit of a diagnosis of pre-diabetes is to introduce annual re-testing for diabetes. As the cut-off employed in the HbA1c_1 scenario does not have the capacity to diagnose pre-diabetes, transitions in this scenario to the diagnosed pre-diabetes health state are not allowed.

A summary of the structure of the mechanics of the economic model is presented in Table 23.

Table 23: Summary of the economic evaluation

Time horizon	50 years
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov model (with half-cycle correction)
Cycle length	1 year
Discount rate	5% for both costs and outcomes
Software package	TreeAge Pro

Patient flow through the model

Patients enter the economic model in one of four health states: NGT, undiagnosed pre-diabetes, diagnosed pre-diabetes or undiagnosed diabetes (as shaded in Figure 17). Within each of these health states, testing for diabetes is available (and is for all subsequent cycles). Dependent on patient uptake rates and accuracy of the testing strategy, the population may either remain untested or testing may conclude a true or false result. The implications for falsely identified cases or non-cases of diabetes are discussed in the 'Inputs to the economic evaluation' section of this report (page 105).

The test outcome pathways for the comparator and intervention testing strategies are presented in Figure 18. Consistent with current guidelines (and with HESP member feedback), test results in the diabetes range in all strategies require confirmation, and a two-out-of-three test rule is applied for concluding or excluding a diagnosis of diabetes (e.g. initial positive test followed by negative/equivocal result would require a third test). Initial equivocal test results additionally require re-testing in the comparator scenario only (consistent with proposed management, see 'Clinical pathway' section). Patient uptake of testing is considered with each initial test and all subsequent tests.

In accordance with NHMRC re-testing guidelines (Colagiuri et al. 2009a), people who receive a conclusion of NGT (true or false) will receive testing every 3 years, and those with a conclusion of pre-diabetes (true or false) will be re-tested annually. Patients who do not

receive testing in the first cycle are assumed to be offered it annually until they uptake testing.

Diabetes disease progression may occur after the first cycle. Consistent with previously published models (Gillies et al. 2008; Mortaz et al. 2012), a number of assumptions have been made regarding transitions between health states, including the following:

- Progression from 'NGT' to 'diabetes' requires progression through the 'pre-diabetes' health state, as it is clinically unlikely that an individual would progress from 'NGT' to 'diabetes' within the space of 1 year (i.e. one model cycle).
- Transitions were not allowed from 'diabetes' to 'pre-diabetes' (because, even if glucose tolerance improves, clinically a patient is still diagnosed as having diabetes), nor from 'pre-diabetes' to 'NGT' (as, even if glucose tolerance improves, the future risk of developing diabetes is considered to be closer to that in people with pre-diabetes than to those who have always been NGT).
- The modelling of sequential disease progression and testing allows for progression and diagnosis to occur within the one cycle (e.g. transition from 'diagnosed pre-diabetes' to 'diagnosed diabetes').

In the current and both proposed scenarios, once a patient has progressed from 'undiagnosed diabetes' to 'diabetes with complications', patient uptake of testing is assumed to be 100%, irrespective of the testing strategy—in the instance of a false negative result it is assumed that the test would be repeated given the incongruence of the test result and the patient's clinical state. This use is consistent with the proposed MBS item descriptors in the Final DAP.

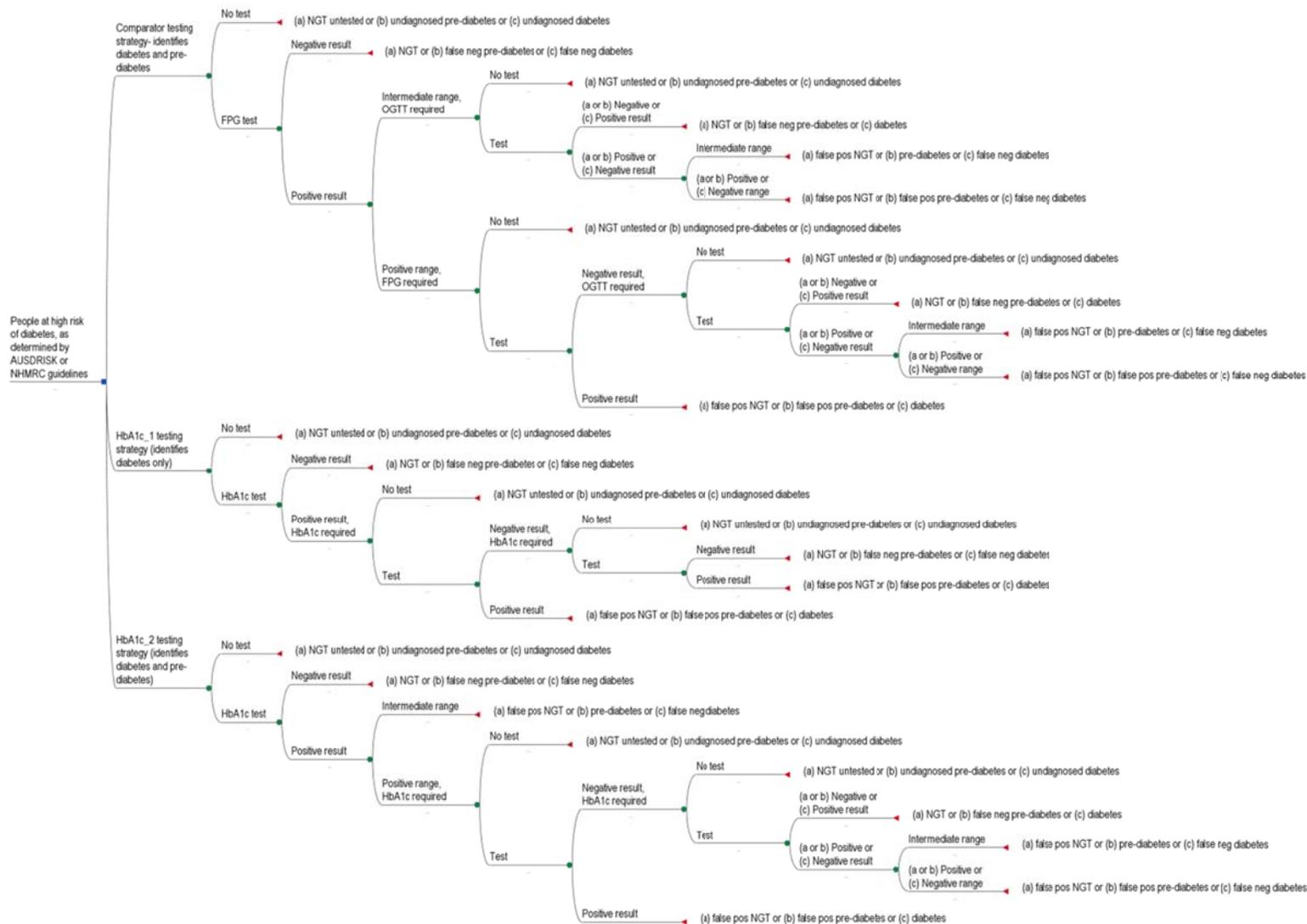


Figure 18: Outcomes for each testing strategy included in the economic evaluation

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test

Note: Based on current and proposed management algorithms. Termination node is dependent on true status: (a) NGT; (b) pre-diabetes; (c) diabetes.

Inputs to the economic evaluation

Test parameters

Test accuracy

The test accuracy parameters used in the economic model include sensitivity and specificity as determined by the meta-analysis of systematic review evidence presented in the 'Effectiveness' section of this report. As discussed, substantial heterogeneity due to differences in testing methodology, threshold values and patient characteristics is common between diagnostic accuracy studies. Although allowances for this are incorporated into the HSROC model, there is also uncertainty as to the most appropriate weighting of the regression (Rutter & Gatsonis 2001). The I^2 values for heterogeneity between studies assessing HbA1c testing compared with FPG with/without OGT testing in high-risk adults varied from 92.7% to 99.98% (Figure 8). Thus, the pooled estimates for sensitivity and specificity calculated in this report may not be a reliable summary measure.

Test performance has been reported in comparison with FPG and OGT testing separately; these have been incorporated into the model where the testing comparison fits (i.e. use HbA1c accuracy data compared with FPG for initial and first re-test, and, where required, compared with OGT for second re-test). However, it should be noted that confirmatory blood tests were not conducted in any of the studies included in the assessment, which, according to guidelines, should happen in Australia. This could have considerable impact on the diagnostic accuracy of all three tests, especially given the day-to-day variability of FPG and OGT testing. This is likely to add further uncertainty to the test accuracy estimates modelled.

As test accuracy has been reported in comparison with both FPG and OGT testing, these tests are assumed to have a sensitivity and specificity equal to 1.

For the base-case (HbA1c_1) scenario only the sensitivity and specificity parameters for the HbA1c test for the diagnosis of diabetes are applied (Table 24). For the alternative (HbA1c_2) scenario sensitivity and specificity parameters for the diagnosis of pre-diabetes/diabetes are used to exclude a diagnosis of diabetes/pre-diabetes and rule in a diagnosis of pre-diabetes; the sensitivity and specificity of HbA1c for the diagnosis of diabetes is used to rule in or exclude a diagnosis of diabetes. The base-case analysis will assume that an HbA1c cut-off of 5.7% will be used to identify pre-diabetes (based on the ADA cut-off for pre-diabetes), with the cut-off of 6.0% tested in sensitivity analyses.

Given that test accuracy data have been determined based on a comparison with an imperfect reference standard, and that the HbA1c test is considered equally predictive of retinopathy, results will additionally be presented assuming equivalent test accuracy for HbA1c as for the comparator testing strategies (i.e. 100%).

Table 24: Sensitivity and specificity parameters of HbA1c testing used in the economic model

Test parameter	Value (95%CI)	Source	HbA1c_1 scenario (base-case)	HbA1c_2 scenario (alternative)
<i>Compared with FPG testing</i>				
Sensitivity of 6.5% cut-off	67.4% (58.9, 74.9%)	Figure 7	Yes	Yes
Specificity of 6.5% cut-off	90.7% (83.9, 94.8%)	Figure 7	Yes	Yes
Sensitivity of 5.7% cut-off	56.2% (49.5, 62.6%)	Table 74	No	Yes
Specificity of 5.7% cut-off	78.3% (74.7, 81.5%)	Table 74	No	Yes
Sensitivity of 6.0% cut-off	78.0% (range: 72.7, 77.4%)	Table 74	No	Sensitivity analyses
Specificity of 6.0% cut-off	48.3% (range: 60.6, 77.0%)	Table 74	No	Sensitivity analyses
<i>Compared with OGT testing</i>				
Sensitivity of 6.5% cut-off	53.5% (36.9, 69.3%)	Figure 9	Yes	Yes
Specificity of 6.5% cut-off	94.7% (89.8, 97.3%)	Figure 9	Yes	Yes
Sensitivity of 5.7% cut-off	36.2% (range: 19.3, 53.8%)	Table 74	No	Yes
Specificity of 5.7% cut-off	82.1% (range: 69.2, 95.0%)	Table 74	No	Yes
Sensitivity of 6.0% cut-off	42.0% (37.1, 47.1%)	Table 74	No	Sensitivity analyses
Specificity of 6.0% cut-off	92.6% (86.6, 96.1%)	Table 74	No	Sensitivity analyses

CI = confidence interval; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance

The comparator and HbA1c_2 testing strategies arms both identify a pre-diabetes range; as the sensitivity and specificity cut-offs used will identify both pre-diabetes and diabetes, an estimate is required of the proportion of results that are confirmed positive, by glucose tolerance status, after initial positive or equivocal FPG results (as, e.g., it is assumed that fewer people with NGT will return a result in the positive range than those with pre-diabetes or diabetes). These proportions have been derived from diagnostic yield estimates reported in Lawrence et al. (2001) and Lu et al. (2010) for the comparator and HbA1c_2 testing strategies, respectively.

The study conducted by Lawrence et al. (2001) was chosen as it was the only one identified that reported data that could be used for this application in the model. This study used FPG testing to screen 876 patients in the UK setting; of these, 60 had a plasma glucose concentration of ≥ 6.1 mmol/L and were invited to attend diagnostic testing—45 participants returned. Of the 45 who completed diagnostic testing, 18 were classed as NGT, 1 of whom returned an initial FPG result in the diabetes range. Consequently, in the comparator arm of the model it is assumed that, in people with true NGT status, 5.6% (1/18) of false positives (above pre-diabetes cut-off) return a result in the diabetes range (Table 25). Likewise, 33.3% and 40% of true pre-diabetics and diabetics, respectively, who return an FPG result above the pre-diabetes cut-off will return a result in the diabetes range. As similar diagnostic yield evidence has not been reported for OGT testing, the model will assume that OGT tests

will correctly identify patients (e.g. no NGT or pre-diabetes in the diabetes range, and no diabetes in the negative range).

To model these estimates in the intervention arm of the model (alternative scenario only), data from Lu et al. (2010) is applied in a similar manner. This study reported HbA1c test results in two Australian populations by glucose tolerance status, as classified by the ADA criteria for OGT testing (Lu et al. 2010). One of the populations reported is likely to represent those at high risk of diabetes, as it included all patients referred by medical practitioners for an OGT test in 2003–08 to a statewide private pathology service. These estimates will be used in the economic model (Table 25).

Table 25: Proportion of positive results in diabetes range observed, compared with modelled estimates

	Lawrence et al. (2001) FPG (n = 876)	Lu et al. (2010) HbA1c high-risk (n = 2,494)
NGT positive in diabetes range	1/18 (5.6%)	33/498 (6.6%)
Pre-diabetes positive in diabetes range	4/12 (33.3%)	149/694 (21.5%)
Diabetes positive in diabetes range	6/15 (40%)	601/845 (71.1%)
Diabetes negative in NGT range	N/A	19/263 (7.2%)

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; N/A = not applicable; NGT = normal glucose tolerance

Patient uptake

Many papers located in the literature search considered that the HbA1c test would be associated with greater patient acceptance compared with the other currently available tests, but no evidence was identified to support this. One study was identified in the economic literature search that considered patient uptake rates of different testing strategies (Icks et al. 2004); it assumed 100% patient uptake of HbA1c testing on the basis that the test did not require fasting. Expert opinion³ suggests that this level of uptake may be overly optimistic, with 75% considered more reasonable (Table 26). This level of uptake of HbA1c testing has been assumed in the base-case of the economic evaluation. For uptake of FPG and confirmatory OGT testing, Icks et al. (2004) cite Lawrence et al. (2001) (described above). This study observed uptake of the initial FPG test of 35%, with an uptake of confirmatory FPG testing of 85% and confirmatory OGT testing of 72%. However, initial patient uptake was based on a response to mailed invitations, rather than occurring at GP consultation and, as such, may be an underestimate. Expert opinion³ has indicated that a 70% uptake of initial FPG testing would be reasonable for the Australian setting. This assumption has been tested in sensitivity analyses. Given the 5-point difference between initial uptake of HbA1c and FPG, according to expert opinion, the same difference has been applied to determine the uptake rate of confirmatory HbA1c testing.

³ Health Expert Standing Panel (HESP) Member advice provided to Assessment Group

Two further assumptions have been made in the model regarding patient uptake of testing:

- i) once patients have been diagnosed with pre-diabetes, they all comply with prescribed tests; and
- ii) all patients with undiagnosed diabetes that progress to diabetes with complications receive testing (Table 26).

Table 26: Patient uptake rates of the available testing options (by circumstance) used in the economic model

Variable	Value	Source
Uptake of FPG test (undiagnosed/NGT)	0.70	Assumption, based on HESP member advice
Uptake of confirmatory FPG test (undiagnosed/ NGT)	0.85	Lawrence et al. (2001)
Uptake of confirmatory OGT test (undiagnosed/ NGT)	0.72	Lawrence et al. (2001)
Uptake of HbA1c test (undiagnosed/NGT)	0.75	Assumption, based on HESP member advice
Uptake of confirmatory HbA1c test (undiagnosed/ NGT)	0.90	Assumption ^a
Uptake of FPG test in known pre-diabetics	1.00	Assumption
Uptake of OGT test in known pre-diabetics	1.00	Assumption
Uptake of HbA1c test in known pre-diabetics	1.00	Assumption
Uptake of testing with diabetes complications	1.00	Assumption

^a Uptake of a confirmatory HbA1c test is assumed to be slightly higher than that of a confirmatory FPG test (as reported in Lawrence et al. (2001)) as patients are not required to fast.

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance

The inputs for the testing strategy decision trees, by glucose tolerance status, are presented for the comparator, HbA1c_1 and HbA1c_2 testing strategies, respectively, in Figure 23, Figure 24 and Figure 25, Appendix E.

Transition probabilities

Prevalence

In the economic model a number of transition probabilities vary depending on the age of the population at a given cycle, based on prevalence, incidence and mortality estimates. The population enters the economic model in one of four health states (NGT, undiagnosed/diagnosed pre-diabetes and undiagnosed diabetes). The distribution of the population within each health state is based on prevalence rates in the general population (reported from baseline estimates in the AusDiab study; Dunstan et al. (2001)) transformed to a high-risk population using data reported in Chen et al. (2010)—the validation study for the AUSDRISK screening tool.

Chen et al. (2010) reported a prevalence of undiagnosed diabetes, based on the 2004–05 follow-up of the AusDiab study, of 362/6060 (6.0%). For the purposes of the model, we have assumed that the current testing strategy (known to be imperfect) is 100% predictive (PPV = 1). Thus, the true population prevalence of diabetes is also assumed to be 6.0%. The AUSDRISK screening tool has been reported to have a sensitivity and specificity of 78%

and 58%, respectively, in identifying previously undiagnosed diabetes (Colagiuri et al. 2009a). Consequently, when people are screened using this tool, the probability that it will correctly identify previously undiagnosed diabetes in those assessed at high risk is 10.6%.⁴ On this basis the probability of correctly identifying diabetes when screening those at high risk is assumed to be 10.6%/6.0% = 1.8 times that in the general Australian population (Table 27). This ratio is similarly applied to estimate the probability that screening will correctly identify pre-diabetes in a high-risk population.

These probabilities in the economic model were transformed to provide prevalence estimates of 28.8% and 6.7%, respectively, for pre-diabetes and undiagnosed diabetes in the high-risk population. The overall prevalence estimates reported in people over the age of 40 years in the AusDiab (Dunstan et al. 2001) study for pre-diabetes (21.0%) and undiagnosed diabetes (5.6%) were transformed to provide modelled prevalence estimates of 37.2% and 9.9%, respectively, in the overall high-risk population over 40 years of age. These transformed estimates were validated by comparison against an Australian moderate- to high-risk population (aged 40–75 years) screened in Laatikainen et al. (2007), where similar although slightly lower prevalences were reported of undiagnosed diabetes (32/343, 9.3%) and pre-diabetes (106/343, 30.9%). However, as Laatikainen et al. (2007) additionally included people with a moderate risk of diabetes, lower prevalences in this population could be expected.

Table 27: Prevalence estimates observed in the general Australian population transformed to the high-risk population in the modelled economic evaluation

Age (years)	Pre-diabetes (Dunstan et al. 2001)	Pre-diabetes High-risk (modelled) ^a	Diabetes (Dunstan et al. 2001)	Diabetes High-risk (modelled) ^a
40–44	12.0%	21.2%	1.4%	2.5%
45–54	16.9%	29.9%	3.0%	5.3%
55–64	23.6%	41.7%	6.5%	11.5%
65–74	29.0%	51.2%	8.8%	15.5%
75+	29.3%	51.8%	12.3%	21.7%
Overall	21.0% ^b	37.2%	5.6% ^b	9.9%

^a Prevalence estimates in the high-risk group are based on the AusDiab estimates multiplied by a factor of 1.8.

^b Weighted by age distribution of population in 1999–00 (Australian Bureau of Statistics (ABS) 2013b).

As the high-risk population for diabetes testing includes both patients with a diagnosis of pre-diabetes and those without a diagnosis of pre-diabetes but other risk factors, it is assumed that the initial ratio of undiagnosed to diagnosed pre-diabetes is 50:50. This weighting was tested in sensitivity analyses. Given that the population assumed to enter the model are 40 years of age, the base-case prevalence rates used in the model are 10.6% in

⁴ Prevalence of undiagnosed diabetes = $(78\% \times 362) / (78\% \times 362 + (1 - 58\%) \times (6,060 - 362))$

each pre-diabetes health state and 2.5% in the undiagnosed diabetes health state (**bolded** in Table 27). Sensitivity analyses around the initial age of the modelled population are also performed.

Incidence

Bertram et al. (2010) reported incidence rates, by age, based on AusDiab data for transition to diabetes (from pre-diabetes) and pre-diabetes (from NGT). The reported incidence rate for diabetes in pre-diabetics has been applied directly in the model for the transition probability from pre-diabetes to diabetes (Table 28).

Bertram et al. (2010) assumed that the probability of transitioning between NGT and pre-diabetes, based on incidence rates observed for the general Australian NGT population, would apply to a population that contained risk factors for developing diabetes. However, this approach is likely to underestimate the incidence of diabetes in a high-risk population, and so these incidence estimates have been transformed for use in the economic model. Sensitivity analyses are performed using the raw estimates. The AusDiab study (Tanamas et al. 2013) reports the incidence of diabetes in the general, non-diabetic population (i.e. NGT and pre-diabetes) as 0.7% and in those who returned an AUSDRISK score ≥ 12 , according to baseline measurements, as 1.6%. As the incidence of diabetes in the high-risk group is $1.6\%/0.7\% = 2.3$ times that of the general population, this ratio has been applied to the incidence of pre-diabetes in the high-risk group (Table 28).

Table 28: Incidence estimates observed in the general Australian population transformed to the high-risk population (pre-diabetes only) in the modelled economic evaluation

Age (years)	Incidence of pre-diabetes in general NGT population ^a	Modelled transition of high-risk NGT to pre-diabetes ^b	Modelled transition of pre-diabetes to diabetes ^c
40–44	1.60%	3.66%	4.70%
45–54	2.55%	5.83%	5.60%
55–64	3.90%	8.91%	5.25%
65–74	4.40%	10.06%	5.05%
75–84	4.00%	9.14%	7.15%
85+	5.65%	12.91%	9.25%

^a Incidence of pre-diabetes, as reported in Bertram et al. (2010)

^b Pre-diabetes incidence estimates in the high-risk NGT population (from Bertram et al. (2010)) have been multiplied by a factor of 2.3 (based on increased relative risk of diabetes associated with patients with AUSDRISK score ≥ 12).

^c Diabetes incidence estimates from a pre-diabetic population have been taken directly from Bertram et al. (2010).
NGT = normal glucose tolerance

As described in the 'Structure and rationale of the economic evaluation' section, the base-case economic model does not consider a specific treatment effect of LMPs in pre-diabetes, despite treatment (including LMPs and medication) having been shown to reduce progression to diabetes (Gillies et al. 2007). This is due to uncertain applicability of these

interventions to the Australian context. A conservative approach has been used in the economic model, where equal probabilities are assumed for the transition from undiagnosed or diagnosed pre-diabetes to diabetes.

Sensitivity analyses will be performed to incorporate the treatment effect of a diet/exercise LMP in the progression from diagnosed pre-diabetes to diabetes, as currently provided by the Victorian Life! program. This program includes six group sessions facilitated by diabetes educators and nurses, and co-facilitated by physiotherapists and dieticians, over the course of 8 months. The Preliminary Melbourne Diabetes Prevention Study (Janus et al. 2012) randomised people at high risk of diabetes to the program and observed a significant reduction in BMI in the intervention arm at 12 months. However, a comparative treatment effect in the reduction of progression to diabetes was not reported due to the small sample size and insufficient follow-up. As such, the treatment effect of LMPs in sensitivity analyses will be based on a meta-analysis conducted by Gillies et al. (2007). This study reported a pooled hazard ratio of diet and exercise programs in people with IGT of 0.51. This estimate will be applied to the incidence of diabetes in people identified with pre-diabetes for 1 year.

Mortality

The Australian Bureau of Statistics (2012) reported mortality rates for the general Australian population by age, and these rates are assumed to apply to the NGT health state in the base-case analysis. As the population is a high-risk NGT one, this approach may underestimate mortality in this population given that the risk factors present are commonly associated with other diseases (e.g. heart disease). This assumption is tested in sensitivity analyses.

For all diabetes-related health states the likelihood of death is assumed to be higher, based on odds ratios reported in the AusDiab study (Tanamas et al. 2013). The increased likelihood of mortality is 20%, 40% and 70% higher in people with pre-diabetes, diabetes and diabetes with complications, respectively (Table 29).

People in the undiagnosed diabetes/pre-diabetes health states are assumed to have the same mortality rates as those in the diagnosed health states.

Table 29: Mortality estimates used in the economic model

Age (years)	NGT (ABS 2012)	Pre-diabetes	Diabetes	Diabetes with complications
<i>Increased risk</i>	-	20% ^a	40% ^a	70% ^a
40	0.12%	0.14%	0.17%	0.20%
45	0.18%	0.22%	0.25%	0.31%
50	0.27%	0.32%	0.38%	0.46%
55	0.41%	0.49%	0.57%	0.70%

Age (years)	NGT (ABS 2012)	Pre-diabetes	Diabetes	Diabetes with complications
<i>Increased risk</i>	-	20% ^a	40% ^a	70% ^a
60	0.63%	0.76%	0.88%	1.07%
65	1.00%	1.20%	1.40%	1.70%
70	1.71%	2.05%	2.39%	2.91%
75	2.95%	3.54%	4.13%	5.02%
80	5.47%	6.56%	7.66%	9.30%
85	13.41%	16.09%	18.77%	22.80%

^a Increased risk of mortality assumed in diabetes-related health states based on AusDiab (Tanamas et al. 2013) mortality odds ratios

NGT = normal glucose tolerance

Transition to diabetes with complications

For the two diabetes health states (undiagnosed and diagnosed) the probability of transitioning to diabetes with complications in the model varies, based on the predicted HbA1c level for that health state. Updated estimates from the United Kingdom Prospective Diabetes Study (UKPDS) have been used (Hayes et al. 2013). In patients with diagnosed diabetes the annual rate of developing complications is assumed to be 4.0%, calculated from the total number of non-fatal events / total patient years reported for people with newly diagnosed diabetes, with a median follow-up of 17.6 years (Hayes et al. 2013).

Upon enrolment into the UKPDS study, the median HbA1c level was 9%, which reduced to 7% following 3 months of dietary modification (UKPDS 1991). These levels are assumed for the undiagnosed and diagnosed diabetes health states, respectively (consistent with Gillies et al. 2008). In the UKPDS population a 1% decrease in HbA1c levels was associated with a 21% (95%CI 17–24%) decrease in risk for any diabetes-related complication, observed for HbA1c levels of 6–10% (Stratton et al. 2000) (Figure 26, Appendix E). It follows then that a 2% decrease in HbA1c levels (from 9% to 7%) is associated with a 42% (range 34–48%) decrease in diabetes-related complications.

As the annual rate of developing complications is assumed to be 4% in controlled diabetes (Hayes et al. 2013) (where the HbA1c level of 7% is assumed, based on UKPDS (1991)), the annual rate of developing diabetes-related complications in undiagnosed diabetes is $4.0\% \times 1/(1 - 0.42) = 6.9\%$. This range is tested in sensitivity analyses.

Healthcare resources

The healthcare resources associated with testing are presented in Table 30, along with the maximum use of each item in the intervention and comparator arms of the model. These costs are based on the relevant MBS item number.

On diagnosis of diabetes, baseline investigations of renal function, lipids and HbA1c are undertaken; with the introduction of HbA1c testing for the diagnosis of diabetes, baseline HbA1c would no longer be required, but would still apply in the comparator arm of the model. As other baseline investigations are required on the diagnosis of diabetes in both arms of the model, along with the associated patient episode initiation fee and subsequent GP consultation, the only difference in modelled cost on the diagnosis of diabetes is that associated with the baseline HbA1c test.

Table 30: Testing-related healthcare resources used in the economic model

Type of resource item	Natural unit of measurement	Unit cost	Source of unit cost	HbA1c test resource use	FPG/OGT test resource use
HbA1c (blood test)	Test	\$16.80	MBS item 66551	Up to 3 tests every 3 years in people with NGT and annually in those with pre-diabetes	On diagnosis of diabetes (to assess severity of disease)
FPG (blood test)	Test	\$9.70	MBS item 66500	N/A	Up to 2 tests every 3 years in people with NGT and annually in those with pre-diabetes
OGT (blood test)	Test	\$18.95	MBS item 66542	N/A	One test in people with discordant/intermediate FPG results
Patient episode initiation (PEI) fee	Initiation of a patient episode	\$6.25	Weighted average of relevant PEIs (see Table 75, Appendix E)	On the initiation of a patient episode of testing (up to a maximum of 3)	On the initiation of a patient episode of testing (up to a maximum of 3)
GP consultation	Visit	\$36.30	MBS item 23	On receipt of test results (up to a maximum of 3)	On receipt of test results (up to a maximum of 3)

Source: based on MBS, effective 1 July 2013

GP = general practitioner; HbA1c = glycated haemoglobin; FPG = fasting plasma glucose; OGT = oral glucose tolerance

Lee, CM et al. (2013) report the annual direct healthcare costs associated with diabetes and pre-diabetes in the Australian setting. The study was based on participants enrolled in the population-based AusDiab study. Participants in the cost analysis attended the 5-year follow-up survey in 2004–05, which included blood glucose measurements (by FPG and OGT) and questions related to use of all health services and health-related expenditure in the previous 12 months, including health-resource use unrelated to diabetes. Costs of visits to GPs, hospitalisation, prescription medication and medically related consumables (blood glucose strips etc.) were included.

Costs for people with diabetes were reported for those with known diabetes (i.e. known prior to participation in the follow-up survey) compared with newly diagnosed diabetes (i.e.

diagnosed as part of the follow-up survey) and also by diabetes complication status (i.e. no complications, microvascular only, macrovascular only, and both types of complications). Costs were also reported for people with NGT, and separately for IFG and IGT (Table 31).

As the economic model does not include separate health states by diabetes complication type, nor by type of pre-diabetes, the weighted cost for these health states is presented in Table 31. To remove costs unrelated to diabetes, as these may be potential confounders, only the excess cost reported for each diabetes-related health state (i.e. health state cost minus NGT health state cost) is used in the economic model (Table 31).

As Lee, CM et al. (2013) did not distinguish between previously known and newly identified pre-diabetes, health state costs for pre-diabetes are assumed to be the same regardless of knowledge of diagnostic status. There is some uncertainty surrounding this assumption; it may be that people with a diagnosis of pre-diabetes access healthcare resources more, out of vigilance in deterring further disease progression, or that those who are undiagnosed access health care more due to progressive deterioration of their health. Given these uncertainties, sensitivity analyses are conducted surrounding this assumption.

Knowledge of a diagnosis of diabetes is likely to be associated with higher resource use due to active management and preventive interventions (for potential complications). Consequently, annual costs differ between diagnosed and undiagnosed diabetes health states. As those who were newly diagnosed with diabetes in Lee, CM et al. (2013) were undiagnosed for the period in which health-resource use was reported, these costs are assumed to apply to the undiagnosed diabetes health state.

Additional sensitivity analyses are conducted to test the effect of health state costs on the results of the economic evaluation, using the ranges reported for the modelled health state cost in Table 31.

Table 31: Annual Australian direct healthcare costs and modelled health state costs, reported by glucose tolerance status

Health state	Derivation	Reported cost	Modelled health state cost ^a
Normal glucose tolerance	Direct healthcare cost of NGT; equivalent to 'background' health costs (assumed to be unrelated to diabetes)	\$1,446 (\$1,343–\$1,550)	\$0 (\$0–\$0)
Pre-diabetes (undiagnosed or diagnosed)	Weighted direct healthcare cost of IFG and IGT	\$1,750 (\$1,410 –\$2,090)	\$304 (\$67–\$540)
Diabetes (undiagnosed)	Direct healthcare cost of newly diagnosed diabetes	\$2,081 (\$1,570–\$2,591)	\$635 \$227–\$1,041)
Diabetes (diagnosed)	Direct healthcare cost of diabetes without complications	\$2,357 (\$1,850–\$2,863)	\$911 (\$507–\$1,313)
Diabetes (complications)	Weighted direct healthcare cost of diabetes with complications	\$4,094 (\$3,179–\$5,009)	\$2,648 (\$1,836–\$3,459)

Source: calculated from Table 2 (Lee, CM et al. (2013))

^a The modelled health state cost is calculated by taking the reported health state cost and subtracting that reported for people with NGT, such that the residual costs are assumed to specifically relate to diabetes.
IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NGT = normal glucose tolerance

Utility values

Health state utilities used in the economic model are presented in Table 32. For the NGT and pre-diabetes health states the utility value is assumed to be 1, which is consistent with utility values applied in the model reported by Gillies et al. (2008). The utility values for the diabetes and diabetes with complications health states were based on those reported in the DiabCo\$t study (Colagiuri et al. 2003), which was conducted in an Australian diabetes population assessing quality of life using the EQ-5D multi-attribute utility instrument. For the diabetes health state the model uses the reported utility in people with diabetes with no complications (0.85). For the diabetes with complications health state the DiabCo\$t study reported EQ-5D scores by the category of complication (microvascular only, macrovascular only and both micro- and macrovascular complications). To derive an average utility weight for use in the model, they were weighted by the population in each complication category observed in the AusDiab study (reported in Lee, CM et al. (2013)). The weighted utility derived was 0.67.

Utility weights used in the model are assumed to be the same for diagnosed and undiagnosed health states. This assumption will be tested in sensitivity analyses, where a utility decrement (−0.05) will be applied to the diagnosed diabetes health state, assuming some side effects/discomfort/inconvenience associated with treatment.

Table 32: Health state utility weights used in the economic evaluation

Health state	Utility weight	Source
Normal glucose tolerance	1	Gillies et al. (2008)
Pre-diabetes (undiagnosed or diagnosed)	1	Gillies et al. (2008)
Diabetes (undiagnosed or diagnosed)	0.85	Colagiuri et al. (2003)
Diabetes (with complications)	0.67	Colagiuri et al. (2003)

Implications for false positive and false negative patients

The implications for false positive and false negative patients in the model relate to the frequency of re-testing and the costs associated with inappropriate treatment with false positive classification; these are depicted in Table 33. Annual health state costs, utility weights, incidence and mortality rates are assumed as per the true health state.

Table 33: Implications for false positive and false negative tests and re-testing in the economic evaluation

True health state	Treated as	Implications
Normal glucose tolerance	Pre-diabetes	Re-tested annually (instead of every 3 years)
	Diabetes	Not re-tested. Assume patient receives minimum care per year to attract the diabetes service incentive program payment (\$157.30 – Table 76, Appendix E)
Undiagnosed pre-diabetes	NGT	Re-tested every 3 years (instead of annually)
	Diabetes	Not re-tested. Assume patient receives minimum care per year to attract the diabetes service incentive program payment (\$157.30 – Table 76, Appendix E)
Undiagnosed diabetes	NGT	Re-tested after 3 years (unless complications develop)
	Pre-diabetes	Re-tested after 1 year

NGT = normal glucose tolerance

Outputs from the economic evaluation

The results of the economic evaluation have been presented in a stepped manner, where the assumptions regarding patient uptake of testing and test accuracy are incorporated consecutively:

1. assuming 100% uptake in each of the testing strategies for all prescribed tests and 100% accuracy of all tests, such that the only difference modelled is the cost of the test and the current/proposed testing algorithms;
2. incorporating patient uptake rates, as described in the 'Inputs to the economic evaluation' section; and
3. incorporating sensitivity and specificity parameters of the HbA1c test, as described in the 'Inputs to the economic evaluation' section.

The results of the economic evaluation have been presented as a comparison of each HbA1c testing scenario compared with the current testing strategy (Table 34 and Table 35, respectively). The stepped evaluation comparing all three testing strategies is presented in Table 77, Appendix E, along with the breakdown of incremental costs and QALYs by model health state (Table 78 and Table 79).

Base-case scenario (HbA1c_1)

For the base-case scenario, where an HbA1c cut-off is proposed to identify diabetes only, the intervention is observed to be less expensive in each of the three steps; however, it is less effective than the current testing strategy (i.e. the ICER lies in the south-west (SW) quadrant of the cost-effectiveness (CE) plane; Figure 27). This is primarily due to the inability of HbA1c in this scenario to identify people with pre-diabetes.

Table 34: Stepped incremental cost-effectiveness of the base-case (HbA1c_1) scenario vs FPG/OGT testing

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
<i>Step 1</i>					
Comparator	\$8,439	-	16.2420	-	-
HbA1c_1	\$8,084	-\$355 (cost saving)	16.2267	-0.0153 (less effective)	\$23,217 (SW quadrant of CE plane)
<i>Step 2</i>					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_1	\$8,049	-\$298 (cost saving)	16.2175	-0.0178 (less effective)	\$16,762 (SW quadrant of CE plane)
<i>Step 3</i>					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_1	\$8,224	-\$200 (cost saving)	16.2015	-0.0326 (less effective)	\$6,133 (SW quadrant of CE plane)

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; CE = cost-effectiveness plane (as depicted in Figure 27, Appendix E); FPG = fasting plasma glucose; ICER = incremental cost-effectiveness ratio; OGT = oral glucose tolerance; SW = south-west

Note: Numbers may not be exact due to rounding.

Alternative scenario (HbA1c_2)

Under the current testing algorithm, people with an initial FPG result in the equivocal range are recommended to undergo re-testing. In the alternative scenario where HbA1c testing similarly identifies a pre-diabetic range, it is observed to dominate the comparator in Step 1, as testing is less expensive due to the requirement of only one test, rather than two, to diagnose pre-diabetes. HbA1c testing is assumed to be equally effective at identifying both diabetes and pre-diabetes in this step, and therefore has equivalent effectiveness.

In Step 2 the alternative scenario continues to dominate the current testing strategy as a more favourable test uptake rate is associated with the HbA1c test. As fewer people uptake testing in the current strategy, the effectiveness in the comparator arm is poorer. Despite comparatively higher patient uptake of the HbA1c test, the alternative scenario remains less expensive; however, the incremental cost difference is reduced from Step 1, as expected.

In Step 3 of the analysis, when the best available but highly uncertain estimates of sensitivity and specificity parameters of the HbA1c test (Table 24) are incorporated into the alternative scenario of the model, diagnostic HbA1c testing *is dominated*. At Step 3 the current testing strategy is assumed to be 100% accurate, even though it is known that it imperfectly predicts diabetes. However, as retinopathy (the 'gold' reference standard) is not a practical testing alternative in clinical practice, the current test strategy of FPG with/without OGT testing has to be assumed to be perfect. This means that by effectively reducing test accuracy (sensitivity and specificity are considerably reduced from the 100% assumed in Step 2) *only* in the HbA1c testing arm, HbA1c testing:

- is more expensive, due to false positive patients inappropriately receiving diabetes treatment; and false negative patients, who do not receive a diagnosis until symptoms of their disease are present, incurring the high costs of treating diabetes complications; and
- is less effective, due to poorer quality of life associated with increased numbers of patients having symptomatic disease.

As described in the 'Effectiveness' section of the report, the reference standards used are imperfect and all three tests appear to diagnose different subpopulations of people with diabetes. Given this, the concordance between tests was poor and there was considerable variability in the diagnostic accuracy of HbA1c compared with currently available tests. As HbA1c testing appears to be equally predictive of retinopathy, the true measure of the cost-effectiveness of HbA1c testing is likely to lie between the estimates reported in Steps 2 and 3 of the economic evaluation.

Table 35: Stepped incremental cost-effectiveness of the alternative (HbA1c_2) scenario vs FPG/OGT testing

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
<i>Step 1</i>					
Comparator	\$8,439	-	16.2420	-	-
HbA1c_2	\$8,185	-\$254 (cost saving)	16.2420	0.0000 (equivalent)	Dominant (SE quadrant of CE plane)
<i>Step 2</i>					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_2	\$8,143	-\$205 (cost saving)	16.2387	0.0034 (more effective)	Dominant (SE quadrant of CE plane)
<i>Step 3</i>					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_2	\$8,503	\$79 (more costly)	16.2139	-0.0202 (less effective)	Dominated (NW quadrant of CE plane)

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; CE = cost-effectiveness plane (as depicted in Figure 27, Appendix E); FPG = fasting plasma glucose; ICER = incremental cost-effectiveness ratio; NW = north-west; OGT = oral glucose tolerance; SE = south-east
 Note: Numbers may not be exact due to rounding.

Base-case scenario (HbA1c_1) vs alternative scenario (HbA1c_2)

When the HbA1c testing scenarios are compared with one another, the alternative scenario (i.e. where a diagnosis of pre-diabetes can be made on the basis of HbA1c results) is consistently more costly but also more effective than the base-case scenario (where no diagnosis of pre-diabetes is made). The ICERs were \$6,611, \$4,421 and \$22,507 per QALY in the three steps, respectively, favouring the alternative scenario (see Table 77 and Table 80, Appendix E for full details).

Sensitivity analyses

Tornado analysis

Where uncertainties were identified in the inputs to the economic evaluation, sensitivity analyses have been performed to quantify the effect of the uncertainty in the economic model. The upper and lower limits of variables were tested using a tornado analysis. The results of the analyses for variables tested are presented in Figure 19 and Figure 20 (tabulated in Table 81 and Table 81, Appendix E, respectively) with detailed results presented in Table 36 and Table 37, respectively, for the base-case and alternative testing scenarios for the five variables with the greatest spread.

The variables that have most effect on the ICERs are reasonably consistent between the base-case (HbA1c_1) and alternative (HbA1c_2) scenarios; however, the effect of some of these variables is somewhat dissimilar, with the largest variation observed in the HbA1c_1 scenario for the annual cost in the undiagnosed pre-diabetes health state. This result was expected, given that the HbA1c_1 scenario does not specifically identify pre-diabetes and is therefore more sensitive to changes in the cost of undiagnosed pre-diabetes.

When sensitivity analyses around the base-case ICERs at Step 3 were performed (including test accuracy data), the overall conclusions of HbA1c testing primarily did not change (less costly and less effective in the HbA1c_1 scenario and dominated in HbA1c_2). No analyses were identified for either scenario in which HbA1c testing was associated with improved effectiveness outcomes (i.e. all ICERs exist in western quadrants of the CE plane).

The results of tornado analyses conducted around the ICERs obtained in Step 2 of the economic evaluation have additionally been presented in Appendix E. These analyses assume that the performance of all testing strategies is 100% (a known overestimate).

The pattern of variables that the HbA1c_1 scenario was most sensitive to in Step 2 was similar to that observed in Step 3 of the economic evaluation. Again, the model was most sensitive to health state costs, with the largest variation in the ICER observed for the cost of the undiagnosed pre-diabetes health state. However, the magnitude of this difference was observed to be much higher than that in sensitivity analyses conducted when HbA1c accuracy data was included (\$88,000 compared with \$40,000). This was the only sensitivity analysis that resulted in the intervention strategy being dominated by the comparator—all other analyses were observed to have less effective and less costly results (i.e. the ICERs lie in the SW quadrant of the CE plane).

In contrast, the variables that the HbA1c_2 scenario was most sensitive to related to patient uptake of testing. This scenario was most cost-ineffective when uptake of FPG or OGT testing was higher than HbA1c testing; however, it would be expected that uptake

associated with HbA1c testing in practice would likely be at least as good as that of the currently available tests, so this is not a risk of concern.

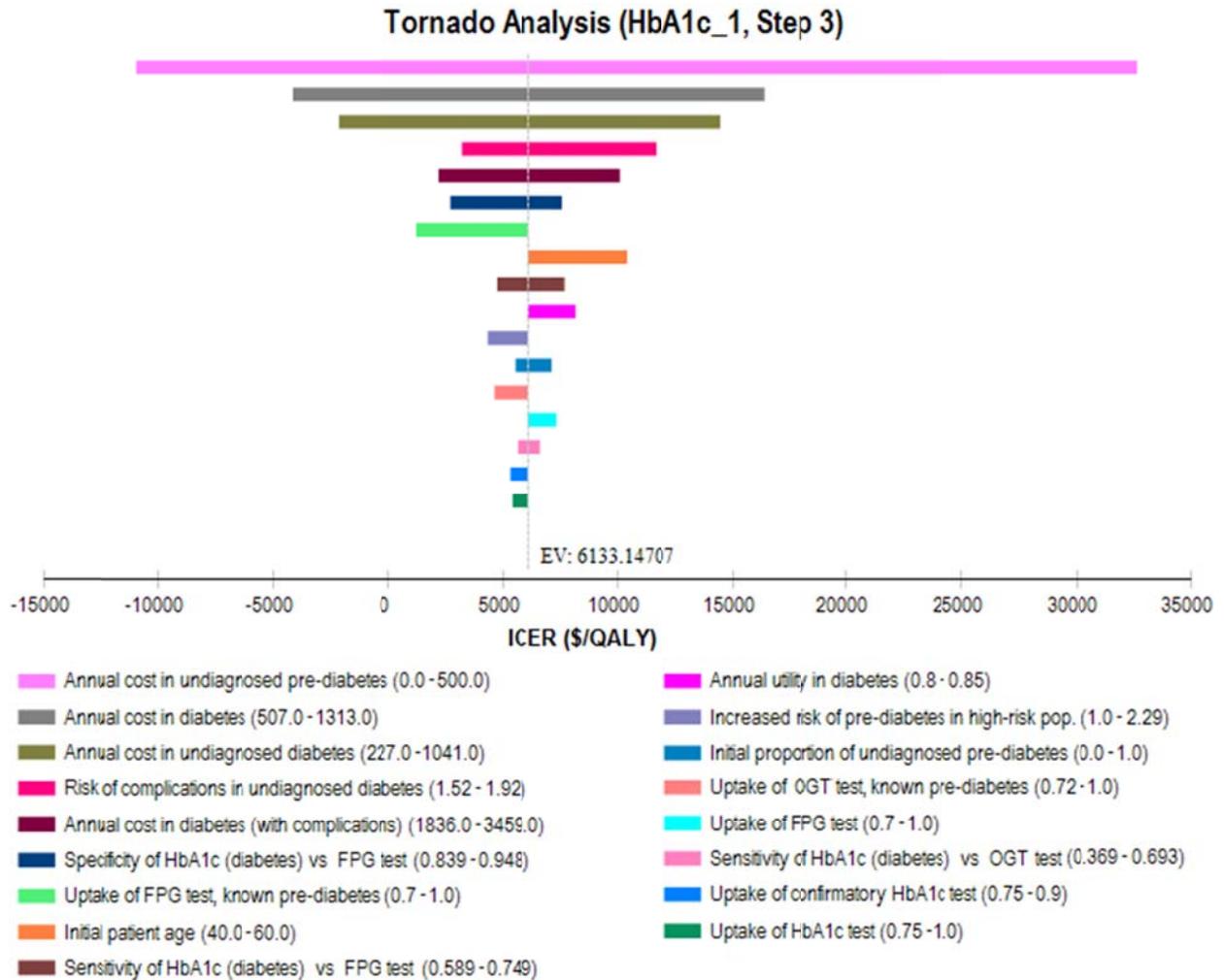


Figure 19: Tornado analysis of the base-case (HbA1c_1) scenario

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

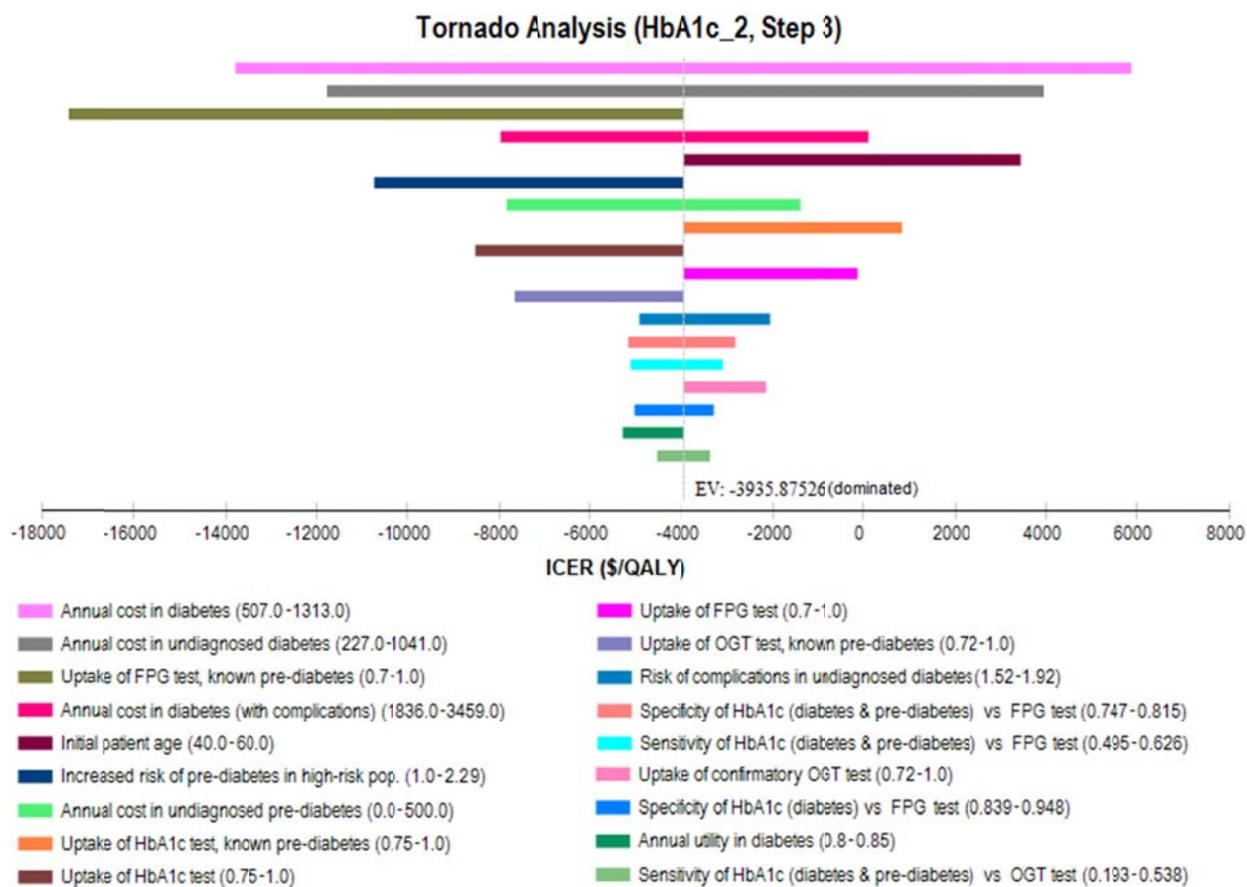


Figure 20: Tornado analysis of the alternative (HbA1c_2) scenario

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Table 36: Five variables with the highest spread observed in the tornado analysis, base-case (HbA1c_1) scenario

Variable tested	Value	Comparator		HbA1c_1		Incremental		ICER	Spread	Interpretation
		Cost	Eff.	Cost	Eff.	Cost	Eff.			
Base-case	-	\$8,423.38	16.2340	\$8,223.71	16.2015	-\$199.67	-0.0326	\$6,133	N/A	N/A
Annual cost of undiagnosed pre-diabetes health state (base-case: \$309)	\$0	\$7,998.65	16.2340	\$6,934.96	16.2015	-\$1,063.69	-0.0326	\$32,674	\$43,652	Decreased incremental cost due to more undiagnosed pre-diabetes in intervention: favours the intervention
	\$500	\$8,697.21	16.2340	\$9,054.62	16.2015	\$357.41	-0.0326	Dominated		Increased incremental costs: favours the comparator
Annual cost of diagnosed diabetes health state (base-case: \$911)	\$507	\$7,361.71	16.2340	\$7,497.12	16.2015	\$135.41	-0.0326	Dominated	\$20,534	As there are fewer cases of diabetes diagnosed in the intervention, incremental costs increase: favours the comparator
	\$1,313	\$9,479.79	16.2340	\$8,946.70	16.2015	-\$533.09	-0.0326	\$16,375		Decreased incremental costs: favours the intervention
Annual cost of undiagnosed diabetes health state (base-case: \$635)	\$227	\$8,333.58	16.2340	\$7,862.18	16.2015	-\$471.40	-0.0326	\$14,480	\$16,653	As there are more cases of undiagnosed diabetes in the intervention, incremental costs decrease: favours the intervention
	\$1,041	\$8,512.73	16.2340	\$8,583.47	16.2015	\$70.74	-0.0326	Dominated		Increased incremental costs: favours the comparator

Variable tested	Value	Comparator		HbA1c_1		Incremental		ICER	Spread	Interpretation
		Cost	Eff.	Cost	Eff.	Cost	Eff.			
Base-case	-	\$8,423.38	16.2340	\$8,223.71	16.2015	-\$199.67	-0.0326	\$6,133	N/A	N/A
Risk of developing diabetes complications in undiagnosed diabetes (base-case: 1.72)	1.52	\$8,397.38	16.2370	\$8,119.40	16.2131	-\$277.98	-0.0239	\$11,660	\$8,464	As there are more cases of undiagnosed diabetes in the intervention, if risk of complications decreases, the incremental effectiveness improves. However, this is outweighed by the increased incremental cost due to more complications: favours the comparator
	1.92	\$8,447.18	16.2314	\$8,318.07	16.1910	-\$129.11	-0.0404	\$3,196		Decreased incremental costs outweigh the decrease in incremental effectiveness: favours the intervention
Annual cost of diabetes (with complications) (base-case: \$2,648)	\$1,836	\$7,354.70	16.2340	\$7,026.42	16.2015	-\$328.28	-0.0326	\$10,084	\$7,897	As there are more cases of diabetes with complications in the intervention arm, incremental costs decrease: favours the intervention
	\$3,459	\$9,490.74	16.2340	\$9,419.53	16.2015	-\$71.21	-0.0326	\$2,187		Increased incremental costs: favours the comparator

Eff. = effectiveness; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness; NGT = normal glucose tolerance

Table 37: Five variables with the highest spread observed in the tornado analysis, alternative (HbA1c_2) scenario

Variable tested	Value	Comparator		HbA1c_2		Incremental		ICER	Spread	Interpretation
		Cost	Eff.	Cost	Eff.	Cost	Eff.			
Base-case	-	\$8,423.38	16.2340	\$8,502.72	16.2139	\$79.34	-0.0202	Dominated	N/A	N/A
Annual cost of diagnosed diabetes health state (base-case: \$911)	\$507	\$7,361.71	16.2340	\$7,639.94	16.2139	\$278.23	-0.0201	Dominated	\$19,683	As there are fewer cases of diabetes are diagnosed in the intervention, incremental costs increase: favours the comparator
	\$1,313	\$9,479.79	16.2340	\$9,361.23	16.2139	-\$118.56	-0.0201	\$5,881		Decreased incremental costs: favours the intervention
Annual cost of undiagnosed diabetes health state (base-case: \$635)	\$227	\$8,333.58	16.2340	\$8,254.14	16.2139	-\$79.44	-0.0201	\$3,941	\$15,715	As there are more cases of undiagnosed diabetes in the intervention, incremental costs decrease: favours the intervention
	\$1,041	\$8,512.73	16.2340	\$8,750.08	16.2139	\$237.35	-0.0201	Dominated		Increased incremental costs: favours the comparator
Uptake of FPG test, known pre-diabetes (base-case: 1.0)	0.70	\$8,256.35	16.2280	\$8,502.72	16.2139	\$246.37	-0.0141	Dominated	\$13,492	Reduced uptake of testing decreases the cost and effectiveness in comparator: favours the comparator, as decrease in incremental effectiveness outweighs the decrease in cost
Annual cost of diabetes (with complications) (base-case: \$2,648)	\$1,836	\$7,354.70	16.2340	\$7,352.41	16.2139	-\$2.29	-0.0201	\$113	\$8,094	As more cases of diabetes with complications in the intervention arm, incremental costs decrease: favours the intervention
	\$3,459	\$9,490.74	16.2340	\$9,651.61	16.2139	\$160.87	-0.0201	Dominated		Increased incremental costs: favours the comparator

Variable tested	Value	Comparator		HbA1c_2		Incremental		ICER	Spread	Interpretation
		Cost	Eff.	Cost	Eff.	Cost	Eff.			
Base-case	-	\$8,423.38	16.2340	\$8,502.72	16.2139	\$79.34	-0.0202	Dominated	N/A	N/A
Initial patient age (base-case: 40 years)	60	\$7,941.60	12.2642	\$7,841.02	12.2350	-\$100.58	-0.0292	\$3,444	\$7,379	Increased prevalence of diabetes and pre-diabetes in population: favours the intervention

Eff. = effectiveness; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness; NGT = normal glucose tolerance

Additional sensitivity analyses

Additional sensitivity analyses were performed to incorporate:

- i) the effect of LMPs in people with pre-diabetes, assuming all pre-diabetics participate in one LMP at a cost of \$300 (Australian General Practice Network 2008), which reduces the probability of progressing to diabetes by 49% (Gillies et al. 2007) for 1 year; and
- ii) alternative HbA1c cut-off for identifying pre-diabetes (6.0%) (see Table 24); this is not relevant for the HbA1c_1 scenario.

Table 38: Additional sensitivity analyses

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
Base-case (HbA1c_1)					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_1	\$8,224	-\$200 (cost saving)	16.2015	-0.0326 (less effective)	\$6,133 (SW quadrant of CE plane)
<i>Lifestyle modification</i>					
Comparator	\$8,453	-	16.2510	-	-
HbA1c_1	\$8,224	-\$230 (cost saving)	16.2015	-0.0495 (less effective)	\$4,639 (SW quadrant of CE plane)
Base-case (HbA1c_2)					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_2	\$8,503	\$79 (more costly)	16.2139	-0.0202 (less effective)	Dominated (NW quadrant of CE plane)
<i>Lifestyle modification</i>					
Comparator	\$8,453	-	16.2510	-	-
HbA1c_2	\$8,535	\$81 (more costly)	16.2391	-0.0119 (less effective)	Dominated (NW quadrant of CE plane)
<i>Alt. HbA1c cut-offs</i>					
Comparator	\$8,423	-	16.2340	-	-
HbA1c_2	\$8,664	\$240 (more costly)	16.2284	-0.0056 (less effective)	Dominated (NW quadrant of CE plane)

Note: Numbers may not be exact due to rounding.

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; Alt. = alternative; CE = cost-effectiveness plane (as depicted in Figure 27, Appendix E); FPG = fasting plasma glucose ; HbA1c = glycated haemoglobin; ICER = incremental cost- effectiveness ratio; NW = north- west; OGT = oral glucose tolerance; SW = south-west.

The inclusion of LMPs for pre-diabetic patients increases the costs and effectiveness in the comparator and HbA1c_2 testing strategies only (as these identify a pre-diabetic range).

The inclusion of LMPs favours HbA1c testing (i.e. lowers the ICER) in the HbA1c_1 scenario and disfavours HbA1c testing (i.e. increases the ICER) in the HbA1c_2 scenario. This is due to the estimated short duration of treatment effect (1 year).

Incorporating the alternative HbA1c cut-offs for the identification of pre-diabetes was associated with improvements in effectiveness, but was additionally associated with increases in the incremental cost.

Overall, the model is most sensitive to the inclusion of HbA1c accuracy data, variations in health state costs and patient uptake rates of testing.

Financial impact

While HbA1c testing is proposed to replace currently available tests, accurate MBS utilisation data could not be retrieved for the FPG test, as the relevant item number lists several other tests. As a consequence, projections of the market costings have been developed using a mix of epidemiological and market-based approaches.

Data sources used in the financial analysis

The data sources used in the estimated budgetary impact of listing HbA1c testing to diagnose diabetes are presented in Table 39.

Table 39: Data sources used in the financial analysis

Data source	Purpose
ABS (2013b) 3101.0 Australian Demographic Statistics, Table 59	To estimate the Australian population aged 40 years or older in 2000–12
ABS (2013c) 3222.0 Population Projections, Australia, Table A9	To estimate the Australian population aged 40 years or older in 2013–19
ABS (2010) 4839.0.55.001, Health Services: Patient Experiences in Australia, 2009, Table 1.2	To estimate the proportion of people aged 40 years or older who attended a GP per year
AusDiab study	Baseline report (Dunstan et al. 2001): <ul style="list-style-type: none"> to estimate the total prevalence of diabetes in the Australian population aged 40 years or older in 1999–00 (11.2%); to estimate the total prevalence of pre-diabetes in the Australian population aged 40 years or older in 1999–00 (21.2%); and to estimate the prevalence of known and unknown diabetes (each 5.6%). Follow-up (Tanamas et al. 2013): <ul style="list-style-type: none"> to estimate the incidence of pre-diabetes in the Australian population aged 40 years or older (1.3%); and to estimate the incidence of diabetes in those with pre-diabetes (2.6%).
Wong, KC, Brown and Li (2011)	To estimate the proportion of GPs that comply with administration of the AUSDRISK assessment tool (14%)
Colagiuri et al. (2009a)	To estimate the proportion of people with diabetes (78%) and pre-diabetes/NGT (42%) who are considered high risk, using the AUSDRISK tool
Medicare Benefits Schedule (effective 1 July 1 2013)	To determine the costs (MBS rebate in the outpatient setting) for FPG (items 66500), OGT (item 66542) and HbA1c (item 66551) testing, including GP consultation (item 23) and patient episode initiation fees (weighted items, see Table 75, Appendix E).
Medicare Benefits Schedule data	To estimate average patient co-payments associated with testing methods

Data source	Purpose
MBS item 66542 statistics data (1999–00 to 2012–13) (Medicare Australia 2013a)	To estimate the population of women with a history of gestational diabetes or polycystic ovary syndrome who are eligible and uptake OGT testing
MBS statistics data for items 66500, 66503, 66506, 66509 and 66512 (2012–13) and items 66512 and 66515 (2007–08) (Medicare Australia 2013a)	2012–13 claims data: <ul style="list-style-type: none"> To estimate the proportion of initial FPG tests ordered in isolation or with other tests listed within MBS item 66500 2007–08 claims data: <ul style="list-style-type: none"> To estimate the proportion of claims for 5 tests only listed within MBS item 66500 of the claims for 5 or more tests
MBS electorate statistics (Medicare Australia 2010)	To estimate the number of people eligible for the Medicare safety net (1,576,350), which is equal to 7.2% of the estimated resident population in 2010 (ABS 2013b)
Chittleborough et al. (2010)	To estimate the uptake of testing in women with a history of gestational diabetes (65%)

AUSDRISK = Australian Diabetes Risk; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGT = oral glucose tolerance

The MBS item for FPG tests is not specific to FPG testing alone, as a number of other tests are additionally listed within this item descriptor; where multiple items are ordered at the same time, different item numbers are applied depending on the number of tests ordered. MBS item statistics for items 66500 (1 test), 66503 (2 tests), 66506 (3 tests), 66509 (4 tests) and 66512 (5 or more tests) indicate that 90% of tests listed in item 66500 are ordered in a group of 5 or more tests, and it is unlikely that initial FPG testing under the current strategy will be ordered in isolation (Table 86, Appendix F).

If the initial FPG test is ordered with 5 or more other tests (i.e. total 6 or more tests), the cost offset of FPG testing with the introduction of HbA1c testing for diagnosis of diabetes is \$nil. The MBS benefit is the same for 6 or more tests as it is for 5 or more. If the initial FPG test is ordered with between 1 and 4 other tests (i.e. total 2 to 5 tests), the cost offset of FPG testing is \$1.70; this is the difference in MBS benefit with the reduction of 1 test. Under both these circumstances GP consultation and PEI fees remain applicable to the remaining tests, and so are not considered as cost offsets.

If the initial FPG test is ordered in isolation, the cost offset of FPG testing is \$8.25. In this instance it is applicable to additionally offsetting the cost of the GP consultation and related PEI fees, to bring the total cost offset to \$49.90.

Prior to 1 July 2008 an additional item number (item 66515) was available for 6 or more tests ordered within item 66500, and item 66512 was limited to 5 listed tests. Medicare item statistics for items 66512 and 66515 indicate that of the 5 or more tests ordered in 2007–08, 99.3% were for orders of 6 or more (Table 86, Appendix F). If it is assumed that 0.7% of item 66512 are for orders of 5 tests, and that 99.3% are for orders of 6 or more tests, the number of tests ordered can be weighted proportionally (detailed in Table 87, Appendix F):

- FPG test in isolation, 5.1%
- FPG test with up to 4 others, 6.0%
- FPG test with 5 or more others, 88.8%.

This equates to an average weighted cost of \$2.65 per initial FPG test. This estimate was applied in the base-case financial analysis, with sensitivity analyses conducted to vary this test cost to \$49.90 (i.e. that for FPG ordered in isolation). The MBS fee and patient co-payment have been similarly calculated (Table 40).

Table 40: MBS item fees and patient co-payments for tests in the financial analysis

	MBS fee ^a	MBS benefit ^b	Patient co-payment ^c
Initial FPG test	\$2.79 ^d	\$2.65 ^d	\$0.34 ^d
Confirmatory FPG test	\$9.70	\$8.25	\$5.49
OGT test	\$18.95	\$16.15	\$12.89
HbA1c test	\$16.80	\$14.30	\$7.72
GP consultation	\$36.30	\$36.30	\$0.00
PEI	\$6.25	\$5.35	\$0.90 ^f

^a MBS fee is taken as MBS benefit if patient is eligible for the Medicare safety net.

^b MBS benefit in the outpatient setting (i.e. 85% of schedule fee) applies to patients who are ineligible for the Medicare safety net.

^c Patient co-payment based on MBS data; assumed to have incorporated the Medicare safety net.

^d Weighted by the estimated number of tests ordered with the initial FPG test (see text).

^e MBS data was not available for item 66551; have assumed same patient co-payment as for FPG test.

^f Assume patient co-payment is equal to the difference between the MBS fee and the MBS benefit.

FPG = fasting plasma glucose; GP = general practitioner; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance; PEI = patient episode initiation

The total cost per test (inclusive of GP consultation and PEI fees) for each of the tests included in the analysis is presented in Table 41. Given that approx. 5.1% of initial FPG tests are ordered alone, this assumption is similarly applied to initial HbA1c tests (and as such, only 5.1% of tests are associated with the PEI and the cost of a follow-up GP consultation).

Table 41: Total test costs used in financial analysis

Test	Total test cost (safety net ineligible)	Total test cost (safety net eligible)	Total patient co-payment
Initial HbA1c (for diagnosis)	\$16.43 ^a	\$18.97 ^a	\$7.77 ^a
Confirmatory HbA1c (for diagnosis)	\$55.95	\$59.35	\$8.62
Initial FPG	\$2.65 ^b	\$2.79 ^b	\$0.39 ^a
Confirmatory FPG	\$49.90	\$52.25	\$6.39
OGT	\$57.80	\$61.50	\$13.79
HbA1c (at baseline following diabetes diagnosis)	\$14.30	\$16.80	\$7.72

^a Assuming 5.1% of initial tests ordered alone, and so 5.1% of general practitioner consultation and patient episode initiation fee are attributed.

^b Weighted by the estimated number of tests ordered with the initial FPG test (see text)

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance

Estimating the population eligible for testing

The three main populations eligible for testing include those with:

- a history of pre-diabetes;
- a history of gestational diabetes or polycystic ovary syndrome; and
- other risk factors that indicate a high risk of developing diabetes.

The number of people in these populations is estimated, in addition to the population with known diabetes (as these people are ineligible for testing). Given the recommendations for repeated risk assessment and testing every 3 years in some people at high risk and annually in those with an even greater risk, population estimations are calculated from 2012–13 data.

Population with diabetes

An epidemiological approach using ABS statistics (2013b) and AusDiab data (Dunstan et al. 2001) is used to estimate the total population with diabetes (known and unknown). To estimate the number of people in 2012–13 to 2018–19 that have undiagnosed or diagnosed diabetes, prevalence and incidence data from the AusDiab study have been used to project the total population with diabetes. The prevalence of diabetes is estimated to range from 2.4% in 40-year-olds to 23.7% in those aged older than 75 years (Dunstan et al. 2001). Using ABS population statistics for 1999–2000, the prevalence (weighted by age) for the population older than 40 years of age was found to be 11.2%, with approximately half with previously undiagnosed diabetes.

For each subsequent year the total population with diabetes was estimated based on incidence data from the AusDiab study (Tanamas et al. 2013), which reported an annual incidence rate of 2.6% in people with pre-diabetes. A weighted average mortality rate in people older than 40 years of age, based on ABS data (ABS 2012), was applied to estimate the overall population with diabetes (Table 88, Appendix F). The estimated prevalence of diabetes in 2012–13 is 12.2% (including undiagnosed and diagnosed diabetes).

To estimate the proportion of people with known diabetes, it is assumed that the ratio of diagnosed to undiagnosed diabetes observed in the baseline AusDiab study applies. Consequently, the estimated prevalence of known diabetes in 2012–13 is 6.1%, and this population is ineligible for testing. This is similar to the prevalence estimate reported in the 2011–12 ABS Biomedical Health survey (ABS 2013a), also 6.1% in people older than 40 years of age, based on a combination of self-report and FPG test results.

For each subsequent year the estimated population with known diabetes is based on those with previously known diabetes in addition to those newly diagnosed with diabetes.

Table 42: Estimated population projection of people with known diabetes or pre-diabetes, 2012–13

	Population	Source	2012–13
A	Population projection (age 40 years or older)	ABS (2013c)	10,716,769
B	Total population with diabetes	Table 88, Appendix F	1,303,238
C	Prevalence of diabetes	B / A	12.2%
D	Proportion of diabetes known	AusDiab (Dunstan et al. 2001)	50.1%
E	Prevalence of known diabetes	C × D	6.1%
F	Population with known diabetes	A × E	635,065
G	Total population with pre-diabetes	Table 88, Appendix F	1,877,373
H	Prevalence of pre-diabetes	B / A	17.3%
I	Prevalence of known pre-diabetes	C × D	8.8%
J	Population with known pre-diabetes	A × E	940,770

Population with pre-diabetes

An epidemiological approach using ABS statistics and AusDiab data was used to estimate the total population with pre-diabetes (known and unknown). To estimate the number of people in 2014–15 to 2018–19 that have pre-diabetes, prevalence and incidence data from the AusDiab study have been used. In the baseline AusDiab study the prevalence of pre-diabetes ranged from 12.0% in 40-year-olds to 29.3% in those older than 75 years of age (Dunstan et al. 2001). Using ABS statistics for 1999–00, the weighted prevalence of pre-diabetes for the population older than 40 years of age was found to be 21%. The ratio of previously known to unknown pre-diabetes was not reported.

For each subsequent year the total population with pre-diabetes was estimated based on incidence data from the AusDiab study (Tanamas et al. 2013), which reported an annual incidence rate of 1.3% (and an annual incidence rate of 2.6% from pre-diabetes to diabetes). A weighted average mortality rate in people aged older than 40 years, based on ABS data, was applied to estimate the overall population with pre-diabetes (Table 88, Appendix F). The estimated prevalence of pre-diabetes in 2012–13 is 17.3%.

To estimate the proportion of people with known pre-diabetes, it was assumed that the ratio of diagnosed to undiagnosed pre-diabetes is the same as for diabetes in the baseline AusDiab study (Dunstan et al. 2001). This assumption was tested in sensitivity analyses. Consequently, the estimated prevalence of known pre-diabetes in 2012–13 is 8.8%, and this population is eligible for testing. For each subsequent year the estimated population with known pre-diabetes is based on those with previously known pre-diabetes in addition to those with newly identified pre-diabetes.

Population with a history of gestational diabetes and polycystic ovary syndrome

A market share approach was used to estimate the population with a history of gestational diabetes and polycystic ovary syndrome (PCOS), as OGT tests are recommended in these

populations (Australian Diabetes Society & Australasian Diabetes in Pregnancy Society 2009; Jean Hailes Foundation for Women's Health 2011). Medicare data identifies a significant excess of OGT testing usage in women aged 15–44 years (compared with the usage in men of the same age group, and which is not seen in other age groups), and this was used to derive a market-based estimate of current rates of testing in this population, and to estimate projected use in 2013–14 to 2018–19 (Table 89, Appendix F).

As these data estimate OGT testing use, and include test uptake, to estimate the population eligible for testing, an uptake rate of 64.7% was derived based on data reported in Chittleborough et al. (2010). This study investigated the long-term follow-up of women with a history of gestational diabetes who enrolled into the South Australian Gestational Diabetes Mellitus Recall Register. This uptake estimate was applied to the estimated current and projected usage in this population (Table 89, Appendix F). The proportion of women who indicated that they had had a glucose test in the previous 12 months ranged from 56.3% to 75%. These upper and lower limits were applied in sensitivity analyses.

To estimate the glucose tolerance status within this population, 2.6% were assumed to have diabetes (i.e. the incidence rate of diabetes in people with pre-diabetes) and 7.6% to have pre-diabetes, based on the weighted average incident rate of pre-diabetes in a high-risk population (Table 28, 'Inputs to the economic evaluation' section) for 2012–13.

High-risk population

NHMRC guidelines recommend that periodic testing for diabetes begin in people from age 40 years. People who attend a GP and do not have a previous diagnosis of diabetes or pre-diabetes are eligible to undergo risk assessment using the AUSDRISK screening tool. Risk assessment is recommended to be repeated every 3 years. Consequently, those who underwent risk assessment in the previous 2 years are not eligible for risk assessment in the current year.

In the base-case financial model it is assumed that 14% of those eligible will undergo risk assessment, including 14% of undiagnosed diabetes and pre-diabetes. This estimate is based on the results of a survey of GPs and general practice registrars that indicated that 14% (11/78) of respondents applied the AUSDRISK tool in their usual practice (Wong, KC, Brown & Li 2011). If only GP survey respondents are considered, the use of the AUSDRISK tool decreases to 5.4% (3/56 respondents). This lower estimate was used in sensitivity analyses.

The AUSDRISK screening tool, using a score of ≥ 12 to indicate those at high risk, has been reported to have a sensitivity and specificity of 78% and 58%, respectively, in identifying undiagnosed diabetes (Colagiuri et al. 2009a). As such, 78% of people with undiagnosed diabetes and 42% (1 minus specificity of AUSDRISK) of those with NGT or pre-diabetes who

undergo risk assessment in each year would be identified as high risk (test positives). As the total number of people identified as high risk is dependent on the number of undiagnosed cases of diabetes in the risk-assessed group, the total proportion identified as at high risk is likely to vary on a yearly basis. When an AUSDRISK score ≥ 12 was applied to the baseline AusDiab population, 43% were identified as being at high risk (Colagiuri et al. 2009a), which is similar to the total proportion identified as high risk in the financial model (45.4%, Row AC, Table 43).

The estimated number of people eligible for testing in the high-risk population is presented in Table 43 for 2012–13 only. For subsequent years the population eligible for testing is influenced by the outcomes of testing in the previous year, as detailed in the following section.

Table 43: Estimated number of people eligible for testing in the high-risk population, 2012–13

	Population	Source	2012–13
K	Population projections (age 40 years or older)	ABS (2013c)	10,716,769
L	Proportion who attend a GP per year	ABS (2010)	86.1%
M	No. who attend a GP per year	$K \times L$	9,231,650
N	Proportion with known diabetes	Row E, Table 42	6.1%
O	Proportion with unknown diabetes	Row C – Row E, Table 42	6.1%
P	No. with diagnosed diabetes	$K \times N$	653,065
Q	Proportion with known pre-diabetes	Row I, Table 42	8.8%
R	Proportion with unknown pre-diabetes	Row H – Row I, Table 42	8.8%
S	No. with diagnosed pre-diabetes	$K \times Q$	940,770
T	Non-diabetic/pre-diabetic population	$K - P - S$	7,637,816
U	Proportion of uptake of risk assessment	Wong, Brown & Li (2011)	14%
V	No. risk assessed in previous 2 years	$T \times 2/3 \times U$	851,474
W	No. eligible for risk assessment in current year	$T - V$	6,904,339
X	No. risk assessed	$W \times U$	966,607
Y	Diabetes in risk assessed	$K \times O \times U$	91,024
Z	Pre-diabetes in risk assessed	$K \times R \times U$	131,125
AA	Proportion of diabetes in high-risk range	Colagiuri et al. (2009a)	78%
AB	Proportion of NGT/pre-diabetes in high-risk range	Colagiuri et al. (2009a)	42%
AC	Total proportion 'at high risk'	$Y \times AA + (X - Y) \times AB$	45.4%

	Population	Source	2012–13
AD	No. at high risk eligible for testing	X × AC	438,744

GP = general practitioner; NGT = normal glucose tolerance

In the years subsequent to 2012–13 the number of people previously risk assessed is made up of those who undertook risk assessment in the previous 2 years and were concluded as low risk, NGT or who do not uptake testing.

Testing outcomes

Under each testing scenario the population eligible for testing is affected by the number of people with known diabetes and pre-diabetes, which in turn is influenced by the accuracy and patient uptake rates of the testing strategy. As only the current testing strategy was available in 2012–13, the outcomes of testing will be described for this strategy for 2012–13 as an example.

The estimated number of people eligible for testing, by glucose tolerance status, is presented in Table 44, based on information in

Table 42 and Table 43, and in Table 89, Appendix F.

Table 44: Estimated number of people eligible for testing, 2012–13

Population	NGT	Pre-diabetes	Diabetes	Total
History of GDM/PCOS	80,479	6,251	2,139	82,254
History of pre-diabetes	-	916,310	24,460	940,770
High-risk	312,673	55,072	70,999	438,744
Total eligible for testing	393,152	959,193	97,789	1,469,134

GDM = gestational diabetes; NGT = normal glucose tolerance; PCOS = polycystic ovary syndrome

The testing pathway for women with a history of GDM/PCOS is presented in Figure 30, Appendix F. The diagnostic conclusion and test utilisation is annotated at each of the termination nodes. The probabilities at each termination node are additionally presented by glucose tolerance status. These probabilities are based on patient uptake of OGT testing in this population, assuming 100% accuracy of the test in identifying NGT, pre-diabetes and diabetes. Testing conclusions are summarised by glucose tolerance status; for example, 35.3% of women with a history of GDM or PCOS who have true NGT status are not uptake tested. Of the 64.7% who receive one OGT test, all are correctly classed as NGT.

Similarly, for people with a history of pre-diabetes or who are at high risk for diabetes, the testing pathway, diagnostic conclusions and test utilisation are presented in Figure 31, Appendix F. The probabilities at each termination node are based on patient uptake and test accuracy inputs, as used in the economic evaluation (and summarised in Figure 23, Appendix F).

Using the estimated number of people eligible for testing presented in Table 44 and the modelled probabilities regarding the combination of current test use to reach a diagnostic conclusion from Figure 30 and Figure 31, Appendix F, the total estimated test utilisation and conclusions from testing for the comparator testing strategy in 2012–13 are presented in Table 45 and Table 90, Appendix F, respectively.

Table 45: Test utilisation of current testing strategy, 2012–13

Test utilisation	True status			Total
	NGT	Pre-diabetes	Diabetes	
Total population eligible for testing	393,152	959,193	97,789	1,469,134
No tests	122,211	18,926	22,122	163,259
1 FPG test	218,871	9,124	11,331	239,326
1 FPG test and 1 OGT test	0	629,377	36,146	665,523
2 FPG tests	0	3,058	26,682	29,740
2 FPG tests and 1 OGT test	0	313,301	0	313,301
1 OGT test	52,070	4,407	1,508	57,985
HbA1c test	0	0	1,508	1,508

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin test; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Those with a diagnosis of diabetes are no longer eligible for future testing. The NGT group are eligible for risk assessment and testing in 3 years, while pre-diabetics are eligible for testing in the subsequent year.

This approach is used to estimate the number of people eligible for testing and the outcomes of testing for 2013–14, which then informs the number of people who enter the financial model in 2014–15 for each testing scenario. As the population eligible for testing in following years is dependent on the testing strategy used (as each are associated with differing rates of uptake and accuracy), the total number of patients eligible for testing will vary each year in the scenarios beyond 2014–15.

The testing pathway, diagnostic conclusions and test utilisation for the HbA1c_1 and HbA1c_2 testing strategies, respectively, are presented in Figure 32 and Figure 33, Appendix F.

Use and costs of proposed testing

Base-case (HbA1c_1) scenario

The estimated population eligible for testing and test utilisation in the HbA1c_1 scenario for 2014–15 to 2018–19 is presented in Table 46. An estimated 1.56 million tests are estimated in 2014–15, decreasing to 1.46 million in 2018–19. The decrease observed over time is primarily due to the inability of the testing strategy to identify pre-diabetes (a population in

whom more frequent testing is recommended), and secondarily to the false positive classification of people with NGT or pre-diabetes who would no longer be eligible for testing.

When the impacts of the Medicare safety net are excluded, the total cost per initial HbA1c test is \$16.43 and per confirmatory test is \$55.95 (inclusive of PEI fees and follow-up GP consultation for results), and the cost to the MBS is estimated to decrease from \$42.2 million in 2014–15 to \$40 million in 2018–19.

When the impacts of the Medicare safety net are considered, 7.2% of the population are assumed to be eligible for the total MBS rebate for HbA1c testing of \$18.97 per initial test and \$59.35 per confirmatory test. The estimated weighted cost to the MBS when the safety net is considered is \$42.5 million in 2014–15, decreasing to \$40.3 million in 2018–19.

Table 46: Total number of tests under the base-case (HbA1c_1) scenario and cost implications

HbA1c_1	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,414,557	1,403,552	1,383,063	1,360,989	1,340,203
NGT in eligible population	363,442	376,227	389,010	396,603	405,231
Pre-diabetes in eligible population	971,145	940,146	907,471	878,143	850,146
Diabetes in eligible population	79,969	87,179	86,582	86,243	84,826
Patients who do not uptake any testing	118,295	122,050	124,680	127,254	130,112
Patients who uptake 1 HbA1c test	1,143,027	1,125,117	1,103,857	1,081,615	1,060,926
Patients who uptake 2 HbA1c tests	41,705	45,181	45,279	45,078	44,405
Patients who uptake 3 HbA1c tests	111,531	111,204	109,247	107,042	104,760
Total number of tests	1,561,028	1,549,092	1,522,156	1,492,896	1,464,016
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial HbA1c test	\$16.43	\$16.43	\$16.43	\$16.43	\$16.43
Total cost per confirmatory HbA1c test	\$55.95	\$55.95	\$55.95	\$55.95	\$55.95
Cost to the MBS	\$42,165,744	\$42,205,729	\$41,538,877	\$40,780,821	\$39,982,615
<i>Including safety net impacts</i>					
Total cost per initial HbA1c test	\$18.97	\$18.97	\$18.97	\$18.97	\$18.97
Total cost per confirmatory HbA1c test	\$59.35	\$59.35	\$59.35	\$59.35	\$59.35
Cost to the MBS ^a	\$42,477,495	\$42,515,658	\$41,843,521	\$41,079,672	\$40,275,670
Cost to the patient					
Proportion bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
Cost per initial HbA1c test to the patient	\$7.77	\$7.77	\$7.77	\$7.77	\$7.77
Cost per confirmatory HbA1c test to the patient	\$8.62	\$8.62	\$8.62	\$8.62	\$8.62
Cost to patient population	\$513,725	\$510,119	\$501,308	\$491,708	\$482,187

^a Assuming 7.2% of tests are eligible for safety net

GP = general practitioner; HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule; PEI = patient episode initiation fee

Medicare data indicate that 95.9% of HbA1c tests (for diabetes management) are bulk-billed and so do not require a patient contribution co-payment; for the 4.1% not bulk-billed, an average patient co-payment of \$7.72 applies for the HbA1c test (assumed based on that for FPG testing) and \$0.90 per episode of patient initiation (of which in initial tests, 5.1% is attributed). The cost to patients / private health insurers is estimated to be \$514,000 in 2014–15, decreasing to \$482,000 in 2018–19.

The total number of tests and cost implications for this scenario, assuming 100% test performance, are presented in Table 91, Appendix F. While a decrease in the number of tests is still observed (due to the inability of the strategy to identify pre-diabetes), the decrease is less pronounced as there is no longer false positive classification of NGT and pre-diabetes.

Alternative (HbA1c_2) scenario

The estimated population eligible for testing and test utilisation in the HbA1c_2 scenario for 2014–15 to 2018–19 is presented in Table 47. An estimated 1.74 million tests are estimated in 2014–15, decreasing to 1.65 million in 2018–19. The decrease observed is primarily due to the false positive classification of people with pre-diabetes who would no longer be eligible for testing, as when all parameters of test accuracy are excluded from the analysis, an overall increase in tests is observed (Table 92, Appendix F).

When the impacts of the Medicare safety net are not considered in the analysis, the cost to the MBS is estimated to decrease from \$56.2 million in 2014–15 to \$53.7 million in 2018–19. When the impacts of the Medicare safety net are considered, the estimated weighted cost to the MBS is \$56.5 million in 2014–15, decreasing to \$54 million in 2018–19, and the cost to patients / private health insurers is estimated to be \$582,000 in 2014–15, decreasing to \$552,000 in 2018–19.

Table 47: Total number of tests under the alternative (HbA1c_2) scenario and cost implications

HbA1c_2	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,414,557	1,412,012	1,397,224	1,375,446	1,356,612
NGT in tested population	363,442	372,232	382,156	388,188	395,112
Pre-diabetes in tested population	971,145	934,099	901,086	873,404	850,467
Diabetes in tested population	79,969	105,681	113,983	113,855	111,032

Patients who do not uptake any testing	118,295	122,417	125,293	126,896	128,809
Patients who uptake 1 HbA1c test	1,047,495	1,031,316	1,014,826	997,072	982,920
Patients who uptake 2 HbA1c tests	50,310	61,689	65,128	64,911	63,457
Patients who uptake 3 HbA1c tests	198,458	196,591	191,977	186,567	181,425
Total number of tests	1,743,487	1,744,466	1,721,014	1,686,596	1,654,110
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial HbA1c test	\$16.43	\$16.43	\$16.43	\$16.43	\$16.43
Total cost per confirmatory HbA1c test	\$55.95	\$55.95	\$55.95	\$55.95	\$55.95
Cost to the MBS	\$56,150,660	\$56,844,893	\$56,184,443	\$54,960,383	\$53,702,068
<i>Including safety net impacts</i>					
Total cost per initial HbA1c test	\$18.97	\$18.97	\$18.97	\$18.97	\$18.97
Total cost per confirmatory HbA1c test	\$59.35	\$59.35	\$59.35	\$59.35	\$59.35
Cost to the MBS ^a	\$56,512,892	\$57,208,355	\$56,543,180	\$55,311,789	\$54,046,397
Cost to the patient					
Proportion bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
Cost per initial HbA1c test to the patient	\$7.77	\$7.77	\$7.77	\$7.77	\$7.77
Cost per confirmatory HbA1c test to the patient	\$8.62	\$8.62	\$8.62	\$8.62	\$8.62
Cost to patient population	\$581,824	\$582,739	\$574,998	\$563,409	\$552,380

^a Assuming 7.2% of tests are eligible for safety net

GP = general practitioner; HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule; PEI = patient episode initiation fee

The total number of tests and cost implications for this scenario, assuming 100% test performance, are presented in Table 92, Appendix F. Under these conditions the number of tests per year increases as there are fewer people with pre-diabetes falsely diagnosed with diabetes (and so these people continue to receive annual testing).

Changes in use and cost of current testing

The estimated population eligible for testing and test utilisation in the current testing scenario for 2014–15 to 2018–19 is presented in Table 48. An estimated 2.63 million FPG/OGT tests are estimated in 2014–15, increasing to 2.69 million in 2018–19, with 54,693 HbA1c tests estimated in 2014–15 on the diagnosis of diabetes, decreasing to 51,656 in 2018–19. A larger number of tests are estimated in the current scenario than either of the intervention strategies, as the current testing algorithm recommends that all equivocal and diabetes-range results be repeated—whereas in the proposed algorithms, only initial test results in the diabetes range require re-testing.

The estimated number of OGT tests in the financial model, approximately 1 million per year, is two to three times more than projections based on MBS item 66542 statistics (projected: 364,270 in 2014–15 to 430,708 in 2018–19). This reflects the uncertainty in the variables used to estimate GP administration of AUSDRISK screening in the opportunistic setting as

well as patient uptake of testing (particularly in those identified with pre-diabetes, as uptake is assumed to be 100%), and is likely to highly overestimate the cost offsets in the financial analysis. Sensitivity analyses around this uncertainty will vary patient uptake rates of OGT testing to estimate numbers closer to those projected.

When the impacts of the Medicare safety net are excluded, the total costs per initial FPG, confirmatory FPG, OGT and HbA1c test are \$2.65, \$49.90, \$57.80 (inclusive of PEI fees and follow-up GP consultation for results) and \$14.30, respectively. PEI fees and GP consultations are not included in the test cost of HbA1c on the initiation of diabetes management, as other baseline investigations are assumed to apply regardless of the testing strategy. The cost to the MBS is estimated to remain steady over the period 2014–15 to 2018–19 at approximately \$80–\$81 million per year.

When the impacts of the Medicare safety net are considered, 7.2% of the population are assumed to be eligible for the total MBS rebates per initial FPG, confirmatory FPG, OGT and HbA1c test of \$2.79, \$52.25, \$61.50 and \$16.80, respectively. The estimated weighted cost to the MBS when the safety net is considered remains steady at approximately \$80.5–\$81.5 million per year over the period 2014–15 to 2018–19.

Table 48: Total number of tests under the current testing scenario and cost implications

Current testing	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,414,557	1,432,470	1,447,474	1,458,833	1,472,254
NGT in tested population	363,442	377,317	390,622	398,916	408,195
Pre-diabetes in tested population	971,145	976,124	979,333	984,304	990,095
Diabetes in tested population	79,969	79,029	77,519	75,613	73,963
Patients who do not uptake any testing	146,313	151,125	154,710	157,277	160,247
Patients who uptake 1 FPG test	219,171	226,678	233,208	236,500	240,539
Patients who uptake 1 FPG test & 1 OGT test	658,213	660,315	662,038	664,151	666,854
Patients who uptake 2 FPG tests	25,154	25,040	24,633	24,243	23,923
Patients who uptake 2 FPG tests & 1 OGT test	312,487	313,630	314,738	316,052	317,616
Patients up uptake 1 OGT test	53,218	55,683	58,147	60,611	63,075
Patients who uptake HbA1c testing	54,693	54,225	53,464	52,486	51,656
Total initial FPG tests	1,215,026	1,225,663	1,234,617	1,240,945	1,248,932
Total confirmatory FPG tests	337,641	338,670	339,371	340,294	341,538
Total OGT tests	1,023,919	1,029,627	1,034,922	1,040,814	1,047,545
Total HbA1c tests	54,693	54,225	53,464	52,486	51,656

Current testing	2014–15	2015–16	2016–17	2017–18	2018–19
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial FPG test	\$2.65	\$2.65	\$2.65	\$2.65	\$2.65
Total cost per confirmatory FPG test	\$49.90	\$49.90	\$49.90	\$49.90	\$49.90
Total cost per OGT test	\$57.80	\$57.80	\$57.80	\$57.80	\$57.80
Total cost per HbA1c test	\$14.30	\$14.30	\$14.30	\$14.30	\$14.30
Cost to the MBS	\$81,278,339	\$80,055,563	\$80,038,760	\$80,441,545	\$80,795,511
<i>Including safety net impacts</i>					
Total cost per initial FPG test	\$2.79	\$2.79	\$2.79	\$2.79	\$2.79
Total cost per confirmatory FPG test	\$52.25	\$52.25	\$52.25	\$52.25	\$52.25
Total cost per OGT test	\$61.50	\$61.50	\$61.50	\$61.50	\$61.50
Total cost per HbA1c test	\$16.80	\$16.80	\$16.80	\$16.80	\$16.80
Cost to the MBS ^a	\$81,540,611	\$80,436,591	\$80,447,963	\$80,851,395	\$81,214,961
Cost to the patient					
Proportion FPG tests bulk-billed	83.9%	83.9%	83.9%	83.9%	83.9%
Proportion OGT tests bulk-billed	97.1%	97.1%	97.1%	97.1%	97.1%
Proportion HbA1c tests bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
Total cost per initial FPG test	\$0.39	\$0.39	\$0.39	\$0.39	\$0.39
Total cost per confirmatory FPG test	\$6.39	\$6.39	\$6.39	\$6.39	\$6.39
Total cost per OGT test	\$13.79	\$13.79	\$13.79	\$13.79	\$13.79
Total cost per HbA1c test	\$7.72	\$7.72	\$7.72	\$7.72	\$7.72
Total cost to patient population	\$853,487	\$857,365	\$860,542	\$863,952	\$868,183

^a Assuming 7.2% of tests are eligible for safety net

FPG = fasting plasma glucose; GP = general practitioner; HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule; OGT = oral glucose tolerance; PEI = patient episode initiation fee

Assuming that an average of 83.9% of people will be bulk-billed for FPG, 95.9% for HbA1c testing, and 97.1% of OGTTs (based on MBS data), these people will not be required to contribute a patient co-payment. For those not bulk-billed, an average patient co-payment of \$0.39, \$6.39, \$13.79 and \$7.72, respectively, applies per initial FPG, confirmatory FPG, OGT and HbA1c test, inclusive of \$0.90 per episode of patient initiation (not applicable for HbA1c testing on initiation of diabetes management). The cost to patients / private health insurers is estimated to be approximately \$860,000 for 2014–15 to 2018–19.

As FPG and OGT tests are considered the reference standards in this report, sensitivity and specificity of these tests is assumed to be 100%; however, as for the economic analysis, diagnostic yield estimates (Table 25) have been incorporated into the financial model to estimate the proportion of positive tests that result in the diabetes range, by glucose tolerance status. The inclusion of this information leads to approximately 54–55% of people tested requiring an OGT test due to an initial equivocal result (compared with 78% when this data is not included). These estimates are consistent with those reported for the

AusDiab study, in which 55% returned an initial equivocal FPG test result (Colagiuri et al. 2009a).

The estimated changes in use and cost of the current testing scenario excluding these diagnostic yield estimates are produced in Table 93, Appendix F.

Financial implications to the MBS

The net financial costs per year to the MBS (excluding and including safety net impacts) for each HbA1c testing scenario are presented in Table 49. Net cost savings to the MBS are associated with both HbA1c testing scenarios. For the base-case (HbA1c_1) scenario the net cost savings to the MBS is approximately \$39 million in the first year, increasing to \$41 million in the fifth year. This is due to decreasing numbers of tests estimated for HbA1c testing (as this strategy does not identify a pre-diabetic range), offset by relatively stable costs under the comparator testing strategy.

The financial implications to the MBS for the alternative (HbA1c_2) scenario exceed that of the HbA1c_1 scenario by \$14 million per year, with approximate cost savings of \$25 million in the first year, increasing to \$27 million in the fifth. This substantial difference observed in the net cost to the MBS between HbA1c scenarios is primarily driven by two factors:

1. the inability of the HbA1c_1 scenario to identify pre-diabetes; and
2. the performance of HbA1c testing in the HbA1c_2 scenario.

Table 49: Net financial cost per year to the MBS for each test scenario

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>HbA1c_1 testing strategy</i>					
<i>Excluding safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$42,165,744	\$42,205,729	\$41,538,877	\$40,780,821	\$39,982,615
Cost to the MBS of current testing	\$81,278,339	\$80,055,563	\$80,038,760	\$80,441,545	\$80,795,511
Net cost to the MBS	-\$39,112,595	-\$37,849,834	-\$38,499,882	-\$39,660,723	-\$40,812,896
<i>Including safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$42,477,495	\$42,515,658	\$41,843,521	\$41,079,672	\$40,275,670
Cost to the MBS of current testing	\$81,540,611	\$80,436,591	\$80,447,963	\$80,851,395	\$81,214,961
Net cost to the MBS	-\$39,063,117	-\$37,920,933	-\$38,604,442	-\$39,771,723	-\$40,939,291
<i>HbA1c_2 testing strategy</i>					
<i>Excluding safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$56,150,660	\$56,844,893	\$56,184,443	\$54,960,383	\$53,702,068
Cost to the MBS of current testing	\$81,278,339	\$80,055,563	\$80,038,760	\$80,441,545	\$80,795,511
Net cost to the MBS	-\$25,127,678	-\$23,210,670	-\$23,854,316	-\$25,481,162	-\$27,093,443

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>Including safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$56,512,892	\$57,208,355	\$56,543,180	\$55,311,789	\$54,046,397
Cost to the MBS of current testing	\$81,540,611	\$80,436,591	\$80,447,963	\$80,851,395	\$81,214,961
Net cost to the MBS	-\$25,027,720	-\$23,228,236	-\$23,904,783	-\$25,539,605	-\$27,168,564

HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule

The increase in net cost savings from 2014–15 to 2018–19 observed in both HbA1c scenarios is due to the decrease in the number of tests ordered per year, resulting from the false positive classification of people with NGT or pre-diabetes who would no longer be eligible for testing. There is uncertainty in the realisation of this increase in net cost savings, as the sensitivity and specificity data used in the financial model are based on heterogeneous data that draw comparisons with an imperfect reference standard (particularly in the HbA1c_2 scenario), where this is the primary cause of the decrease in test numbers. It is also likely that there will be financial implications for people falsely diagnosed with diabetes, due to closer GP management, in addition to potential increases in the service incentive payments for diabetes.

When all test performance parameters are excluded from the analyses, the pattern of net financial costs to the MBS per year is observed to be similar in terms of direction and magnitude in the base case scenario (Table 50). However, the net cost to the MBS for the HbA1c_2 scenario is observed to increase (i.e. reduced cost savings) over the 5-year projection. This is driven by an increase in the number of tests per year due to fewer people with pre-diabetes falsely diagnosed with diabetes (and so these people continue to receive annual testing).

Table 50: Net financial cost per year to the MBS for each test scenario, excluding test accuracy parameters in analysis

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>HbA1c_1 testing strategy</i>					
<i>Excluding safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$27,247,501	\$26,565,158	\$25,836,594	\$25,388,894	\$24,979,962
Cost to the MBS of current testing	\$65,534,756	\$64,481,668	\$64,455,080	\$64,846,825	\$65,199,615
Net cost to the MBS	-\$38,287,255	-\$37,916,510	-\$38,618,485	-\$39,457,931	-\$40,219,653
<i>Including safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$27,504,447	\$26,817,989	\$26,084,873	\$25,633,596	\$25,221,427
Cost to the MBS of current testing	\$65,754,225	\$64,806,907	\$64,809,186	\$65,201,306	\$65,561,680
Net cost to the MBS	-\$38,249,778	-\$37,988,919	-\$38,724,314	-\$39,567,710	-\$40,340,252

<i>HbA1c_2 testing strategy</i>					
<i>Excluding safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$27,247,501	\$27,642,067	\$27,980,709	\$28,198,605	\$28,457,115
Cost to the MBS of current testing	\$65,534,756	\$64,481,668	\$64,455,080	\$64,846,825	\$65,199,615
Net cost to the MBS	-\$38,287,255	-\$36,839,601	-\$36,474,370	-\$36,648,220	-\$36,742,500
<i>Including safety net impacts</i>					
Cost to the MBS of HbA1c testing	\$27,504,447	\$27,903,833	\$28,246,911	\$28,468,322	\$28,730,646
Cost to the MBS of current testing	\$65,754,225	\$64,806,907	\$64,809,186	\$65,201,306	\$65,561,680
Net cost to the MBS	-\$38,249,778	-\$36,903,074	-\$36,562,276	-\$36,732,984	-\$36,831,033

HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule

Testing uncertainty

Sensitivity analyses were conducted around a number of variables, including the cost of the initial FPG test, the initial proportion of known to unknown pre-diabetes patients, the number of women with a history of gestational diabetes or PCOS, and OGT testing uptake to meet estimated projected utilisation (Table 94 and Table 95, Appendix F). These were performed using the net implications to the MBS, including safety net impacts as the base-case analyses.

The financial implications were sensitive to all changes tested, except those to the population with a history of gestational diabetes or PCOS; these analyses have been summarised in Table 51 and Table 52 for strategies HbA1c_1 and HbA1c_2, respectively. Assuming that the initial FPG and HbA1c tests were offset in isolation, estimated annual cost savings increased to approximately \$50 million, while costed estimates projected based on MBS data for the number of OGT tests, rather than modelled estimates, determined annual net cost savings to the MBS of \$5 million per year for the base-case scenario, and ranged between \$5 million net costs savings to \$11 million net costs for the alternative scenario.

Table 51: Sensitivity analyses around net financial implications to the MBS, base-case (HbA1c_1) scenario

	2014–15	2015–16	2016–17	2017–18	2018–19
Base-case	-\$39,063,117	-\$37,920,933	-\$38,604,442	-\$39,771,723	-\$40,939,291
<i>Excluding test accuracy variables</i>	-\$38,249,778	-\$37,988,919	-\$38,724,314	-\$39,567,710	-\$40,340,252
Assuming all initial FPG and HbA1c tests ordered alone (base case: 5.1%)	-\$52,860,108	-\$51,950,305	-\$52,580,693	-\$55,117,400	-\$57,525,024
<i>Excluding test accuracy variables</i>	-\$48,359,327	-\$48,086,631	-\$48,448,386	-\$50,394,373	-\$52,144,850

	2014–15	2015–16	2016–17	2017–18	2018–19
Proportion of initial known pre-diabetes 0% (base-case: 50.1%) <i>Excluding test accuracy variables</i>	\$4,918,553 \$1,547,045	\$3,084,901 -\$377,892	-\$367,488 -\$3,499,093	-\$3,777,192 -\$6,388,925	-\$6,918,245 -\$9,062,711
Proportion of initial known pre-diabetes 100% (base-case: 50.1%) <i>Excluding test accuracy variables</i>	-\$82,850,028 -\$77,870,374	-\$78,745,186 -\$75,433,396	-\$76,672,076 -\$73,793,550	-\$75,606,863 -\$72,599,574	-\$74,809,686 -\$71,479,291
Uptake of AUSDRISK screening (5.4%) (base-case: 14.0%) <i>Excluding test accuracy variables</i>	-\$42,200,890 -\$40,074,617	-\$40,783,399 -\$39,315,855	-\$40,699,982 -\$39,251,482	-\$40,901,732 -\$39,226,378	-\$41,214,489 -\$39,225,305
Uptake OGT test (41%) (base-case: 64.7–100%) <i>Excluding test accuracy variables</i>	-\$3,969,754 -\$5,288,754	-\$3,536,092 -\$4,798,127	-\$4,234,859 -\$5,190,006	-\$4,983,088 -\$5,531,842	-\$5,601,455 -\$5,784,105

FPG = fasting plasma glucose; OGT = oral glucose tolerance

Table 52: Sensitivity analyses around net financial implications to the MBS, alternative (HbA1c_2) scenario

	2014–15	2015–16	2016–17	2017–18	2018–19
Base-case <i>Excluding test accuracy variables</i>	-\$25,027,720 -\$38,249,778	-\$23,228,236 -\$36,903,074	-\$23,904,783 -\$36,562,276	-\$25,539,605 -\$36,732,984	-\$27,168,564 -\$36,831,033
Assuming all initial FPG and HbA1c tests ordered alone (base case: 5.1%) <i>Excluding test accuracy variables</i>	-\$42,606,436 -\$48,359,327	-\$40,970,836 -\$45,499,652	-\$41,405,437 -\$43,250,263	-\$44,232,004 -\$43,038,484	-\$46,842,255 -\$42,646,953
Proportion of initial known pre-diabetes 0% (base-case: 50.1%) <i>Excluding test accuracy variables</i>	\$4,506,285 \$1,547,045	\$7,547,751 \$1,526,645	\$7,758,491 \$238,073	\$6,805,871 -\$1,592,692	\$5,698,624 -\$3,239,248
Proportion of initial known pre-diabetes 100% (base-case: 50.1%) <i>Excluding test accuracy variables</i>	-\$54,430,942 -\$77,870,374	-\$53,867,941 -\$75,162,620	-\$55,427,845 -\$73,199,666	-\$57,741,850 -\$71,717,669	-\$59,890,211 -\$70,274,068
Uptake of AUSDRISK screening (5.4%) (base-case: 14.0%) <i>Excluding test accuracy variables</i>	-\$27,544,805 -\$40,074,617	-\$27,243,519 -\$38,861,111	-\$28,462,995 -\$38,337,923	-\$29,945,686 -\$37,922,004	-\$31,380,007 -\$37,527,702
Uptake OGT test (41%) (base-case: 64.7–100%) <i>Excluding test accuracy variables</i>	\$9,761,837 -\$5,288,754	\$10,885,332 -\$3,712,698	\$10,291,349 -\$3,013,408	\$9,184,187 -\$2,661,288	\$8,173,310 -\$2,227,431

FPG = fasting plasma glucose; OGT = oral glucose tolerance

Costs to private health insurers and/or patients

The net financial costs per year to patients (including safety net impacts) for each HbA1c scenario are presented in Table 53. All estimated cost projections show cost savings to

patients associated with diagnostic HbA1c testing. The annual net cost savings to patients is initially approximately \$340,000 per year for the base-case (HbA1c_1) scenario and \$272,000 per year for the alternative scenario, increasing to \$390,000 per year for the base-case (HbA1c_1) scenario and \$316,000 per year for the alternative scenario over the 5-year time frame.

As all testing is assumed to occur in the outpatient setting, costs to private health insurers are not anticipated.

Table 53: Net financial costs per year to patients for each test scenario, including safety net impacts

	2014–15	2015–16	2016–17	2017–18	2018–19
HbA1c_1 testing strategy					
Cost to patients of HbA1c testing	\$513,725	\$510,119	\$501,308	\$491,708	\$482,187
Cost to patients of current testing	\$853,487	\$857,365	\$860,542	\$863,952	\$868,183
Net cost to patients	-\$339,762	-\$347,246	-\$359,234	-\$372,245	-\$385,995
HbA1c_2 testing strategy					
Cost to patients of HbA1c testing	\$581,824	\$582,739	\$574,998	\$563,409	\$552,380
Cost to patients of current testing	\$853,487	\$857,365	\$860,542	\$863,952	\$868,183
Net cost to patients	-\$271,664	-\$274,626	-\$285,545	-\$300,543	-\$315,803

HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule

As observed for the net cost to the MBS, when all test performance parameters are excluded from the analyses, the pattern of net financial costs to patients / private health insurers per year is different (Table 54), being smaller in magnitude with a less pronounced increase observed in the net cost savings from the first to the fifth year in the HbA1c_1 scenario, while the HbA1c_2 scenario is associated with an decrease in the net cost savings from the first to the fifth year.

Table 54: Net financial costs per year to private health insurers and/or patients for each test scenario, including safety net impacts, excluding test accuracy parameters in analysis

	2014–15	2015–16	2016–17	2017–18	2018–19
HbA1c_1 testing strategy					
Cost to patients of HbA1c testing	\$439,235	\$432,718	\$425,454	\$419,485	\$414,091
Cost to patients of current testing	\$554,336	\$556,857	\$558,803	\$560,612	\$563,039
Net cost to patients	-\$115,102	-\$124,140	-\$133,349	-\$141,127	-\$148,948
HbA1c_2 testing strategy					
Cost to patients of HbA1c testing	\$439,235	\$447,719	\$455,579	\$461,916	\$468,744
Cost to patients of current testing	\$554,336	\$556,857	\$558,803	\$560,612	\$563,039
Net cost to patients	-\$115,102	-\$109,138	-\$103,224	-\$98,696	-\$94,295

HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule

Discussion

Is it safe?

No data were identified that investigated the safety of the HbA1c test. However, as the test is already in use for monitoring diabetes, requires the same or fewer blood withdrawals than the comparators, and does not require taking a glucose load that may induce vomiting, it is reasonable to conclude that the test is safe.

Is it effective?

When compared against the 'gold' standard of diabetic retinopathy, three studies with some considerable biases (not least of which was including people with diabetes in the population, thus introducing a treatment effect) showed that although the accuracy of the tests varied between studies, it did not vary between the tests *within* studies. The analysis found each of the three blood glucose measures (FPG, 2hPG and HbA1c) in these studies to be equally good at predicting retinopathy. One of the studies used an old methodology for measuring HbA1c (using HbA1) and also diagnosed retinopathy based on examination only, without any photographs and external grading. This limits the applicability of the results to current practice in Australia. The more recent French study, with fewer methodological flaws and likely greater applicability to current Australian clinical practice, found that HbA1c testing and FPG testing were equally predictive of diabetes according to ROC curve analysis (0.64 for each test strategy).

The evidence-base, consistency, generalisability and applicability of this body of evidence varied from poor to good quality across the domains, as seen in Table 55.

A pooled data analysis that was not eligible for the review because it included population-based studies, and studies that did not compare HbA1c with a comparator, was also critically appraised, as it forms the basis for several recommendations about using HbA1c testing for diagnosis. This analysis also found equivalent and good discriminatory power between HbA1c, FPG and 2hPG testing to predict retinopathy. Although this study used populations ineligible for our review, and there were other problems with reporting (e.g. follow-up time not reported), its findings are still valuable for several reasons. First, it included a diverse range of populations in terms of age and ethnicity; although they were not all deemed at risk of diabetes at entry to the study, this probably does not have a large influence on whether the blood glucose measures can predict retinopathy. A bigger impact on accuracy would be found if many subjects with diabetes were included, as treatment of the known diabetics would influence the progression to diabetic retinopathy. Second, the study was very large, which enabled analysis of outcomes that are relatively rare. Third, the results are

consistent with the included studies, despite their limitations, in that no difference in accuracy was found between the tests; all were equally good at predicting retinopathy.

Table 55: Body of evidence matrix for diagnostic accuracy of HbA1c testing against diabetic retinopathy

Component	
Evidence-base ^a	D – Poor Level III studies with a high risk of bias The studies were prospective cohort studies and one cross-sectional study, level III-2. Bias associated with population selected, particularly treatment-related confounding, and methodology of the tests.
Consistency	B – Most studies consistent and inconsistency can be explained There was inconsistency between studies, reflecting differences between the populations in the studies. However, although there was between-study variation, within the studies the results consistently found no difference between the three tests.
Generalisability	C – Evidence not directly generalisable but could be sensibly applied The populations included two that were unique (American Indians and Egyptians), but one of the studies (the better one) predominantly included Europeans at high risk of diabetes (albeit including some people with diabetes).
Applicability	D – Poor Not applicable to Australian healthcare context Study settings were different in two studies and testing methodologies were mostly outdated—not-so-accurate retinopathy exams and all used pre-standardisation HbA1c assays; unsure if results can be applied to current practice in Australia.

Source: adapted from(NHMRC 2008)

^a Level of evidence determined from the NHMRC evidence hierarchy – Table 3

Due to the limitations of the findings regarding the ability of HbA1c testing and the comparators to diagnose diabetes (using the reference standard of retinopathy), the test performance of HbA1c relative to the imperfect (but currently used) blood glucose measurement test strategies was assessed in supplementary analyses.

The overall findings from the body of evidence for the diagnostic accuracy component of this abridged linked evidence assessment are summarised in Table 56.

The body of evidence received three satisfactory (C) ratings and one good (B) rating. All studies included in the assessment were cross-sectional, although some were embedded in cohort or intervention studies. Overall, the body of evidence was characterised by poor reporting of study population and methodology, which made bias difficult to assess. However, from the information that was available, the studies were methodologically quite similar in that they selected high-risk subjects and gave each two of the three tests, and assessed diagnosis by pre-specified criteria.

Table 56: Body of evidence matrix for diagnostic accuracy with no reference standard of retinopathy

Component	
Evidence-base ^a	C – Satisfactory One or two level III studies with a low risk of bias All the studies were cross-sectional in nature, level III-2; several had a low risk of bias.
Consistency	C – Satisfactory Some inconsistency reflecting genuine uncertainty around clinical question There was considerable variability in the results of the tests; however, on the whole, the studies were methodologically similar and there was limited scope for bias; thus, the variability reflects genuine uncertainty.
Generalisability	C – Satisfactory Population(s) studied in the body of evidence differ to the target population for the test, but it is clinically sensible to apply this evidence to target population ^a The populations were diverse but high-risk and sourced from community settings, as the target population would be; some studies had limited generalisability because of the ethnicity of the subjects, but most in diabetes meta-analysis were generalisable.
Applicability	B – Good Applicable to Australian healthcare context with few caveats Study settings and testing methodologies were similar to Australia.

Source: adapted from(NHMRC 2008)

^a Level of evidence determined from the NHMRC evidence hierarchy – Table 3

The HbA1c test is intended for use in community settings in Australia, for the general population at risk for diabetes, and this is a diverse population. Selection bias and the applicability of the included studies may therefore not be as much of an issue as it may be in a more defined population. Additionally, the tests used in the studies are very common and usually conducted in the same, or very similar, ways around the world. Results are usually returned from laboratories as a number and are classified according to pre-specified criteria. Thus, there is probably only a small likelihood of bias from the conduct or interpretation of the tests.

Concordance between the tests was very poor, and there was considerable variability in the diagnostic accuracy of HbA1c testing in the diagnosis of diabetes. The amount of variability made it very difficult to draw conclusions; however, given that the studies were, on the whole, conducted in a similar manner, it is likely that the variability reflects genuine population differences or clinical uncertainty. Also, the cut-off points made a considerable difference to the sensitivity and specificity of the HbA1c test—the lower the cut-off for HbA1c, the higher the sensitivity but the lower the specificity. Should the test be used for diagnosis, it would require new guidelines that should consider the optimal HbA1c cut-off point with relation to the test accuracy at that point, as well as the implications for false positives (with low specificity) and false negatives (with low sensitivity). In this case it would probably be better to err on the side of high sensitivity and low specificity, as the first-line treatment for diabetes is lifestyle intervention, which would entail almost no harm to anyone falsely diagnosed with diabetes.

The clinical impact (one of the domains included in the body of evidence matrix when direct evidence is available) could not be formally determined through the evidence linkage, as changes in patient management were not reported in the evidence-base. However, as described previously, it is unlikely that the management of diabetes and pre-diabetes patients identified with HbA1c testing will differ from what occurs with FPG, with/without OGT, testing currently. The only concern would be if the treating health professional decided that FPG and/or OGT testing is required even after an initial HbA1c test (i.e. management would not change but an additional unnecessary test would be done). There is no evidence available to substantiate speculation in either direction.

Many opinions located in the literature search espoused greater patient acceptance of the HbA1c test compared with the other tests, but no evidence could be identified to support this.

Are there other relevant considerations?

Imperfect reference standard

In this assessment the reference standards used (FPG and 2hPG) are imperfect and these two tests, when compared with each other or used together and compared with one test alone, diagnose different people with diabetes (Colagiuri et al. 2011). Indeed, an International Expert Committee (Nathan & The International Expert Committee 2009) on diagnosis of diabetes declared that there was 'no single assay related to hyperglycaemia that can be considered the gold standard, as it relates to the risk for microvascular or macrovascular complications'. This is probably partly explained by the daily variation in blood glucose levels (due to, e.g., exercise or acute illness, medications or other illnesses), some of the practical issues of collecting and storing blood (because the concentration of glucose falls quickly ex vivo) and the factors that can impact on the OGT test, including correct preparation. Thus, it should be considered that all three tests diagnose different people with diabetes, and that the comparators cannot be considered perfect, even when criteria from both FPG and OGT testing (i.e. the maximum information) are used to diagnose diabetes. It should also be noted that confirmatory blood tests were not conducted in any of the studies included in the assessment, and this, according to NHMRC guidelines, should happen in Australia. This could have considerable impact on the diagnostic accuracy of all three tests, especially given the day-to-day variability of FPG and 2hPG levels.

Is HbA1c testing suitable for everyone?

It is clear that in some groups, such as those with haemoglobinopathies or other disorders affecting red cell turnover, the HbA1c assay may not be the most reliable test for diagnosis of diabetes (the same applies for monitoring diabetes). The test could not, therefore, completely replace the comparator tests.

What are the economic considerations?

Economic evaluation

The quantitative results derived from the model-based economic evaluation are highly uncertain. Accurate knowledge of test performance (i.e. sensitivity and specificity) is essential to assess the cost-effectiveness of a diagnostic test; however, in this analysis, there was little good quality data to accurately identify these parameters. Where sensitivity and specificity were incorporated into the economic model, they were based on findings from the 'Effectiveness' section of the report, but given the high degree of variability and comparisons made to imperfect reference standards, a high degree of uncertainty remains. The inclusion of these estimates in the stepped model has a substantial impact on the results of the economic evaluation. Irrespective of the inclusion of test accuracy data, the base case scenario (which does not identify pre-diabetes) appears consistently less costly and less effective than the comparator (SW quadrant of CE plane).

Before the inclusion of test accuracy data in the alternative scenario, HbA1c testing is observed to dominate current testing—due to the requirement for fewer confirmatory tests and improved benefits because of improved patient acceptance and more pre-diabetes identified. The inclusion of these estimates in the alternative scenario alters the cost-effectiveness of the intervention substantially, from being likely to be relatively cost-effective to being dominated. This is due to increased expense (increased false positives who incur treatment costs, and false negatives who have a delayed diagnosis, potentially not until symptoms occur), and reduced effectiveness, due to poorer quality of life associated with increased levels of symptomatic disease.

Sensitivity analyses conducted were fairly robust around the base-case ICERs in that the overall conclusion of cost-effectiveness did not often change (e.g. where the base-case ICER existed in the SW plane, so too did the ICERs in the majority of sensitivity analyses tested). When accuracy data is not included in the sensitivity analyses, the base-case scenario continues to be less costly and less effective than the comparator in all analyses tested, except the cost of undiagnosed pre-diabetes (relative to diagnosed pre-diabetes). As this strategy does not identify people with pre-diabetes, when the cost of the undiagnosed pre-diabetes health state is comparatively higher than that of the diagnosed health state, HbA1c testing is dominated. In the alternative scenario HbA1c testing is observed to dominate current testing in all scenarios tested, except where there is improved uptake of FPG testing as opposed to HbA1c testing. In these scenarios HbA1c testing is observed to be less costly and less effective than the comparator. As it is generally accepted that uptake will be improved with HbA1c testing, the realisation of these scenarios are unlikely.

As HbA1c testing appears to be equally predictive of retinopathy as FPG or OGT testing, and these are known to be imperfect reference standards, the best estimate of its cost-

effectiveness is likely to lie between estimates that either include or do not include test accuracy data. However, it should be noted that where test accuracy data has not been included, sensitivity and specificity parameters of testing have been assumed to be 100%, which is likely to overestimate the performance of HbA1c and currently available (imperfect) tests.

Financial implications

A number of issues are present that contribute to uncertainty in the results of the financial analysis. Those relating to uncertainty in the estimated population likely to be tested include the proportion of pre-diabetics undiagnosed, uptake rates of diabetes risk assessment (given that screening is recommended opportunistically), patient uptake of testing, and accuracy of the comparator and intervention tests. These issues are further compounded by recommendations for repeated testing in subsequent years. Additionally, there is substantial uncertainty in the cost of the initial FPG test (which varies depending on whether the test is ordered alone or with other tests listed in the same item number), and this leads to overall uncertainty in the costs that are offset with the introduction of HbA1c testing.

The inclusion of accuracy data does not have a substantial impact on the net financial implications of the base-case scenario (which identifies diabetes only). Before these data are included, annual net cost savings are estimated in the range of \$38–\$40 million, increasing to \$38–\$41 million when data are included. However in the alternative scenario (which identifies diabetes and pre-diabetes), the inclusion of test accuracy data leads to a substantial increase in costs. Before data are included, net cost savings of \$37–\$38 million per year are estimated, decreasing to \$23–\$27 million per year when data are included. This is primarily driven by an increase in the number of HbA1c tests ordered per year, from approximately 1.3–1.7 million.

The financial implications were sensitive to most changes tested. This was particularly noticeable if (i) if the initial known proportion of pre-diabetes in the population is varied (0% known, net costs up to \$8 million and 100%, net cost savings up to \$83 million) and (ii) where there is a reduction in OGT testing uptake to meet estimated projected numbers based on current utilisation of OGT testing (MBS item 66542) (cost savings between \$4–\$6 million estimated for the base case scenario and net costs up to \$11 million in alternative scenario). As it may be unlikely that the initial proportion of people with known pre-diabetes be at either extreme, these estimated costs and cost savings are unlikely to be realised, while substantially reduced cost savings (or net costs) associated with reducing OGT test uptake to closer to the estimated projected utilisation are much more likely.

Conclusions

Safety

Although safety was not investigated in any of the studies considered for the assessment, the HbA1c test can be considered as safe or safer than the comparators. The index test and the comparators are already in use in Australia.

Effectiveness

An abridged linked evidence approach was taken for this assessment, limiting the analysis to diagnostic accuracy and change in management because the other component of the linked evidence approach (treatment effectiveness) is well established.

A variable body of evidence supported the accuracy of HbA1c testing in the diagnosis of diabetes against the reference standard of diabetic retinopathy. Although the quality of the evidence was only poor to good, and the results were inconsistent between studies and difficult to apply to the current clinical situation in Australia, the findings were consistent in terms of within-study test comparisons, in that all the tests had equivalent discriminatory power for predicting retinopathy. This finding was echoed by a large pooled analysis of studies. This analysis was not eligible for inclusion due to the populations included; however, it is the primary evidence source for recommendations about the accuracy HbA1c testing for diabetes diagnosis from the relevant groups in Australia, and is also part of the body of evidence that informs the WHO recommendation to use HbA1c for the diagnosis of diabetes.

To supplement the analysis using retinopathy as the reference standard, diagnostic accuracy between HbA1c testing and the comparator (imperfect) test strategies was undertaken. The level of evidence was generally satisfactory for all the cross-sectional studies included. The quality of the studies was in many cases difficult to ascertain due to poor reporting but, from the information that was available, methodology was consistent across all studies. There is probably little likelihood of bias in the conduct or interpretation of the tests. Although the studies were conducted in diverse populations, all were at risk for diabetes. As the population that the test would be used for in Australia is also diverse, the body of evidence is somewhat generalisable to Australia, with some limitations due to ethnicity. The conduct of the tests and the settings in which they were undertaken are applicable to the Australian setting. Unfortunately, however, the use of the imperfect reference standard makes the results unreliable.

Diagnostic accuracy

It is difficult to draw conclusions about the accuracy of HbA1c testing in the diagnosis of diabetes because of the considerable heterogeneity in the results. It is clear that the three tests (HbA1c, FPG and 2hPG) diagnose different people, as evidenced by the low concordance rates. The sensitivity and specificity of the HbA1c test varies by cut-off point, and also between studies with the same cut-off points. Diagnostic accuracy was satisfactory in some studies and unsatisfactory in others. The same is true of diagnosing pre-diabetes; there was too much variability in the results to be able to draw any conclusions about the accuracy of HbA1c testing. In none of the included studies was a confirmatory test of any type undertaken. According to current practice guidelines in Australia, and also recommended by WHO, diabetes diagnosis should be confirmed by the same test at a later time (or an OGT test in the case of an FPG result in the intermediate range) (Colagiuri, S et al. 2009; Nathan & The International Expert Committee 2009). It is likely that confirmatory tests would have had a considerable impact on the diagnostic accuracy of HbA1c versus FPG and OGT tests, given the variability of the latter two on a daily basis.

Other relevant considerations

The impact of the imperfect (but currently used) reference standard on the supplementary test accuracy results should be considered. While all three tests are equally predictive of retinopathy, they diagnose different people and none alone could be considered a gold standard.

Given that diagnosis and treatment of diabetes at the earliest stage possible is recommended, the HbA1c test may have some advantages in terms of patient compliance as it requires no preparation and can be done at any time of the day. This could help people obtain a diagnosis sooner than they may have, had they been putting off having a fasting test or an OGT test.

Should the test become available for diagnosis, guidelines would need to carefully assess which cut-off points are best for defining a pre-diabetic state.

Economic considerations

Conclusions regarding the cost-effectiveness of HbA1c testing for the diagnosis of diabetes are difficult to draw, given the uncertainties around inputs, particularly regarding test accuracy. Irrespective of the inclusion of test accuracy data, the base-case scenario (which does not identify pre-diabetes) appears consistently less costly and less effective than the comparator (i.e. the ICERs lie in the SW quadrant of the CE plane). The inclusion of test accuracy estimates in the alternative scenario alters the cost-effectiveness of the intervention substantially, from being likely to be relatively cost-effective to being

dominated. Sensitivity analyses conducted were fairly robust around the base-case ICERs in that the overall conclusion of cost-effectiveness did not often change (e.g. where the base-case ICER existed in the SW plane, so too did the ICERs in the majority of sensitivity analyses tested).

The true measure of cost-effectiveness of HbA1c testing is likely to lie between estimates that either include (i.e. ICERs in the vicinity of \$6,133/QALY; SW quadrant of CE plane for HbA1c_1 scenario or dominated for the HbA1c_2 scenario) or do not include test accuracy data (i.e. ICERs in the vicinity of \$16,762/QALY; SW quadrant of CE plane for HbA1c_1 scenario or dominant for the HbA1c_2 scenario). However, it should be noted that when test accuracy data were not included in the analyses, 100% test performance has been assumed and this is likely to overestimate the performance of HbA1c testing as well as the currently available tests.

The limited clinical data suggest that HbA1c testing may have similar (poor) performance to the current testing strategies at predicting diabetic retinopathy (the appropriate reference standard)—and thus, by definition, diabetes. If these data are accurate, overall test accuracy is likely to be similar between the HbA1c_2 test strategy (which includes pre-diabetes) and FPG with/without OGT testing. However, the test accuracy in each testing strategy would be considerably lower than 100%, and it is likely that different groups of patients within the spectrum of diabetes presentation would be identified by each of the strategies. If this is the case, the most efficient scenario from an economics perspective would be that which identifies both pre-diabetes and diabetes (the alternative scenario, HbA1c_2). However, the clinical uncertainty associated with this conclusion is significant.

Costing

The expected uptake of HbA1c testing for the diagnosis of diabetes is estimated to be in the range 1.3–1.8 million tests for 1.1–1.4 million patients per year. However, there is substantial uncertainty in some inputs used to estimate these numbers, including GP administration of diabetes risk assessment, patient uptake of testing and test accuracy.

The total net cost to the MBS (including costs offset by currently available tests) for HbA1c testing is estimated to range between cost savings of \$40 million and net costs of \$11 million annually. Given the uncertainty in the estimated population eligible for testing and other testing parameters, the financial implications to the MBS cannot be confidently estimated.

Appendix A Health Expert Standing Panel and Assessment Group

MSAC Application 1267, HbA1c testing in the diagnosis of diabetes

Health Expert Standing Panel (HESP)

<u>Member</u>	<u>Expertise or affiliation</u>
Prof Stephen Colagiuri	Professor of Metabolic Health Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders The University of Sydney

Assessment group

AHTA, University of Adelaide, South Australia

<u>Name</u>	<u>Position</u>
Ms Jacqueline Parsons	Team leader (Medical HTA)
Ms Arlene Vogan	Health economist
Dr Judy Morona	Research officer
Ms Camille Schubert	Team leader, senior health economist
Assoc Prof. Tracy Merlin	Managing director

Noted conflicts of interest

There were no conflicts of interest.

Appendix B Search strategies

HTA websites

AUSTRALIA

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) <http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm>

Centre for Clinical Effectiveness <http://www.southernhealth.org.au/cce>

Centre for Health Economics, Monash University <http://www.buseco.monash.edu.au/centres/che/>

AUSTRIA

Institute of Technology Assessment / HTA unit <http://www.oeaw.ac.at/ita>

CANADA

Institut national d'excellence en sante et en services sociaux <http://www.inesss.qc.ca/en/home.html>

Alberta Heritage Foundation for Medical Research (AHFMR) <http://www.ahfmr.ab.ca/publications.html>

Alberta Institute of Health Economics <http://www.ihe.ca/>

The Canadian Agency for Drugs And Technologies in Health (CADTH) <http://www.cadth.ca/index.php/en/>

Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database <http://www.mycabot.ca>

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <http://www.chepea.org>

Centre for Health Services and Policy Research (CHSPR), University of British Columbia <http://www.chspr.ubc.ca>

Health Utilities Index (HUI) <http://www.fhs.mcmaster.ca/hug/index.htm>

Institute for Clinical and Evaluative Studies (ICES) <http://www.ices.on.ca>

Saskatchewan Health Quality Council (Canada) <http://www.hqc.sk.ca>

DENMARK

Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.sst.dk/english/dacehta.aspx?sc_lang=en

Danish Institute for Health Services Research (DSI) <http://dsi.dk/english/>

FINLAND

Finnish Office for Health Technology Assessment (FINOHTA) <http://finohta.stakes.fi/EN/index.htm>

FRANCE

The Haute Autorité de santé (HAS) - or French National Authority for Health http://www.has-sante.fr/portail/jcms/c_5443/english?cid=c_5443

GERMANY

German Institute for Medical Documentation and Information (DIMDI) / HTA <http://www.dimdi.de/static/en/index.html>

Institute for Quality and Efficiency in Health Care (IQWiG) <http://www.iqwig.de>

THE NETHERLANDS

Health Council of the Netherlands Gezondheidsraad <http://www.gezondheidsraad.nl/en/>

Institute for Medical Technology Assessment (Netherlands) <http://www.imta.nl/>

NEW ZEALAND

New Zealand Health Technology Assessment (NZHTA) <http://nzhta.chmeds.ac.nz/>

NORWAY

Norwegian Knowledge Centre for the Health Services <http://www.kunnskapssenteret.no>

SPAIN

Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud "Carlos III"/Health Technology Assessment Agency (AETS) <http://www.isciii.es/>

Andalusian Agency for Health Technology Assessment (Spain) <http://www.juntadeandalucia.es/>

Catalan Agency for Health Technology Assessment (CAHTA) <http://www.gencat.cat>

SWEDEN

Center for Medical Health Technology Assessment <http://www.cmt.liu.se/?l=en&sc=true>

Swedish Council on Technology Assessment in Health Care (SBU) <http://www.sbu.se/en/>

SWITZERLAND

Swiss Network on Health Technology Assessment (SNHTA) <http://www.snhta.ch/>

UNITED KINGDOM

National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) <http://www.hta.ac.uk/>

NHS Quality Improvement Scotland <http://www.nhshealthquality.org/>

National Institute for Clinical Excellence (NICE) <http://www.nice.org.uk/>

The European Information Network on New and Changing Health Technologies <http://www.euroscan.bham.ac.uk/>

University of York NHS Centre for Reviews and Dissemination (NHS CRD) <http://www.york.ac.uk/inst/crd/>

UNITED STATES

Agency for Healthcare Research and Quality (AHRQ) <http://www.ahrq.gov/clinic/techix.htm>

Harvard School of Public Health <http://www.hsph.harvard.edu/>

Institute for Clinical and Economic Review (ICER) <http://www.icer-review.org/>

Institute for Clinical Systems Improvement (ICSI) <http://www.icsi.org>

Minnesota Department of Health (US) <http://www.health.state.mn.us/htac/index.htm>

National Information Centre of Health Services Research and Health Care Technology (US) <http://www.nlm.nih.gov/hsrph.html>

Oregon Health Resources Commission (US) http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml

Office of Health Technology Assessment Archive (US) <http://fas.org/ota>

U.S. Blue Cross/ Blue Shield Association Technology <http://www.bcbs.com/blueresources/tec/>

Evaluation Center (Tec)

Veteran's Affairs Research and Development Technology
Assessment Program (US)

<http://www.research.va.gov/default.cfm>

Bibliographic databases

Electronic database	Time period
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	
Web of Science – Science Citation Index Expanded	
Current Contents	
Embase.com (including Embase and Medline)	
PubMed	
CINAHL	
EconLit	
PsycINFO (for ethical issues only)	

Additional sources of literature

Source	Location
Internet	
NHMRC – National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
International Clinical Trials Registry Platform	
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand searching (journals in last 2 years)	
Studies other than those found in regular searches	Library or electronic access
Expert clinicians	MSAC Medical Expert Standing Panel (MESP)
Peering	
All included articles had their reference lists searched for additional relevant source material	

Additional databases searched for economic evaluations

Electronic database
Cost-effectiveness Analysis (CEA) Registry
Database of Abstracts of Reviews of Effects or Reviews of Effects (DARE)
Health Technology Assessment database
NHS Economic Evaluation Database (NHS EED)
European Network of Health Economics Evaluation Databases (EURONHEED)

Appendix C Study profiles of included studies

Table 57: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes with retinopathy as the reference standard

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	Reference standard	Index test	Comparator(s)	Outcomes
Massin (2011) Central Western France	Level III-2 Population-based longitudinal cohort study, recruited in 1994–96 and followed up for 9–10 years; invited at 10 years to participate in microvascular examination.	High risk of bias as it included people with diabetes—therefore treatment effect likely. No applicability concerns in terms of setting or population.	N=733 people who were recruited into longitudinal study; n=237 had been treated for diabetes or had a diabetes-range FPG level during the 9-year study period; n=246 had IFG level at any time during study; n=249 with normal FPG level during study. Average age at baseline 52 years. No other descriptors provided.	N=33 excluded because photographs not gradable; no other criteria described.	Retinal photography by non-mydratic retinal camera, all graded by same observer according to simplified Wisconsin protocol.	HbA1c continuum	FPG continuum	ROC analysis, sensitivity and specificity, AUC, predefined and optimal cut-offs
McCance (1994) Gila River Indian community, Arizona, USA	Level III-2 Population-based longitudinal cohort study that has been going since 1965; all community members over 5 years invited to participate.	High risk of bias as it used HbA1c as measure for many subjects, and retinopathy diagnosed by direct ophthalmic examination; likely that quality of tests	N=927 people but participation rates not reported. Included subjects not described, other than being 25 years of age or older. Baseline measures from Jan 1982 to Nov 1991, mean follow up of 4.5 years.	Excluded subjects with retinopathy or receiving insulin or oral hypoglycaemics; also excluded those with missing blood glucose measures at baseline.	Ophthalmoscopic exam by physician.	HbA1c continuum	FPG and 2hPG continuum	ROC analysis, sensitivity, specificity, predefined and optimal cut-offs

		has changed since this study was done. Limited applicability to Australian setting.						
Englegau (1997) Cairo and rural surrounds, Egypt	Level III-2 High-risk subgroup of randomly sampled population invited for further testing including OGT and retinal photographs; further testing appears concurrent.	Low risk of bias in conduct of study, although likely that quality of tests has changed since this study was done. Limited applicability to Australia given Egyptian setting.	N=1,018 people who had a random blood glucose measure of ≥ 5.6 mmol/L at baseline survey, plus random sample of those below; about 2/3 sample at high risk or with diabetes. Analysis conducted with and without people with diabetes. Description limited; mean age 45 years, 41% male.	Analysis included subjects with all blood glucose and retinopathy measures; overall participation rate 50%.	Retinal photo taken and graded by external staff using modified Airlie house classification.	HbA1c continuum	FPG and 2hPG continuum	ROC analysis, only sensitivity and specificity reported

Table 58: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes: studies included in meta-analysis

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
--------------------	---	--------------------	------------------	------------------------------	----------------------------	------------------------	---	---	----------

Mostafa (2010a) (also reported in Mostafa (2013) and Mostafa (2010b)) Leicester-shire, England	Level III-2 Population-based study recruited from primary care, tests undertaken at same time but blinding unclear. All participants with result on OGT test in diabetes range underwent second OGT test.	Low risk of bias. No applicability concerns. Appropriate cut-offs.	N=9,494, n=40 excluded as under 40 years of age and n=198 excluded due to incomplete results. 47.7% male, mean age 57.3 ± 9.7 years, 74.7% white European, 22.8% South Asian and 2.5% other. Sourced from primary care population for two previous systematic screening programs— one general but where 2/3 had a risk factor, and in the other all had a risk factor—total cohort 75% with a risk factor.	Cohort included males and females aged 25–75 years from Leicestershire. At-risk had one or more of: previous IGT/IFG, history of CVD, hypertension, dyslipidaemia, gestational diabetes, PCOS and overweight first-degree relative with type 2 diabetes, overweight and sedentary, or obese. Excluded people under 40 years of age as no white Europeans in that group. Excluded n=198 due to incomplete test results.	6.0% ≥ HbA1c <6.5%; 5.7% ≥ HbA1c <6.5%	≥6.5%	Included IGT and IFG: 2hPG ≥7.8 mmol/L	2hPG ≥11.1 mmol/L	Diagnostic accuracy 2x2 table (sensitivity, specificity, AUROC for some)
Bianchi (2012) Italy	Level III-2 Population-based study recruited from community referrals to diabetes clinic.	Low risk of bias. No applicability concerns.	N=844 participants, 44% male, mean age 49.5 ± 11 years, all referred because of suspected diabetes and therefore at high risk.	N=766 included in analysis but exclusions not described.	5.7–6.4% But pre-diabetes results not reported.	≥6.5%	Included IGT: 7.8–11.1 mmol/L on OGT test; IFG: 6.1–7.0 mmol/L on FPG test; but results not reported	FPG >7.0 mmol/L; or 2hPG >11.1 mmol/L	2x2, some diagnostic accuracy, some ROC analysis
Hutchinson (2013) Tromso, Norway	Level III-2 Population-based study recruited from longitudinal study.	Unclear risk of bias. Some concerns about applicability of index test due	All participants in larger population study had HbA1c test, those in range 5.8–6.9% plus random sample of others	N=4,393 invited to participate, n=3,476 completed OGT testing. Exclusions not described.	Not reported	≥6.5%	Not reported	FPG >7.0 mmol/L; or 2hPG >11.1 mmol/L	2x2

		to timing.	recruited into OGT test study. Overall, 79% of participants had original HbA1c $\geq 5.7\%$ so considered high-risk. N=3476 participants, 51% male, age under 60 years 35%, age 60 years or older 65%.						
Alqahtani (2013) Khamis Mushayt, Saudi Arabia	Level III-2 Database review of participants who visited outpatient clinic of armed forces hospital and had tests on suspicion of diabetes.	Low risk of bias in study design. Some concerns about applicability given very specific population; unlikely to be relevant to Australia.	N=1,814 records of patients who had undergone concurrent OGT, FPG and HbA1c testing on suspicion of diabetes. N=622 males (34.3%), mean age 54.3 ± 13.6 years.	Database review so the only inclusion criteria were having the test results available and 'suspicion of diabetes', but this not described.	IFG: 5.7–6.4%	$\geq 6.5\%$	IFG: FPG 5.6–6.9 mmol/L; IGT: 2hPG 7.8–11.0 mmol/L	FPG ≥ 7.0 mmol/L; 2hPG ≥ 11.1 mmol/L	3x3 table
Baral (2000) Dharan, Nepal	Level III-2 Hospital-based study of patients referred for OGT testing.	Risk of bias unclear overall. Reference standard cut-offs differ from Australia, very little information about study design. Some concerns about applicability,	N=920 subjects referred to hospital for OGT testing. Age range 30–65 years. No other details.	Pregnant women excluded. No other details.	Not reported	$\geq 6.0\%$	FPG 6.1–6.9 mmol/L; 2hPG 7.8–11.1 mmol/L	FPG ≥ 7.0 mmol/L; 2hPG ≥ 11.1 mmol/L	2x3 table

		no information on patient selection, Nepalese population unlikely to be relevant to Australia.							
Cosson (2011) Bondy, France	Level III-2 Hospital-based study of patients referred for weight management.	Low risk of bias. Applicable to Australian setting. Relevant cut-off points.	N=1,157 consecutive patients referred to hospital weight-management clinic who fitted ADA risk criteria for diabetes and underwent diabetes tests; 17% male, mean age 41 ± 13 years.	Exclusions not detailed.	5.7%≥ HbA1c <6.5%	≥6.5%	5.5 mmol/L≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmo l/L	3x3 table, ROC analysis
Du (2013) Wuhan, China	Level III-2 Patients referred to diabetes outpatient clinic of hospital in China.	Low risk of bias. Applicability to Australian setting unclear as Chinese study. Relevant cut-off points.	N=2,856 in sample, n=2,318 recruited patients referred to hospital outpatient clinic on suspicion of diabetes; age 18–80 years, mean 47.5 years.	Exclusions were chronic disease (n=45), blood disorder (n=13), pregnancy (n=112), other medical reason (n=10), currently have diabetes (n=157), rejection of blood collection (n=103) and no information on tests (n=98), leaving total sample of n=2,318.	5.7%≥ HbA1c <6.5%	≥6.5%	100 mmol/L≥ FPG <126 mg/dL	FPG ≥126 mg/d L	2x2 table, ROC analysis
Lee, H (2013) 10 sites in South Korea	Level III-2 10 hospital outpatient clinics in South Korea, each participant had OGT and HbA1c as part of battery of	Low risk of bias. Applicability to Australian setting unclear as Korean study. Relevant cut-off points.	N=4,616 patients who were referred to or voluntarily attended hospital clinic for diabetes diagnosis; 55% male, mean age 50 ± 13 years.	Excluded patients with known diabetes, renal impairment, life-shortening conditions, conditions known to impact on glucose tolerance. Numbers excluded not given.	Not reported	≥6.1%		FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmo l/L	2x2 table, ROC analysis

	tests.								
Lu (2010) Melbourne, Australia	Level II-2 All patients referred to a statewide private pathology service in Victoria, Australia.	Low risk of bias. Highly applicable to Australian setting. Relevant cut-off points.	Data from n=2,494 patients referred by GPs for OGT and HbA1c testing to private pathology service during 2003–08. No description of study population.	Excluded patients without concurrent HbA1c and OGT test results.	Two categories: 5.6–6.0%; 6.1–6.4%;	Two categories: 6.5–6.9% ≥7.0%	5.6 mmol/L≥ FPG <6.9 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	3x3 table
Manley (2009) and Manley (2010) Melbourne, Australia; Birmingham, UK	Level III-2 Study of patients in two settings (UK and Australia) referred for OGT testing.	Risk of bias is unclear as population not described well. Applicable to Australian setting. Different cut-offs used for diagnosis.	High risk (UK: patients with FPG 6.1–6.9 mmol/L; Aust: patients with elevated glucose, symptoms or medical risk) patients referred for OGT testing; UK participants n=500, mean age 62 years, 52% male; Aust participants n=1,182, mean age 57 years, 54% male.	UK excluded people with initial FPG ≥7.0 mmol/L; Aust excluded people with 'more than a trace of glucose in their urine'. Also n=7 patients with HbA1c 7.2–13.3% did not do OGT testing.	Not reported	≥6.0%	6.1 mmol/L≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	2x3 table, ROC analysis
Ko (1998a) and Ko (1998b) Hong Kong, China	Level III-2 Study of Hong Kong Chinese referred to hospital for diabetes testing.	Risk of bias unclear due to limited reporting. Limited applicability to Australia given Chinese setting. Different cut-offs used.	Hong Kong Chinese referred because of high risk for diabetes to hospital diabetes clinic for testing; n=2,877, males 19%, mean age 36.6 ± 0.2 years.	All included subjects had known risk factors for glucose intolerance. No exclusions described.		≥5.5% ≥6.1%	7.8 mmol/L≥ 2hPG <11.1 mmol/L (WHO 1985)	FPG ≥7.8 mmol/L and/or 2hPG ≥11.1 mmol/L (WHO 1985); FPG ≥7.0 mmol/L (ADA 1997)	2x2 table, ROC analysis
Peter (2011) Tubingen,	Level III-2	Risk of bias unclear as	Caucasian participants at risk of	Participants were not taking medication known to affect insulin	5.6%> HbA1c	≥6.5%	6.1 mmol/L≥ FPG	FPG ≥7.0 mmol/L	3x3 table,

Germany	Study of participants in ongoing cohort studies about pathogenesis of diabetes.	selected population not well described. Probably applicable to Australian setting but limited information provided. Different cut-offs for pre-diabetes used.	diabetes, involved in ongoing studies of pathogenesis of diabetes over 10-year period; mean age 40.3 ± 13.4 years, 65% female.	sensitivity or secretion. No other exclusions described, numbers not provided.	<6.5%		<7.0 mmol/L; 7.8 mmol/L \geq 2hPG< 11.1 mmol/L	L; 2hPG ≥ 11.1 mmo I/L	Additional 2x2 analysis
Saiedullah (2011) Dhaka, Bangladesh	Level III-2 Cross-sectional study of people who underwent tests at Institute of Health Sciences in Dhaka, 2009–10.	High risk of bias due to very limited description of population and methods. Applicability concerns as conducted in Bangladesh. Different cut-offs for diabetes used.	Convenience sample of n=800, 40% males and mean age 43.32 ± 12.19 years; range 11–85 years. No other description of population.	None described.	6.0% \geq HbA1c <6.5%	$\geq 6.5\%$	6.1 mmol/L \geq FPG <7.0 mmol/L; 7.8 mmol/L \geq 2hPG <11.1 mmol/L	FPG ≥ 7.0 mmol/ L; 2hPG ≥ 11.1 mmo I/L	3x3 table
Marini (2012a) and Marini (2012b) Rome and Cantanzaro, Italy	Level II-2 Cross-sectional study of people assessed for cardiometabolic risk factors; two papers reported different parts of	Some concerns with selection bias as all participants self-referred; other aspects of study low	Caucasian subjects who underwent OGT testing as part of a battery of tests; two papers give different numbers in the study. 2012a: n=2,051 (included n=1,091), mean age 44 years,	Included people aged 20 years or older with one or more of: hypertension, dyslipidaemia, overweight/obesity or family history of diabetes. Excluded subject with known diabetes or taking hypoglycaemic medication (n=611), glucocorticoid treatment, chronic pancreatitis, history of malignant	5.7% \geq HbA1c <6.5%	HbA1c $\geq 6.5\%$	5.6 mmol/L \geq FPG <7.0 mmol/L; 7.8 mmol/L \geq 2hPG <11.1 mmol/L	FPG ≥ 7.0 mmol/ L; 2hPG ≥ 11.1 mmo I/L	2x2 tables, one for diabetes, one for pre- diabetes; some ROC analysis

	the same study.	concern. Applicable to population in question; high-risk population in Italy.	33% male; 2012b: n=780, mean age 45 ± 13 years, 42% male (exclusions not described).	disease, chronic gastrointestinal disease, history of alcohol or drug abuse (n=91); n=330 excluded due to missing data. Total n=1,019. Also excluded if positive to hepatitis C or B, or if anaemic, but numbers not provided. Study on pre-diabetes excluded people found to have diabetes from analysis.					
Cavagnoli (2011) Porto Alegre, Brazil	Level III-2 Study of high-risk subjects referred to hospital clinical pathology department for OGT tests.	Low risk of bias. Few applicability concerns; Brazilian study but majority of subjects of European descent. Cut-offs appropriate.	Patients with high risk of diabetes referred (unclear where from) for OGT tests, all Brazilians with 84% white, 39% males.	Included patients with hypertension, family history of hypertension, diabetes or cardiovascular disease. Excluded participants with conditions known to interfere with HbA1c results (e.g. anaemia, variant haemoglobin).	6.0%≥ HbA1c <6.5%	≥6.5%	5.6 mmol/L≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	3x3 table, ROC analysis

Table 59: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes: studies not included in meta-analysis but providing diagnostic accuracy data

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
Colagiuri (2004) Australia	Level III-2 Subgroup analysis of participants in population-based study of diabetes prevalence.	Risk of bias unclear; population-based study, results given on a subgroup with at least one risk factor. High applicability as Australian setting. Different cut-offs to current recommendations.	Subgroup of AusDiab study, population-based study of diabetes prevalence. Subgroup determined by presence of at least one risk factor, but subgroup not described at all.	Subgroup not described. Larger population study recruited from stratified random sample.	≥5.3%	≥5.3%	6.1 mmol/L≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.0 mmol/L	ROC analysis for people with HbA1c ≥5.3%
Cosson (2010) Paris, France Cohort also reported in meta-analysis (Cosson 2011)	Level III-2 Inpatients without known diabetes referred for OGT testing as part of battery of tests.	Low risk of bias. Applicable to Australian setting. Appropriate cut-offs.	Patients referred to hospital clinic for treatment of overweight or obesity, free of any acute disease but likely to be at high risk. N=1,287, 82%	Excluded patients with known diabetes. Included patients with comorbidities but no acute disease.	Not reported	Not reported	6.0 mmol/L> FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	Sensitivity and specificity

			female, mean age 39 ± 14 years, range 16–76 years.						
Gomyo (2004) Various locations, Japan	Level III-2 Patients identified with pre-diabetes after initial screening for an RCT of interventions for diabetes prevention; subjects recruited to have OGT test.	Low risk of bias. Applicability uncertain as population not well described; Japanese population. Cut-offs different to current criteria.	Population not well described; n=997.	Exclusions not reported. To have OGT test, patients had to have: (1) 100 mg/dL ≤ FPG <126 mg/dL; (2) 140 mg/dL ≤ casual plasma glucose (CPG) <200 mg/dL (less than 2 hours after a meal); (3) 110 mg/dL ≤ CPG <140 mg/dL (more than 2 hours after a meal); (4) IGT by 75 g OGT at original screen for recruitment to the RCT.	Not reported	Not reported	IGT: FPG <126 mg/dL; 140 mg/dL ≥ 2hPG <200 mg/dL; IFG: 110 mg/dL ≥ FPG <126 mg/dL; 2hPG <140 mg/dL	FPG ≥126 mg/d L; 2hPG ≥200 mg/d L	ROC analysis
Hajat (2011) Abu Dhabi, United Arab Emirates	Level III-2 Patients recruited from population- based screening program in community setting in Abu Dhabi; after initial screen, patients with possible diabetes recalled for further testing including OGT.	Risk of bias unclear as only patients with HbA1c >6.1%, random glucose ≥11.1 mmol/L or missing data recalled for OGT test. Middle Eastern population, so some concerns about applicability. Appropriate cut-offs.	N=1,028 people 18 years of age or older included, but not described.	Not reported. Unknown how many were recalled for OGT test and how many actually had tests.	Not reported	Not reported	Not reported	FPG ≥7.0 mmol/ L; 2hPG ≥11.1 mmo l/L	ROC analysis
Hu (2010)	Level III-2	Low risk of	N=2,298 participants,	Participants had at least one of:	Not	Not	IGT:	FPG	ROC

Shanghai, China	Participants with at least one risk factor for diabetes were identified from medical examination database and invited to attend for diabetes screening at a hospital in Shanghai.	bias in study design. Some concerns with applicability to Australian setting as Chinese population. Cut-offs appropriate.	42% male, mean age 52.4 years (SD 13.3).	family history of diabetes, history of gestational diabetes, obesity or history of IGT. Excluded subjects with previously diagnosed diabetes, receiving medication for diabetes or who were pregnant.	reported	reported	FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L; IFG: 6.1 mmol/L≥ FPG <7.0 mmol/L; 2hPG <7.8 mmol/L	≥7.0 mmol/L; or 2hPG ≥11.1 mmol/L	analysis
Jesudason (2003) Adelaide, Australia	Level III-2 Patients recruiting for a screening study at a hospital endocrine unit; voluntary and referred patients accepted.	Some risk of bias in selection of study population as self-referred and unclear if high-risk status confirmed. Applicable to Australian setting. Cut-offs appropriate.	N=505 participants, 43% male, mean age 53.8 years, range 19–88 years.	Participants had family history of diabetes, previous gestational diabetes, obesity or symptoms, or were referred from another doctor. All who responded to advertisements included. Unclear if risk status confirmed. Excluded subjects under 18 years or who were pregnant.	Not reported	Not reported	IGT: FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L; IFG: 6.1 mmol/L≥ FPG <7.0 mmol/L; 2hPG <7.8 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	ROC analysis
Khoo (2012) Singapore	Level III-2 Analysis of patients who underwent OGT testing in outpatients clinic of a Singapore hospital.	Unclear level of bias in study as population selection and test timing not well described. Applicability unclear as	Patients who underwent OGT testing (n=762) in outpatients clinic between 2001 and 2007; reason for referral not described. N=511 had OGT test and HbA1c (included in analysis), 50%	Excluded patients with prior diagnosis of diabetes. N=251 of patients who underwent OGT testing did not have HbA1c and were not included in analysis.	Not reported	Not reported	Not reported	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	ROC analysis stratified by age

		cannot ascertain if relevant population.	male, mean age 52.4 ± 14.5 years, range 14–93 years.						
Kumaravel (2012) Norfolk, England	Level III-2 Participants recruited for feasibility components of a diabetes intervention program, from primary care family practices in England.	Level of bias related to patient selection unclear, although conduct of study has low level of bias. Applicable to Australian setting as culturally similar and general practice setting. Appropriate cut-offs.	Patients with risk factors recruited for feasibility elements of diabetes intervention program between Dec 2009 and April 2010. N=3,921, age 45–70 years. No further details reported.	Patients without diagnosed diabetes and with at least one risk factor (first-degree relative with type 2 diabetes, overweight or obese, large waist circumference, history of coronary disease, history of gestational diabetes). Excluded n=15 patients but no reasons given.	Not reported	Not reported	IFG: 5.6 mmol/L≥ FPG <7.0 mmol/L	FPG ≥7.0 mmol/ L	Logistic regression analysis
Santos-Rey (2010) Seville, Spain	Level III-2 Study of patients from a cardiovascular risk clinic in a Spanish Hospital; study primarily concerned with diagnosing IGT.	Low risk of bias in study design. High-risk population applicable to population in question, although Spanish. Appropriate cut-offs.	Consecutive patients aged 18–70 years with at least two risk factors recruited between March 2005 and Nov 2008 from a cardiovascular risk clinic. N=713, mean age 51 ± 12 years, 50% male, 98% Caucasian.	Patients with two or more risk factors: obesity, dyslipidaemia, hypertension, previous IGT or family history of diabetes) were included. Patients aged less than 18 years or 70 years or older were excluded. Only patients with FPG <7.0 mmol/L had OGT tests and are included in ROC analysis.	Not reported	Not reported	FPG: 5.6 mmol/L≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	Not reported	ROC analysis for IGT
Snehalatha (2000) Chennai,	Level III-2 Study of patients who	Risk of bias unclear due to inadequate	Patients recruited from diabetes clinic between July and Dec	Patients had no known history of diabetes. No other criteria described.	Not reported	Not reported	Not reported	FPG >125 mg/d L;	ROC analysis

India	underwent diabetes testing in a hospital diabetes clinic in India.	description of population. Questionable applicability to Australia as Indian population. Appropriate cut-offs.	1998, but recruitment not described. N=1,261 participants, mean age 40 ± 12 years, 67% male. Many had strong family history of diabetes or other risk factors, but not described.					2hPG ≥200 mg/d L	
Tanaka (2001) Tokyo, Japan	Level III-2 Study of patients suspected of having diabetes, assessment at two hospitals in Tokyo.	Risk of bias and applicability unclear due to inadequate description of population. Study in Japan so questionable applicability to Australian population. Appropriate cut-offs.	Patients suspected of having diabetes and undergoing OGT testing as part of a battery of tests in hospitals in Japan, June 1995 – April 1999. N=866 enrolled, 66% male, mean age 56 ± 0.4 years, range 20–82 years.	Patients with anaemia, renal or hepatic dysfunction excluded.	Not reported	6.5%	IGT: 7.8 mmol/L ≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	ROC analysis
Tankova (2012) Sofia, Bulgaria	Level III-2 Study of diabetes diagnosis in people who were doctor- or self-referred to the study conducted in a university hospital department.	Risk of bias in conduct of study low. Few applicability concerns—Bulgarian population. Cut-offs differ from Australian guidelines.	N=2,231 patients with at least one risk factor for diabetes, referred by doctor or self-referred to screening program from April 2006 – Oct 2010; mean age 50.3 ± 13.9 years, 41% male.	Patients had at least one of: first-degree relative with diabetes, overweight or central obesity, history of gestational diabetes, had baby over 4 kg, history of IFG or IGT, hypertension, lipid abnormalities or atherosclerotic vascular disease. Exclusions not described.	Not reported	Not reported	6.1 mmol/L ≥ FPG <7.0 mmol/L; 7.8 mmol/L ≥ 2hPG < 11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	ROC analysis

Table 60: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in older adults

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
Rathmann (2012) Augsburg, Germany	Level III-2 Elderly subgroup of participants recruited as part of population-based health survey, selected using random sampling.	Low risk of bias. No applicability concerns. Cut-offs appropriate.	Patients who formed part of a population-based cohort study: subjects who were aged 61–75 years without pre-existing diabetes underwent OGT testing. N=896, males 51.5%, mean age 67 ± 3.7 years.	Included patients without diabetes aged 61–75 years. Excluded patients with acute illness who could not undergo OGT testing, and people whose data was incomplete.	5.7% ≥ HbA1c <6.5%	≥6.5%	IFG: 6.1 mmol/L ≥ FPG <7.0 mmol/L; 2hPG <7.8 mmol/L; IGT: 7.8 mmol/L ≥ 2hPG <11.1 mmol/L; FPG <6.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥7.8 mmol/L	3x3 table, ROC analysis
Kramer (2010) San Diego, USA	Level III-3 Cross-sectional study of community-dwelling older adults; subgroup analysis of larger cohort.	Unclear level of bias in study as population selection, and study flow and timing, not well described. Applicability unclear as difficult to ascertain if relevant	Older participants in a cross-sectional study who underwent concurrent OGT and HbA1c tests between 1984 and 1987; selection and recruitment not described. N=2,107 subjects, 43% males, mean age 69.4 ± 11 years.	Included patients without known diabetes; no other inclusion or exclusion criteria described.	Not reported	Not reported	Not reported	Not reported	ROC analysis

		population; however, likely to be similar to Australia.							
--	--	---	--	--	--	--	--	--	--

Table 61: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in ethnic minorities

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
Araneta (2010) California and Hawaii, USA	Level III-2 Cross-sectional study of ethnic minorities recruited from community.	Risk of bias unclear due to poor reporting. Limited applicability due to ethnic minorities not applicable to Australia. Appropriate cut-off points.	N=933 Filipino-Americans, Japanese-Americans, native Hawaiians; mean age 54.2 years, 27% male.	Excluded individuals with known diabetes.					
Wang, H (2011) and Wang, W (2011) Four states of USA	Level III-2 Baseline and follow-up measures of subjects in large cohort study of heard disease.	Risk of bias unclear as selection of population not described and people with CVD excluded. Limited applicability	American Indians from Arizona, Oklahoma, North and South Dakota. Baseline n=3850, follow-up n=1670. Age range 45–74 years.	Excluded people with CVD; at follow up, excluded people with diabetes diagnosed at baseline.	5.5%≥ HbA1c <6.5% 6.0%≥ HbA1c <6.5%	HbA1c ≥6.5%	5.6 mmol/L≥ FPG <7.0 mmol/L	FPG ≥7.0 mmol/L	3x3 table

		due to ethnic minority, not relevant to Australia. Appropriate cut-off points.							
Exebio (2012) Florida, USA	Level III-2 Cross-sectional analysis of control arm of patients recruited into case-control study.	Risk of bias unclear as patient recruitment and selection not well described. Limited applicability due to ethnic minority not relevant to Australia. Appropriate cut-off points.	Patients of Haitian origin (2 Haitian parents), n=128, all aged 35 years or older but no other details provided.	Excluded people less than 35 years of age, and pregnant and breastfeeding women, n=1 who had missing HbA1c value.	Not reported	Not reported	Not reported	FPG ≥7.0 mmol/L	ROC analysis
Lin (2012) Fujian province, China	Level III-2 Cross-sectional study; population-based multi-stage, stratified, cluster random sample.	Low risk of bias. Limited applicability to Australia as Chinese ethnic minority. Appropriate cut-offs	Population of She ethnic minority in China, n=687, age range 20–77 years, 40% males.	Excluded people with anaemia and pregnant women. Excluded n=12 for any reason (ineligible or missing data).	6.1%≥ HbA1c <6.9%	HbA1c ≥6.9%	6.1 mmol/≥ FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	FPG ≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	ROC analysis
Rowley (2005) Australia and Canada	Level III-2 Analysis of data collected in community-based screening program	Low risk of bias. Very applicable to Australia.	Participants in community-based screening for diabetes and coronary risk factors.	None reported.	Not reported	HbA1c ≥7.0%	Not reported	FPG ≥7.0 mmol/L	ROC analysis

	in high-risk communities of Aboriginal, Torres Strait Islander (TSI) and First Nations people.	Appropriate cut-offs.	N=107 Aboriginal, n=51 men, mean age 36.8 years, n=56 women, mean age 41.2 years. N=154 TSI, n=79 men, mean age 36 years, n=75 women, mean age 33.6 years. N=170 First Nations, n=57 men, mean age 41.5 years, n=113 women, mean age 41.5 years.						
Mostafa (2010a) (also reported in Mostafa (2013) Leicestershire, England	Level III-2 Population-based study recruited from primary care. All participants with result on OGT testing in diabetes range underwent second OGT test. Results separated into white Europeans and South Asians	Low risk of bias. No applicability concerns Appropriate cut-offs.	N=9,494, n=40 excluded as under 40 years of age and n=198 excluded due to incomplete results. 47.7% male, mean age 57.3 ± 9.7 years, 74.7% white European, 22.8% South Asian and 2.5% other. Sourced from primary care population for two previous systematic screening programs—one general but where 2/3 had a risk factor, and in the other all had a risk factor—total cohort 75% with a risk factor.	Cohort Included males and females aged 25–75 years from Leicestershire. At-risk had one or more of: previous IGT/IFG, history of CVD, hypertension, dyslipidaemia, gestational diabetes, PCOS and overweight first-degree relative with type 2 diabetes, overweight and sedentary, or obese. Excluded people under 40 years of age as no white Europeans in that group. Excluded n=198 due to incomplete test results	Two categories: 6.0–6.4% and 5.7–6.4%	≥6.5%	Included IGT and IFG ≥7.8 mmol/L on OGT test	2hPG ≥11.1 mmol/L	Diagnostic accuracy (sensitivity, specificity, AUROC for some)
Vlaar	Level III-2	Risk of bias	Patients of Hindustani	Only people of Hindustani	Optimal	Optimal	5.6 mmol/L≥	FPG	ROC

(2013) The Hague, The Netherlands	Cross-sectional analysis of patients participating in a larger lifestyle intervention trial.	unclear as sample selection and recruitment not well described. Limited applicability to Australia as not a relevant ethnic group. Appropriate cut-offs.	Surinamese descent, n=944, median age 43.9 years, 39% male.	Surinamese descent aged 18–60 years and without diabetes eligible. Also excluded n=24 who did not have test or had incomplete tests.	cut-offs reported	cut-offs reported	FPG <7.0 mmol/L; 7.8 mmol/L≥ 2hPG <11.1 mmol/L	≥7.0 mmol/L; 2hPG ≥11.1 mmol/L	analysis
Young (1988) Manitoba and Ontario, Canada	Level III-2 Cross-sectional study of some randomly sampled and some volunteers from six American Indian communities in Canada.	Risk of bias unclear due to poor reporting. Limited applicability as not a relevant ethnic minority. Cut-offs only defined for FPG.	American Indians recruited from the community, n=704, aged 20–64 years. No other details.	Excluded pregnant women but included people with pre-existing diabetes.	Optimal cut-offs reported	Optimal cut-offs reported	Not reported	FPG ≥7.8 mmol/L	ROC analysis

Table 62: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in children

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
Lee	Level III-2	Some risk of	Subgroup analysis of	Included overweight and obese	6.0%≥	HbA1c	100 mg/dL≥	FPG	ROC

(2011) Multiple sites, USA	Cross-sectional study of nationally representative non-institutionalised population in USA, selected with stratified random sampling and with adolescents oversampled (NHANES). Data collected between 1999 and 2006.	bias as results from as far back as 1999, which may not be equivalent to more recent results. No applicability concerns.	larger population-based cross-sectional study; n=1,156 overweight and obese adolescents aged 12–18 years who had both FPG and HbA1c tests, 52% male. Also n=267 had OGT test.	adolescents. Excluded those who were pregnant or known to be diabetic.	HbA1c <6.5% 5.7%≥ HbA1c <6.5%	≥6.5%	FPG <126 mg/dL; 140 mg/dL≥ 2hPG <200 mg/dL	≥126 mg/dL; OGT test ≥200 mg/dL	analysis
Lee (2012) Suwon, Korea	Level III-2 Chart review of children who were patients of the Paediatric Endocrine Unit of a hospital, children who had completed an OGT test between 2003 and 2010.	Risk of bias unclear as chart review with no discussion of underlying population. Applicability concerns relating to population and to Korean setting. Appropriate cut-offs.	Chart review of n=126 patients who were overweight or obese and had undergone OGT testing between 2003 and 2010; 55% male, mean age 9.9 ± 3 years.	Excluded children with presence of endocrine or genetic disorders, previously diagnosed diabetes and receiving hypoglycaemic treatment.	Not reported	Not reported	IGT: 7.8 mmol/L≥ 2hPG <11.1 mmol/L; IFG: 5.6 mmol/L≥ FPG <7.0 mmol/L	2hPG ≥11.1 mmol/L	ROC analysis
Nowicka (2011) Connecticut, USA	Level III-2 Baseline cross-sectional comparison of children recruited from paediatric obesity clinics; part of ongoing study investigating diabetes during	Low risk of bias. Some applicability to Australian setting, although substantial proportion of the cohort African-	Baseline results of children and adolescents in ongoing study of glucose metabolism in obese children; n=1156, mean age 13.2 ± 2.8 years, range 4.8–23.1 years; 41% male; 36%	Excluded children with diabetes or taking medication known to affect glucose metabolism. Included obese subjects.	5.7%≥ HbA1c ≤6.4%	HbA1c >6.4%	100 mg/dL≥ FPG ≤125 mg/dL; 140 mg/dL≥ 2hPG ≤199 mg/dL	FPG >125 mg/dL; 2hPG ≥200 mg/dL	3x3 table, ROC analysis

	2005–10.	American or Hispanic.	Caucasian, 35% African-American, 29% Hispanic.						
Ogawa (2012) Tokyo, Japan	Level III-2 School-based recruitment of children into cross-sectional study between 1988 and 2009.	Some risk of bias due to long time frame of study and likely changes to quality of HbA1c test over that time. Methodology not well described. Limited applicability to Australian setting due to Japanese subjects.	Children with two recordings of glucosuria in school-based screening program had OGT tests. N=298 subjects, mean age 11.9 ± 2.5 years, male: female ratio 1:1.1.	Excluded (OGT test not performed) if extremely high FPG or ketonuria.	Not reported	HbA1c ≥6.5%	7.8 mmol/L ≥ 2hPG <11.1 mmol/L	2hPG ≥11.1 mmol/L	2x3 table, correlations
Sharma (2012) California, USA	Level III-2 Baseline cross-sectional analysis of participants in a community-based lifestyle modification program to reduce risk of type 2 diabetes.	Some likelihood of bias as participants recruited through community, not from referral. Limited applicability to Australian setting as all African-American children.	Subjects were African-American children with BMI at or above 85th percentile; n= 172 children, mean age boys 9.96 years, girls 9.80 years; 41% males.	Inclusion criteria were aged 8–11 years, BMI at or above 85th percentile; exclusion criteria FPG ≥120 mg/dL, other metabolic disease or taking medications known to affect study outcomes.	5.7% ≥ HbA1c ≤6.4%	HbA1c ≥6.5%	5.6 mmol/L ≥ FPG <7.0 mmol/L	FPG ≥7.0 mmol/L	Limited 3x3 table

Yesiltepe Mutlu (2013) Kocaeli, Turkey	Level III-2 Chart review of children who underwent OGT testing between Feb 2010 and Feb 2011.	Level of bias and applicability unclear as population and other methodology not well described.	N=106 obese or overweight children who underwent OGT testing; mean age 13.4 ± 2.6 years, range 7–18 years, 33% male.	No inclusion or exclusion criteria described.	HbA1c ≥5.5%	Not reported	100 mg/dL ≥ FPG <126 mg/dL; 140 mg/dL ≥ 2hPG <200 mg/dL	FPG ≥126 mg/dL; 2hPG ≥200 mg/dL	ROC analysis
--	--	---	--	---	-------------	--------------	--	------------------------------------	--------------

Table 63: Study profiles of included studies on diagnostic accuracy of HbA1c testing for diagnosing diabetes in people with CVD

Study and location	Diagnostic level of evidence and study design	Quality assessment	Study population	Inclusion/exclusion criteria	HbA1c cut-off—pre-diabetes	HbA1c cut-off—diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—pre-diabetes	Reference standard cut-off(s): (FPG and/or OGT test)—diabetes	Outcomes
Doerr (2011) Germany	Level III-2 Study of test accuracy against non-blinded reference standard.	Low risk of bias. No applicability concerns.	N=1,015 patients; 69% male. Mean age 68.2 ± 9.0 years.	Included patients 54 years of age or older admitted for acute (n=146) or elective (n=866) coronary angiography. Excluded patients with known diabetes or history of taking glucose-lowering agents, or with pancreatic, hepatic or kidney disease, or presence of endocrine diseases or treatment with steroid medication.	5.7–6.4%	≥6.5%	IGT: FPG <126 mg/dL and OGT test ≥140 mg/dL; IFG: FPG ≥100 mg/dL and <126 mg/dL	FPG ≥126 mg/dL and/or OGT test ≥200 mg/dL	Sensitivity, specificity
Gianchandani	Level III-2	Low risk of bias.	N=92/116	Included patients	5.7–6.4%	≥6.5%	IFG:	FPG	Sensitivity/

(2011) Unites States	Study of test accuracy against non-blinded reference standard.	No applicability concerns.	patients (12 excluded to rescheduled surgery, 10 declined, 1 withdrew, 1 did not meet criteria). Mean age 56–64 years.	participating in ongoing study following cardiothoracic surgery procedures. Excluded patients with history of diabetes or of taking medication that interferes with glucose metabolism (glucocorticoids, immunosuppressive agents).			FPG 100–125 mg/dL; IGT: OGT test 140–199 mg/dL	≥126 mg/dL and/or OGT test ≥200 mg/dL	specificity (2x2)
Hanna (2012) United Kingdom	Level III-2 Study of test accuracy against non-blinded reference standard.	Moderate risk of bias due to missing data without explanation. No applicability concerns.	N=198/200 patients (data from 2 missing). Demographics not stated.	Included consecutive patients investigated for acute coronary syndrome. Excluded patients previously known to have diabetes.	6.0–6.4%	≥6.5%	WHO OGT test classification	WHO OGT test classification	Sensitivity, specificity
Hjellestad (2013) Norway	Level III-2 Study of test accuracy against non-blinded reference standard.	Low risk of bias. No applicability concerns.	N=275/466 consecutive patients (121 declined, 67 with diabetes, 3 with missing data). Mean age 69.5 years (range 35–89 years); 73.1% male.	Included consecutive patients admitted for elective surgery due to peripheral artery disease. Excluded patients with previous history of known diabetes.	5.7–6.4%	≥6.5%	IGT: FPG <7.0 mmol/L and OGT test 7.8–11.1 mmol/L; IFG: FPG 6.1–7.0 mmol/L and OGT test <7.8 mmol/L	FPG ≥7.0 mmol/L and/or OGT test ≥11.1 mmol/L	AUC, Sensitivity, specificity
Somani (2013) India	Level III-2 Study of test accuracy against non-blinded reference standard.	Potential risk of bias (poor reporting regarding recruitment and patient flow). Applicability concerns due to	N=195/311 Mean age 58.6 ± 7.6 years; 100% male.	Included males with clinical and ECG evidence of coronary artery disease (CAD) and undergoing angiography for CAD, found to have occlusion	NA	≥6.5%	FPG and 2hOGT test ADA criteria and WHO criteria	FPG and 2hOGT test ADA criteria and WHO criteria	Sensitivity, specificity (2x2)

		including patients with history of diabetes.		of >50%; tertiary cardiac care hospital. Excluded haemoglobinopathies.					
Wang (2013) Taiwan	Level III-2 Study of test accuracy against non-blinded reference standard.	Moderate risk of bias due to non-consecutive/non-random sampling. No applicability concerns.	N=400/780 eligible patients. Mean age 65 ± 13 years; 75.9% male; CAD 67.8%.	Included patients admitted for coronary angiography. Excluded known diabetics.	5.7–6.4%	≥6.5%	FPG 5.6–6.9 mmol/L; or OGT test 7.8–11.0 mmol/L	FPG ≥7.0 mmol/L; or OGT test ≥11.1 mmol/L	Sensitivity, specificity (2x2), AUC

AUC = area under the curve; CAD = coronary artery disease; FG = fasting glucose; FPG = fasting plasma glucose; RCT = randomised controlled trial; ICU = intensive care unit; IGT = impaired glucose tolerance; NS = not stated; WHO = World Health Organization; ADA = American Diabetes Association

Appendix D Extra results

Table 64: Summary of concordance results across categories of diabetes, pre-diabetes and no diabetes, for studies providing raw (3x3) data

Study	Reference standard cut-off for diabetes (mmol/L)	Reference standard range for pre-diabetes (mmol/L)	HbA1c cut-off for diabetes	HbA1c range for pre-diabetes	Concordance — kappa [95% CI]
Lu (2010) Australia	FPG: ≥ 7.0 2hPG ≥ 11.1	FPG 5.6–6.9 2hPG 7.8–11.0	6.5%	5.6–6.4%	0.350 [0.320, 0.379]
Cosson (2011) France	FPG: ≥ 7.0 2hPG ≥ 11.1	FPG 5.6–6.9 2hPG 7.8–11.0	6.5%	5.7–6.4%	0.168 [0.116, 0.219]
Cavagnolli (2011) Brazil	FPG: ≥ 7.0 2hPG ≥ 11.1	FPG 5.6–6.9 2hPG 7.8–11.0	6.5%	6.0–6.4%	0.164 [0.102, 0.227]
Peter (2011) Germany	FPG: ≥ 7.0 2hPG ≥ 11.1	FPG 6.1–6.9 2hPG 7.8–11.0	6.5%	5.7–6.4%	0.298 [0.251, 0.344]
Saiedullah (2011) Bangladesh	FPG: ≥ 7.0 2hPG ≥ 11.1	FPG 6.1–6.9 2hPG 7.8–11.0	6.5%	6.0–6.4%	0.494 [0.441, 0.547]

Table 65: Summary of diagnostic accuracy results for HbA1c vs FPG and/or 2hPG testing for pre-diabetes

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity [95%CI]	Specificity [95%CI]	PPV [95%CI]	NPV [95%CI]
Du (2013) China	$5.6 \geq \text{FPG} < 7.0$	ROC	nr	5.7% ^a	46.8%	83.1%	55.3%	77.7%
Kumaravel (2012) UK	$5.6 \geq \text{FPG} < 7.0$	Logistic regression	NA	5.7% 6.1%	63.0% 21.4%	80.7% 98.1%	PLR = 3.26 PLR = 11.1	NLR = 0.46 NLR = 0.80
Gomyo (2004) Japan	$7.8 \geq 2\text{hPG} < 11.1$ IGT: IGT + diabetes:	ROC	0.72 ± 0.02	5.3% ^a 5.3%	57.2% 66.4%	67.4% 67.4%		
Santos-Rey (2010) Spain	$7.8 \geq 2\text{hPG} < 11.1$	ROC	0.85 [0.62, 0.88]	5.4% ^a 5.7%	85% 46%	73% 92%	29% 43%	97% 93%

Study	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off	Sensitivity [95%CI]	Specificity [95%CI]	PPV [95%CI]	NPV [95%CI]
				6.0%	18%	99%	70%	90%
Hu (2010) China	7.8≥ 2hPG <11.1	ROC	0.647 [0.62, 0.68]	5.6% ^a	66.2% [63.8, 68.6]	51.0% [48.5, 53.5]	PLR = 1.35	NLR = 0.66
Mostafa (2010a), Mostafa (2010b), Mostafa (2013) UK	7.8≥ 2hPG <11.1 White Europeans: South Asians:	ROC	0.69 [0.67, 0.71] 0.72 [0.69, 0.75]	5.7%	70.5% [67.4, 73.4]	57.9% [56.6, 59.2]		
				5.8% ^a	61.5% [58.2, 64.4]	67.9% [66.6, 69.1]		
				6.0%	39.5% [36.3, 42.7]	83.5% [82.5, 84.5]		
				5.7%	85.6% [81.4, 88.9]	41.3% [38.9, 43.7]		
				6.0% ^a	63.8% [58.6, 68.7]	69.4% [67.1, 71.6]		
Cosson (2010) France	7.8≥ 2hPG <11.1	ROC	nr	6.0%	36.8%	84.4%	45.1%	79.3%
Colagiuri (2004) Australia	5.6≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	nr	5.3%	42.0%	88.2%	43.2%	
Lee, H (2013) Korea	5.6≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	0.712	5.6%	58.6%	50.6%	69.0%	75.9%
				5.8% ^a	35.0%	81.7%	75.9%	38.5%
Du (2013) China	5.6≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	nr	5.7% ^a	54.3%	100%	100%	70.2%
Cosson (2011) France	5.6≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	0.616 [0.58, 0.65]	5.7%	57.9%	59.3%		
				6.1% ^a	22.3%	90.1%		
Peter (2011) Germany	6.1≥ FPG <7.0 7.8≥ 2hPG <11.1	2x2 analysis		5.5%	69.8%	64.3%		
				5.7%	57.9%	78.6%		
				6.1%	33.5%	94.8%		
Tankova (2012) Bulgaria	6.1≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	0.729 [0.70, 0.76]	5.5%	71% [66, 81]	64% [57, 69]		
Bianchi (2012) Italy	6.1≥ FPG <7.0 7.8≥ 2hPG <11.1	ROC	0.726 [0.69, 0.76]	5.7%		74%		

^a Optimal cut-off point

NA = not applicable; nr = not reported; AUC = area under the curve; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver-operator characteristic; PPV = positive predictive value; NPV = negative predictive value

Table 66: Summary of diagnostic accuracy results for HbA1c vs FPG and/or 2hPG testing in people with conditions that increase the risk of developing diabetes

Study	Condition	Reference standard (mmol/L)	Analysis method	AUC [95%CI]	HbA1c cut-off point	Sensitivity [95%CI]	Specificity [95%CI]	PPV [95%CI]	NPV [95%CI]	Concordance
Fitzgerald (2012) Ireland	Obstructive sleep apnoea syndrome	FPG ≥7.0	2x2 table	NA	6.5%	93.3% [70.2, 98.8]	93.5% [89.6, 96.0]	48.3% [31.4, 65.6]	99.5% [97.4, 99.9]	0.605 [0.42, 0.79]
Liberopoulos (2010) Greece	Metabolic syndrome and FPG >100 mg/dL	FPG ≥7.0	2x2 table	NA	6.5%	76.4% [63.7, 85.6]	58.6% [48.1, 68.4]	53.8% [42.9, 64.5]	79.7% [68.3, 87.7]	0.325 [0.17, 0.48]
Jun (2011) Korea	Non-alcoholic fatty liver disease	2hPG ≥11.1	ROC	nr	6.5%	86.4%	71.1%	nr	nr	nr
Yang (2013) China	Graves' hyperthyroidism	FPG ≥7.0 2hPG ≥11.1	2x2 table ^b	NA	6.5%	43.8%	76.9%	62.2%	61.1%	nr
Eckhardt (2012) USA	HIV infection	FPG ≥7.0	2x2 table ROC	NA nr	6.5% 5.8% ^a 6.5%	40.9% [23.3, 61.3] 81.8% 40.9%	97.6% [95.5, 98.7] 77.5% 97.5%	50.0% [29.0, 71.0]	96.6% [94.2, 98.0]	0.421 [0.19, 0.66]
Kumpatla (2013) India	Tuberculosis infection	2hPG ≥11.1	ROC	0.754 [0.68, 0.83]	6.5%	59.1%	91.7%	39.8%	96%	nr
Tatar (2013) Turkey	Renal transplant recipients	FPG ≥7.0 2hPG ≥11.1	ROC	0.71	5.05% ^a	50%	75%	47%	93%	nr
Valderhaug (2009) Norway	Renal transplant recipients	FPG ≥7.0 2hPG ≥11.1	ROC	0.817 [0.76, 0.88]	5.5% 5.6% 5.7% 5.8% ^a 5.9% 6.0%	98% 92% 91% 83% 74% 64%	nr	nr	nr	nr

^a Optimal cut-off point

^b Only summary data was presented.

NA = not applicable; nr = not reported; AUC = area under the curve; nr = not reported; PLR = positive likelihood ratio; NLR = negative likelihood ratio; ROC = receiver–operator characteristic; PPV = positive predictive value; NPV = negative predictive value

Summary of results for conditions that may interfere with HbA1c measurement

Table 67: Summary of data for comparison of HbA1c levels in patients with and without chronic renal disease

Case series	Summary of findings
De Boer (1980)	Found that in patients with renal failure there was no correlation between HbA1c and FPG levels. It was concluded that renal failure itself causes an increase in HbA1c.
De Marchi (1983)	Found that there was no significant difference in HbA1c levels between dialysed and non-dialysed patients with chronic renal failure. There was also no significant difference in HbA1c levels between NGT and IGT patients with chronic renal failure, unlike the significant difference seen between NGT and IGT control patients. The authors concluded that blood sugar levels do not play a major role in increasing HbA1c levels in patients with chronic renal failure.
Lindholm (1986)	The mean HbA1c level was higher in the patients with chronic renal failure than in the controls. HbA1c remained elevated after the start of continuous ambulatory peritoneal dialysis and the levels did not change during the 12-month study period.
Nakao (1998)	EPO treatment significantly influenced HbA1c levels, and the more erythropoiesis fluctuated by changing the dose of EPO, the more HbA1c levels changed, although there were no significant changes in blood glucose levels during the study period.
Ng (2008)	Found that Hb levels increased and HbA1c levels decreased after treatment with EPO. Thus, the authors concluded that treatment of renal anaemia with erythropoietin leads to a decrease in HbA1c levels.
Sabatar (1991)	Patients with end-stage renal disease had the highest HbA1c levels of all studied groups, so the authors concluded that abnormal non-enzymatic glycosylation of proteins is elevated in uraemia.

EPO = erythropoietin

Table 68: Summary of data for comparison of HbA1c levels in patients with and without anaemia

Case series	Summary of findings
Ahmad (2013)	Narrative systematic review of case series, which forms the available data on iron deficiency anaemia. Iron deficiency has been shown to shift HbA1c slightly upward independent of FPG level by the majority of investigators. However, the shift occurred at the lower end of the HbA1c spectrum. Therefore, the authors suggest that people with anaemia who are close to the diagnostic threshold may require re-testing or the use of another diagnostic method to confirm presence of absence of diabetes or pre-diabetes.
Bae (2013)	Found that participants with lower Hb had significantly higher HbA1c at any given FPG level in both men and women. There was a negative correlation between Hb level and HbA1c value. HbA1c decreased steadily with increasing Hb level.
Camargo (2004)	Found that 42 out of 57 patients who did not have a haemoglobinopathy and had low HbA1c levels had anaemia. It was concluded that anaemia is a source of negative interference. Thus, the haematological status of the patient should be considered for the correct interpretation of HbA1c results.
Ford (2011)	Found a significant positive correlation between Hb concentrations and HbA1c concentrations after adjusting for age, gender, and race or ethnicity. Participants with Hb <100 g/L had a mean HbA1c of 5.28%. Participants with Hb ≥170 g/L had a mean HbA1c of 5.72%. The adjusted mean concentrations of HbA1c were 5.56% and 5.46% among participants with and without iron deficiency, respectively (p = 0.095).

Table 69: Summary of diagnostic accuracy for HbA1c testing vs WHO criteria (2006) for diagnosing diabetes and pre-diabetes in people with and without anaemia

Patients	Reference standard (mmol/L)	HbA1c cut-off point	Sensitivity [95%CI]	Specificity 95%CI]	PPV [95%CI]	NPV [95%CI]	Concordance
N = 77 non-anaemic patients	FPG \geq 6.1 2hPG \geq 7.8	5.7%	37.5% [13.7, 69.4]	84.1% [73.7, 90.9]	21.4% [7.6, 47.6]	92.1% [82.7, 96.6]	0.162 [0.000, 0.527]
N = 39 anaemic patients	FPG \geq 6.1 2hPG \geq 7.8	5.7%	75.0% [30.0, 95.4]	62.9% [46.3, 76.8]	18.8% [6.6, 43.0]	95.7% [79.0, 99.2]	0.163 [0.000, 0.514]

Source: Hardikar (2012)

Table 70: Summary of data for comparison of HbA1c levels in patients with and without haemoglobinopathies

Study	HbA1c analysis method	Haemoglobinopathy	Mean HbA1c ± SD (range)	Comparator mmol/L ± SD (range)	Conclusion
Al-Fadhli (2001) Kuwait	Immunoassay	N=28 β-thal minor N=16 HbAS N=15 Healthy HbAA N=22 Diabetic HbAA	7.7% (6–15%) 5.0% (4–6%) 5.0% (4–6%) 7.4% (6–15%)		Synchron LX20 immunoassay method gave falsely high HbA1c results with β-thalassemia minor patient samples.
Camargo (2004) Brazil	Ion exchange HPLC	N=73 Haemoglobinopathies (n=69 HbAS, n=1 HbAC, n=1 HbSC, n=2 HbAD) N= 57 HbAA with low HbA1c levels (n=42 anaemia, n=15 other)	4.1% (2.9–4.7%) 4.4% (3.4–4.7%)		Patients with or without diabetes were included. The presence of an Hb variant may falsely lower HbA1c values.
Koethe (1999) USA	2 Ion exchange HPLC analysers	N=5 Diabetic HbAS N=3 Diabetic HbAC N=26 Diabetic HbAA	Variant Express 8.5% (7.1–12.5%) 10.3% (7.4–15.1%) 12.2% (10.0–16.4%)	Diamat 6.4% (4.5–8.8%) 7.1% (5.5–9.6%) 12.2% (10.1–16.4%)	The Diamat HbA1c values of 2 HbAS patients and 1 HbAC patient placed them in the 'near normal glycaemia' (6–7%) category of glucose control. Thus, the Diamat may be underestimating the true HbA1c values in HbAS and HbAC samples.
Weykamp (1994) The Netherlands, Antilles	6 BA-HPLC, 6 IE-HPLC, 2 immuno assays and 1 electrophoresis assay	N=17 HbAA N=37 HbAS N=22 HbAC	5.1% (4.0–6.8%) 5.0% (3.7–7.2%) 4.9% (3.7–7.7%)		Subjects with HbAS and HbAC do not show differences in HbA1c levels compared with subjects with HbAA.
Moutet (1988) Guadeloupe	Ion exchange HPLC	N=9 Healthy HbAS N=6 IGT HbAS N=8 Diabetic HbAS N=109 Healthy HbAA N=12 IGT HbAA N=25 Diabetic HbAA	3.7 ± 0.4% 3.8 ± 0.7% 5.1 ± 1.6% 4.4 ± 0.7% 6.1 ± 0.8% 9.4 ± 1.2%		HbA1c levels are lower in HbAS patients than in normal HbAA patients and do not reflect the glycaemic status of the patient.
Ama (2012) Cameroon	Ion exchange HPLC	N=14 Diabetic HbAS N=59 Diabetic HbAA	7.0 ± 1.7% 7.4 ± 1.7%	FPG 7.1 ± 2.7 7.1 ± 3.7	No observed difference in HbA1c levels.

Study	HbA1c analysis method	Haemoglobinopathy	Mean HbA1c ± SD (range)	Comparator mmol/L ± SD (range)	Conclusion
Bleyer (2010) USA	Ion exchange HPLC	N=109 HbAS N=21 HbAC N=254 Healthy HbAA AA N=445 Healthy HbAA EA	7.5 ± 1.2% 7.5 ± 1.3% 7.3 ± 1.3% 7.0 ± 1.3%	RSG 7.5 ± 3.4 9.0 ± 4.5 7.8 ± 3.6 7.9 ± 3.5	The mean % HbA1c and serum glucose levels were similar between AA participants with and without SCT.
Choudhary (2013) USA	HPLC	N=3 Diabetic β-thal major N=2 Normal β-thal major	7.6% (7.3–7.9%) 6.7% (6.6–6.7%)	2hPG 12.6 ± 0.4 5.4 ± 1.5	DM is a common complication in β-thal major. The utility of HbA1c is limited as both the haemoglobinopathies and transfusions are known to interfere with HbA1c analysis. The results may be falsely increased or decreased depending on the proximity to transfusion, shortened erythrocyte lifespan and assay used. Given the above limitations, OGT testing has been proposed as the recommended screening method for diagnosing glucose abnormalities in thalassemia.
Reid (1992) Nigeria	Bio-Rad micro-chromatography	N=71 Non-diabetic HbAA N=21 Non-diabetic HbAS N=36 Non-diabetic HbSS	4.73 ± 1.33% 3.73 ± 0.99%, p<0.001 6.06 ± 3.20%, p<0.02	Corrected HbS and HbF 5.77 ± 1.52%, p<0.02 4.91 ± 2.08%, p<0.10	The mean % HbA1c was significantly lower in the HbAS group than in the HbAA controls. The group mean uncorrected % HbS1c levels in HbSS subjects were considerably higher than % HbA1c levels in HbAA and HbAS subjects. However, after correction for HbS and HbF, the HbAS group had a significantly higher % HbA1c level than the % HbS1c level in the HbSS group.
Robertson (1992) UK	Diagnostic laboratory—method not reported	N=3 people with 2–4% HbF	Range 11–14%	RPG range 4–11	Two patients were treated with anti-diabetic drugs and suffered hypoglycaemic episodes requiring cessation of drugs.

AA = African-Americans, EA = European-Americans; RSG = random serum glucose; RPG = random plasma glucose

Table 71: Summary of data for comparison of HbA1c levels using different methods in patients with haemoglobinopathies

Study	Haemoglobinopathy	Mean HbA1c ± SD (range)			Conclusion
		Method 1	Method 2	Method 3	
Schnedl (2007) Austria	N=1 elevated HbF N=6 Hb Graz N=1 Hb Sherwood Forest N=1 HbSS	IE-HPLC analyser HA-8140 Extra peak < normal No result No result No result	No Abn sep Abn sep Abn sep		Underscores the need for laboratories and physicians to be aware of the limitations of their HbA1c assay method. Samples from patients with silent or suspected Hb variants should be analysed using a different assay principle, preferably BA-HPLC or an enzymatic assay.
Koethe (1999), USA	N=5 Diabetic HbAS N=3 Diabetic HbAC N=26 Diabetic HbAA	Variant Express IE-HPLC 8.5% (7.1–12.5%) 10.3% (7.4–15.1%) 12.2% (10.0–16.4%)	Diamat IE-HPLC 6.4% (4.5–8.8%) 7.1% (5.5–9.6%) 12.2% (10.1–16.4%)		The Diamat HbA1c values of 2 HbAS patients and 1 HbAC patient placed them in the 'near normal glycaemia' (6–7%) category of glucose control. Thus, the Diamat may be underestimating the true HbA1c values in HbAS and HbAC samples.
Lee, (2011) Taiwan	N=6 HbAE (β-thal) N=9 HbAH (α-thal) N=22 HbAG (α-thal)	Variant II IE-HPLC 7.2 ± 1.0% 9.6 ± 2.3% 7.9 ± 2.5%	Primus CLC 385 BA-HPLC 6.2 ± 1.2% 5.6 ± 0.7% 8.2 ± 3.1%		The HbA1c values determined by IE-HPLC were significantly higher than those by BA-HPLC for HbE and HbH variants but not for HbG variants.
Lorenzo-Medina (2012) Spain	N=23 diabetic HbAD (mean FPG = 8.4 mmol/L) N=4 healthy HbAD (Mean FPG = 5.0 mmol/L)	ADAMS HA-8160 IE-HPLC 4.7% 3.3%	COBAS Tina-quant immunoassay 7.6% 5.0%		The COBAS results were consistent with the fasting blood glucose concentrations for each patient. HbA1c levels using the ADAMS HA-8160 HPLC method gave falsely low or unquantifiable results.
Lorenzo-Medina (2013) Spain	N=4 HbAN Baltimore (mean FPG = 13.1 ± 4.6 mmol/L)	ADAMS HA-8160 IE-HPLC 5.8 ± 1.4%	Tina-quant immunoassay 10.0 ± 2.7%		For patients that were heterozygous for the HbN-Baltimore variant, determining HbA1c levels using the ADAMS HA-8160 HPLC method gave falsely low results.
Zhu (2010) USA	N=129 HbAA N=42 HbAS	IE-HPLC analyser VARIANT II 6.6 (48.6) 8.1 (65.0)	UniCel DxC 800 TI method 6.3 (45.3) 7.1 (54.1)		The ADA has recommended that estimated average glucose (eAG) values be calculated from the measured HbA1c result and reported along with HbA1c.

Study	Haemoglobinopathy	Mean HbA1c ± SD (range)			Conclusion	
		Method 1	Method 2	Method 3		
					The difference in eAG between these two methods was statistically significant (p<0.001), with a mean bias of 0.5 mmol/L for HbAA and 1.6 mmol/L for HbAS. This indicates that different HbA1c methods give significantly different eAG results when the same equation is used.	
Nakanishi (2000) Japan	N= 1 Le Lamentin (α20) N=1 M Bostin (α58) N=1 J Meenut (α120) N= 2 Nigata (β1) N=1 Okayama (β2) N=1 Hoshida (β43) N=1 Hokusetsu (β52) N=5 Hamadan (β56) N=1 J Lome (β59) N=2 G Szuhu (β80) N=1 Agenogi (β90) N=1 Yoshizuka (β108) N=1 Peterborough (β111) N=1 Masuda (β114) N=2 Riyadh (β120) N=1 Takamatsu (β120) N=1 Camden (β130) N=1 Sagami (β139)	HA-8150 IE-HPLC analyser 3.7 4.5 4.7 13.5 21.9 2.5 6.2 2.6 2.8 2.4 2.6 3.0 2.6 2.9 4.75 2.5 1.3 1.1	Immunoassays DCA2000Unimate 4.8 5.5 5.2 3.4 5.5 5.2 11.0 4.9 4.8 4.7 4.9 5.0 3.8 4.8 8.25 4.5 3.8 1.1	4.8% 5.4% 5.1% ND 5.7% 5.1% 11.0% 4.8% ND 4.75% 5.2% 4.9% 4.0% 4.8% 8.6% 4.5% ND 4.6%	ESI/MS reference standard 4.6 4.2 4.0 3.75 5.1 4.1 9.1 3.8 4.2 3.4 3.4 3.9 4.1 4.1 7.3 3.7 2.9 3.2	In most samples containing Hb variants, HPLC divided glycated Hb into two fractions—glycated HbA and glycated Hb variant—which leads to underestimation of HbA1c. For Hb Okayama and Hb Niigata the HbA1c value obtained by HPLC was much higher than that obtained by ESI/MS. Some variants also gave values by immunoassay (DCA2000) that were considerably different from those obtained by ESI/MS.
Piras (1993) Italy	N=30 Diabetic β-thal-minor (HbA2 >3.4%) N=170 Diabetic normal (HbA2<3.4%)	Diamat IE-HPLC Median = 9.3% (4.3–12.7%) Median = 9.0% (4.0–14.7%)	HA-8121 IE-HPLC analyser Median = 6.4% (4.2–9.2%) Median = 7.1% (3.9–11.0%)	Tina-quant immunoassay Median = 7.3% (4.8–11.1%) Median = 8.0% (4.7–13.9%)	No statistically significant differences between the two groups by the three methods were observed.	

Study	Haemoglobinopathy	Mean HbA1c ± SD (range)								Conclusion				
		Method 1				Method 2					Method 3			
Mongia (2008) USA	(Mean diff to Ref) N=72 HbAS N=58 HbAC	6 IE-HPLC analysers At 6% HbA1c At 9% HbA1c 0.03 ± 0.29% -0.25 ± 0.42% -0.08 ± 0.28% -0.13 ± 0.27%				2 BA-HPLC analysers At 6% HbA1c At 9% HbA1c -0.04 ± 0.09% -0.10 ± 0.01% -0.03 ± 0.04% -0.11 ± 0.02%				4 Immunoassays At 6% HbA1c At 9% HbA1c 0.02 ± 0.24% -0.15 ± 0.22% 0.08 ± 0.44% -0.13 ± 0.34% Olympus AU400 Immunoassay 1.36% 2.25% 2.28% 3.57%				Clinically significant differences compared with the Reference Primus CLC 385 BA-HPLC analyser (>0.6% or >0.9% HbA1c at 6% or 9% HbA1c, respectively) were found with only one immunoassay method (Olympus AU400)
Roberts (2002) USA and UK	Mean diff to Ref – CLC 330 BA-HPLC N=61 HbAS N=43 HbAC	BA-HPLC analysers G-T, Provalis Variant, Nyco At 6% At 9% At 6% At 9% 0.42 0.55 0.14 0.27 1.0 ^a 1.09 ^a 0.41 0.33				IE-HPLC analysers HA8140 Variant II At 6% At 9% At 6% At 9% 0.81 ^a 0.57 0.57 0.43 0.22 0.28 0.42 0.42				Immunoassays Synchron Integra At 6% At 9% At 6% At 9% -0.41 -0.19 1.45 ^a 2.74 ^a -0.52 -0.27 2.18 ^a 4.10 ^a				^a p>0.05 The presence of HbC or HbS can produce clinically significant differences in gHb results for some methods. For all the methods examined in this study that had clinically significant effects, the percentage of HbA1c was overestimated.
Schnedl (2000) Austria	N=1 Hb Graz diabetic (mean FPG = 9.0 mmol/L) N=2 Hb Graz non-diabetic (mean FPG = 4.4 mmol/L) N=1 Hb Sherwood Forest (mean FPG = 5.0 mmol/L) N=2 HbO-Padova (mean FPG = 3.6 mmol/L) N=1 HbD (mean FPG = 6.0 mmol/L) N=1 HbS diabetic (mean FPG =	BA-HPLC analysers Diamat IMax 48.3 6.7 48.5 4.8 2.2/49.5 4.5 7.1 7.05 3.4 5.3 6.1 6.1 0/6.1 5.4				IE-HPLC analysers Variant Hitachi HA8140 53.7 No result Abn sep 52.7 No result Abn sep 49.2 1.2 Abn sep 5.75 4.75 8.5 (var Hb) 3.9 2.9 7.6 (var Hb) 3.6 2.9 7.1 (var Hb) 0.3/4.1 0/3.1 Abn sep/ 7.1 (var Hb)				Immunoassays DCA Integra Tina Uni 4.9 5.2 5.6 5.7 3.65 4.05 4.6 4.25 4.9 5.0 5.5 5.4 7.25 7.45 7.5 8.0 5.7 4.6 4.6 6.6 5.7 6.9 6.0 7.8 4.5 6.35 6.1 6.3				In managing diabetic patients, knowledge of haemoglobinopathies influencing HbA1c determination methods is essential because haemoglobin variants could cause mismanagement of diabetes resulting from false HbA1c determinations.

Study	Haemoglobinopathy	Mean HbA1c ± SD (range)								Conclusion
		Method 1		Method 2		Method 3				
	6.2 mmol/L) N=2 HbS non-diabetic (mean FPG = 5.3 mmol/L)									
Schnedl (2004) Austria	N=2 Hb Graz diabetic (mean FPG = 13.7 mmol/L) N=2 Hb Graz non- diabetic (mean FPG = 4.8 mmol/L) N=1 Hb Sherwood Forest (mean FPG = 5.2 mmol/L) N=1 HbD diabetic (mean FPG = 5.9 mmol/L) N=1 HbO-Padova diabetic (mean FPG = 5.9 mmol/L) N=1 HbO-Padova normal (mean FPG = 6.1 mmol/L)	Enzymatic Arkray 8.7 5.2 5.1 5.1 7.3 5.9	BA-HPLC Primus 8.55 5.35 4.8 5.4 7.6 5.3	IE-HPLC analysers HA8160 No result No result No result 4.1 5.9 3.8	HLC-723 No result No result 2.8 3.5 7.6 5.4	Immunoassays DCA Tina 5.85 5.8 4.05 4.35 4.7 5.2 6.2 5.7 7.8 7.6 5.8 5.4	Unimate 5.9 4.05 5.1 5.9 8.0 5.7	Rapida 5.15 2.6 4.4 5.7 8.3 5.6	The enzymatic and boronate affinity HPLC method did not interfere with any of the variants evaluated. Hb Graz interfered with all immunoassay and ion-exchange HPLC methods evaluated. The Tosoh ion-exchange HPLC method HLC-723 did not detect the late migrating HbO-Padova in the chromatogram, but this haemoglobin variant still interfered, causing artificially low HbA1c results.	

Study	Haemoglobinopathy	Mean HbA1c ± SD (range)						Conclusion
		Method 1		Method 2		Method 3		
Schnedl (2008) Austria	N=2 HbO-Padova diabetic N=2 Hb Graz diabetic N=1 Hb Graz non-diabetic N=1 HbD diabetic	BA-HPLC CLC 330 7.3 9.6 5.7 5.6	IE-HPLC analysers 2.2 plus G7 Variant Variant II 6.9 7.0 5.2 7.6 47.1 49.7 45.5 Abn sep 46.7 48.9 45.3 Abn sep 5.8 5.7 7.5 6.7	Immunoassay Ref standard DCA IFCC MS CE 6.6 7.6 7.5 6.2 11.1 10.0 4.2 6.5 6.6 5.6 5.9 5.9				The HbA1c results with immunoassay were low compared with all other methods. In Hb Graz the HbA1c values were lower (0.2–1.9%) compared with the IFCC reference methods. The BA-HPLC assay compared reasonably well with the IFCC reference methods.
Weykamp (1994) The Netherlands, Antilles	15 diagnostic laboratories N=17 HbAA N=37 HbAS N=22 HbAC N=8 HbSC N=6 HbSS N=3 HbCC	6 BA-HPLC 5.1% (4.5–6.4) 5.2% (4.2–6.5) 5.5% (4.2–7.7) 4.3% (3.1–7.4) 3.1% (2.3–4.5) 5.2% (3.6–8.7)	6 IE-HPLC 5.4% (4.0–6.8) 5.2% (3.7–7.2) 4.9% (3.7–6.6) 2.2% (1.7–2.8) 1.8% (0.9–3.0) 4.8% (4.4–5.3)	2 Immunoassays 1 Electrophoresis 5.3% (5.1–5.4) 4.8% 5.9% (5.8–5.9) 4.7% 5.8% (5.7–5.8) 4.0% 4.2% (4.1–4.3) 2.4% 3.3% (2.9–3.7) 3.0% 5.1% (5.0–5.2) 6.7%			Subjects with HbAS, HbAC do not show differences in HbA1c levels compared with subjects with HbAA. Subjects with HbSC have about 1.8 times shorter erythrocyte half-life (12–25 days) compared with subjects with HbAA, and lower GHb percentages were observed with all methods except for the Helena affinity chromatographic method. Subjects with HbSS have about 4.3 times shorter erythrocyte half-life (5–10 days) compared with subjects with HbAA, and GHb levels were lower. Subjects with HbCC have about 1.6 times shorter erythrocyte half-life (18–22 days) compared with subjects with HbAA. Most methods showed somewhat decreased or comparable GHb percentages.	
Ohwovoriole (1984) Nigeria	N=12 HbAS N=20 HbSS N=33 Healthy HbAA N=27 Diabetic HbAA	Micro-chromatography (BioRad) 6.50 ± 0.43% (4–9%) 9.73 ± 0.38% (7.5–14%) 7.63 ± 0.35% (5–9%) 11.51 ± 0.56% (6.5–15%)	C-TBA method (A443/10 mg Hb) 0.172 ± 0.004 0.163 ± 0.004 0.170 ± 0.003 0.268 ± 0.10				Micro-chromatography results must be interpreted with caution in sickle cell disease. The results of the colorimetric TBA method are not greatly affected by sickle cell trait (HbAS) or sickle cell anaemia (HbSS)	

BA-HPLC = boronate affinity HPLC; C-TBA = colorimetric thiobarbituric acid; ESI/MS = electrospray ionisation mass spectrometry; IE-HPLC = ion-exchange HPLC; TI = turbidimetric immunoinhibition

Appendix E Additional economic information

Structure and rationale of the economic evaluation

Test cost per person tested

The economic analysis will consider two intervention testing scenarios:

- where a single HbA1c cut-off is applied for the diagnosis of diabetes (or no diabetes) only (the base-case scenario, as proposed in the Final DAP); and
- where two diagnostic cut-offs are applied to enable a diagnosis of either pre-diabetes or diabetes (or neither) (alternative scenario).

Two test cost comparison analyses will be presented—the first (analysis 1) assumes no difference in the performance of the testing strategies (i.e. 100% test accuracy for FPG, OGT and HbA1c tests), while the second (analysis 2) incorporates the performance of the HbA1c test identified in the 'Effectiveness' section of this report. Both analyses assume 100% uptake of testing for all tests.

The inputs used in the test cost analysis include:

- the prevalence of pre-diabetes and diabetes in the overall high-risk population (37.2% and 9.9%, respectively) (see Table 27);
- testing-related costs (presented in Table 72), including patient episode initiation fee and GP consultation associated with the receipt of each test result (excluding HbA1c test on diagnosis of diabetes in comparator arm of the model); and
- test accuracy parameters (sensitivity, specificity and diagnostic yield), as described in the 'Inputs to the economic evaluation' section of the report (analysis 2 only).

The structure of each testing scenario analysis (comparator, base-case HbA1c and alternative HbA1c) is based on the current and proposed testing algorithms, as described in the 'Clinical pathway' section of the report.

Table 72: Testing-related healthcare resources used in the test cost analysis

Type of resource item	Natural unit of measurement	Unit cost	Source of unit cost	HbA1c resource use	FPG/OGT test resource use
HbA1c (blood test)	Test	\$16.80	MBS item 66551	Up to 3 tests	On diagnosis of diabetes (to assess severity of disease)
FPG (blood test)	Test	\$9.70	MBS item 66500	N/A	Up to 2 tests

Type of resource item	Natural unit of measurement	Unit cost	Source of unit cost	HbA1c resource use	FPG/OGT test resource use
OGT (blood test)	Test	\$18.95	MBS item 66542	N/A	One test in people with discordant/intermediate FPG results
Patient episode initiation (PEI) fee	Initiation of a patient episode	\$6.25	Weighted average of relevant PEIs (see Table 75)	On the initiation of a patient episode of testing (up to a maximum of 3)	On the initiation of a patient episode of testing (up to a maximum of 3)
GP consultation	Visit	\$36.30	MBS item 23	On receipt of test results (up to a maximum of 3)	On receipt of test results (up to a maximum of 3)

Source: based on MBS, effective 1 July 2013

HbA1c = glycated haemoglobin; FPG = fasting plasma glucose; OGT = oral glucose tolerance

The cost to reach a diagnosis of diabetes under each testing scenario depends on the number of tests required (two or three); and for the comparator testing scenario depends on what combination of tests are used to reach the diagnostic conclusion. The range of test costs for each diagnostic conclusion is presented in Table 73, with the results of the test cost analyses presented in Figure 21 and Figure 22, respectively, for analyses 1 and 2. The average test cost per person tested is presented in Table 21.

Table 73: Range of test costs to reach each diagnostic conclusion for comparator and HbA1c testing

Test strategy	NGT conclusion	Pre-diabetes conclusion	Diabetes conclusion
Comparator testing	\$52.25–\$166.00	\$113.75–\$166.00	\$121.30–\$182.80
HbA1c testing	\$59.35–\$178.05	\$59.35–178.05	\$118.70–\$178.05

HbA1c = glycated haemoglobin test; NGT = normal glucose tolerance

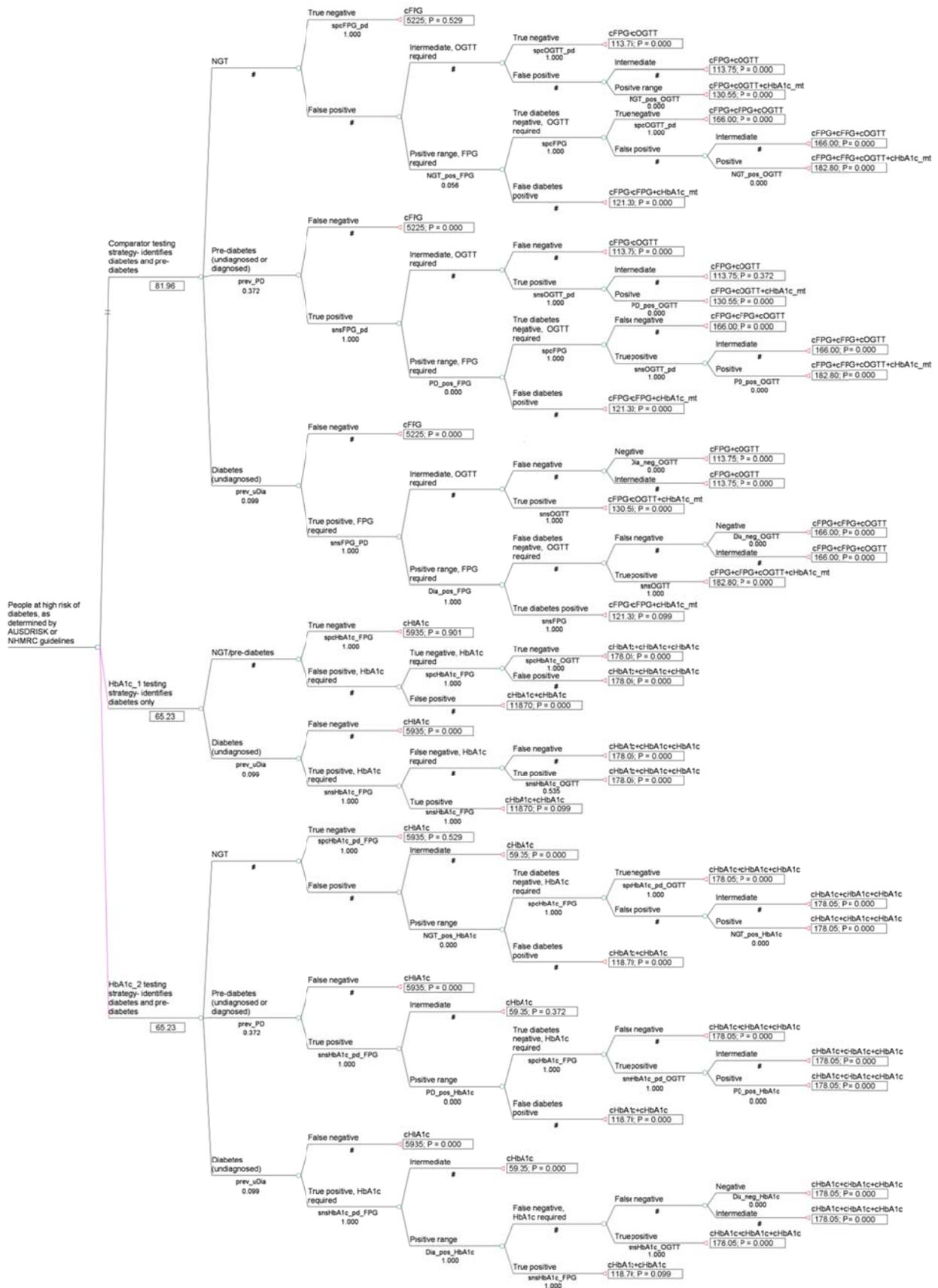


Figure 21: Test cost per person tested for current and proposed testing strategies (Analysis 1)

Source: based on current and proposed algorithms.

AUSDRISK = Australian Diabetes Risk; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; NHMRC = National Health and Medical Research Council; OGTT = oral glucose tolerance test

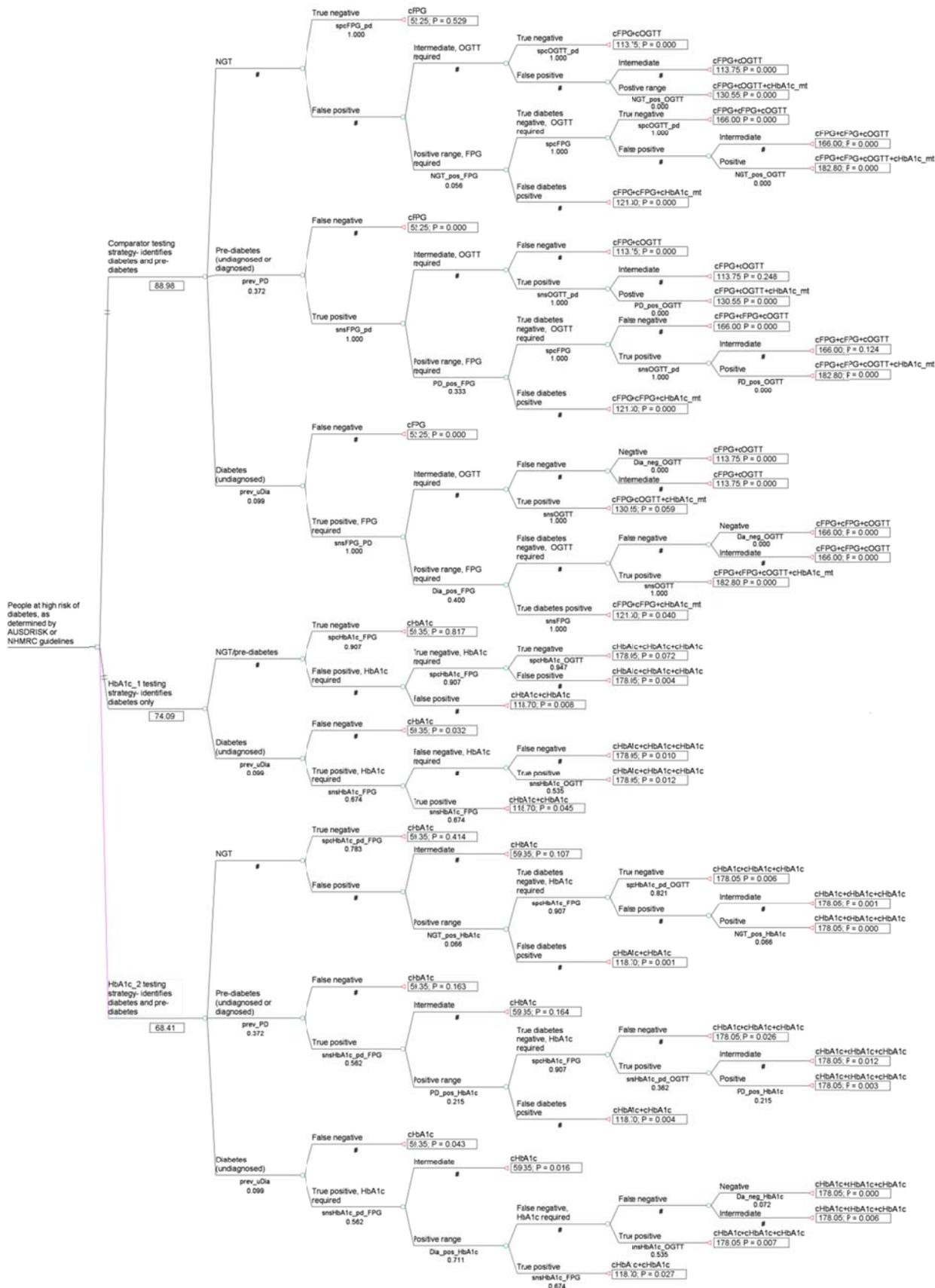


Figure 22: Test cost per person tested for current and proposed testing strategies (Analysis 2)

Source: based on current and proposed algorithms.

AUSDRISK = Australian Diabetes Risk; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; NHMRC = National Health and Medical Research Council; OGTT = oral glucose tolerance test

Literature search

(type 2 diabetes OR Diabetes Mellitus, Type 2[MeSH Terms]) AND (Mass Screening[MeSH Terms] OR screening OR diagnosis OR diagnosis[MeSH Terms] OR early detection) AND (cost effectiveness OR cost utility OR economic evaluation OR markov OR monte carlo)

Database	Last updated
Centre for Reviews and Dissemination database – including Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, the NHS Economic Evaluation Database	11 October 2013
PubMed	11 October 2013

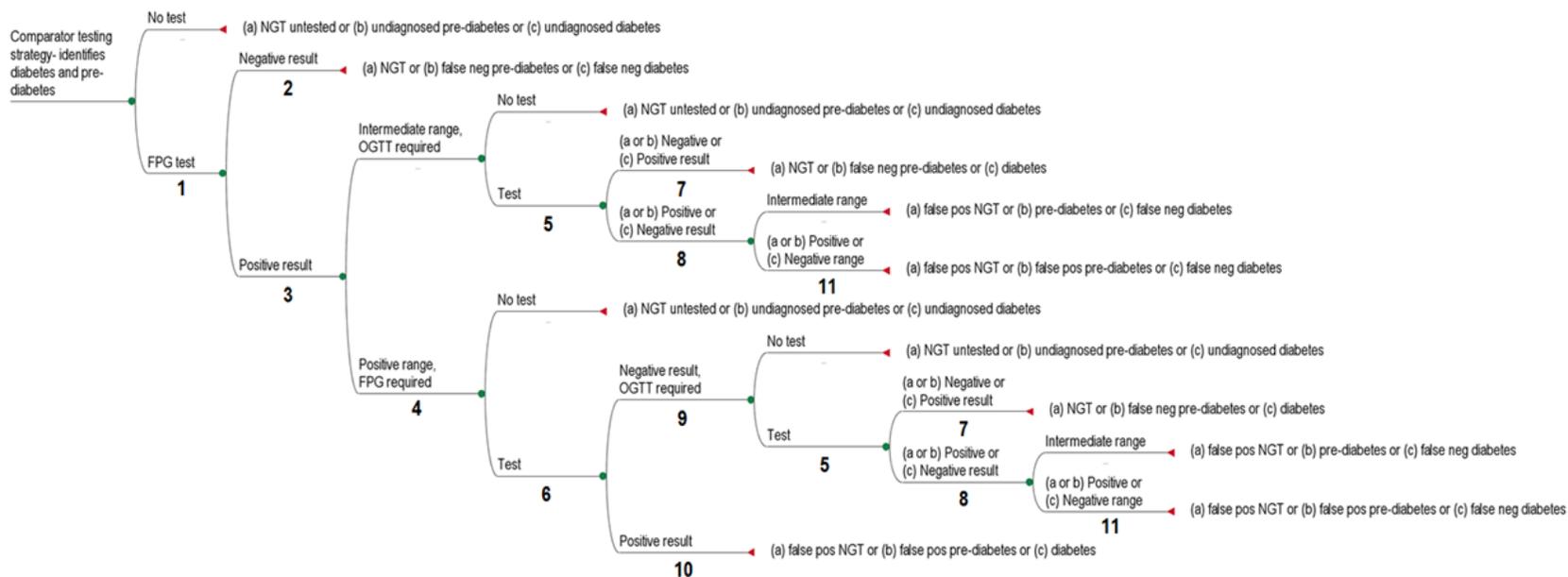
Inputs to the economic evaluation

Test parameters

Table 74: Test accuracy estimates for pre-diabetes and diabetes (from studies identified in the systematic review, compiled for the economic evaluation)

Pre-diabetes + diabetes	Studies	HbA1c cut-off	PG cut-off (mmol/L)	Sensitivity (95%CI)	Specificity (95%CI)
HbA1c vs FPG test	(Marini, Succurro, Arturi, et al. 2012)	≥5.7%	FPG ≥5.6	56.2% (49.5, 62.6)	78.3% (74.7, 81.5)
HbA1c vs FPG test	(Manley, SE et al. 2009): Australian population UK population	≥6.0%	FPG ≥6.1	79.2% [75.3, 82.6] 76.8% [72.3, 80.8] Median = 78.0%	62.3% [58.6, 65.8] 34.2% [26.3, 43.0] Median = 48.3%
HbA1c vs OGT test	(Bianchi et al. 2012) (Cosson et al. 2011)	≥5.7%	FPG ≥5.6	53.8% [48.6, 59.0] 19.3% [15.7, 23.6] Median = 36.2%	69.2% [64.6, 73.4] 95.0% [93.2, 96.3] Median = 82.1%
HbA1c vs OGT test	(Cavagnoli et al. 2011)	≥6.0%	FPG ≥5.6 2hPG ≥7.8	42.0% (37.1, 47.1)	92.6% (86.6, 96.1)

2hPG = 2-hour postprandial glucose; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OGT = oral glucose tolerance; PG = plasma glucose

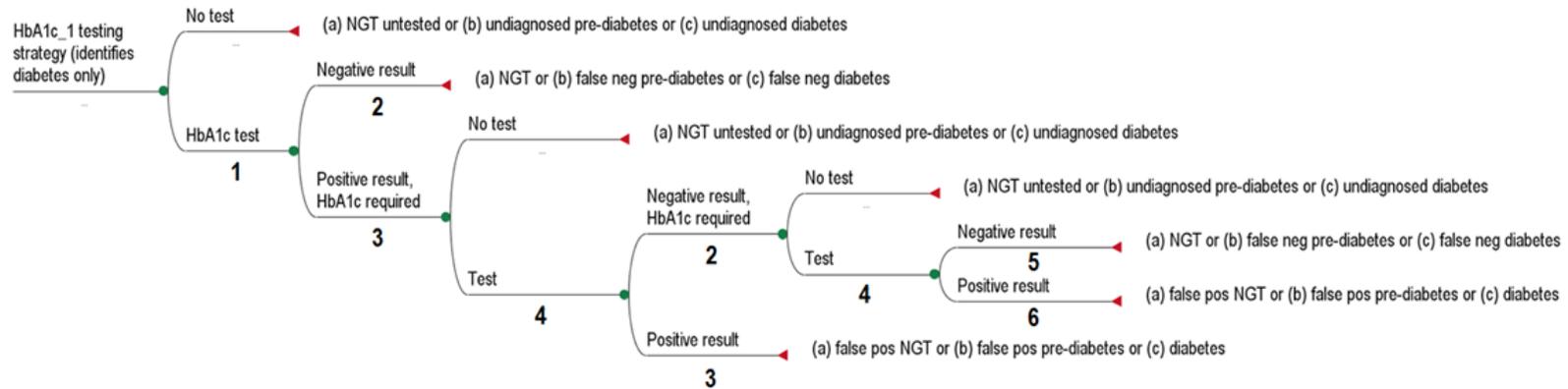


	Normal glucose tolerance status (a)	Pre-diabetes (b)	Diabetes (c)
1	Uptake of FPG = 0.70	Uptake of FPG = 0.70	Uptake of FPG = 0.70
2	Specificity of FPG (diabetes/pre-diabetes) = 1.0	#	#
3	#	Sensitivity of FPG (diabetes/pre-diabetes) = 1.0	Sensitivity of FPG (diabetes/pre-diabetes) = 1.0
4	Proportion of positive results in diabetes range = 0.056	Proportion of positive results in diabetes range = 0.333	Proportion of positive results in diabetes range = 0.400
5	Uptake of OGTT = 0.72	Uptake of OGTT = 0.72	Uptake of OGTT = 0.72
6	Uptake of confirmatory FPG = 0.85	Uptake of confirmatory FPG = 0.85	Uptake of confirmatory FPG = 0.85
7	Specificity of OGTT (diabetes/pre-diabetes) = 1.0	#	Sensitivity of FPG (diabetes) = 1.0
8	#	Sensitivity of OGTT (diabetes/pre-diabetes) = 1.0	#
9	Specificity of FPG (diabetes) = 1.0	Specificity of FPG (diabetes) = 1.0	#
10	#	#	Sensitivity of OGTT (diabetes) = 1.0
11	Proportion of positive results in diabetes range = 0.0	Proportion of positive results in diabetes range = 0.0	Proportion of negative results in NGT range = 0.0

Figure 23: Testing parameters in the comparator testing strategy decision tree

FPG = fasting plasma glucose; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test

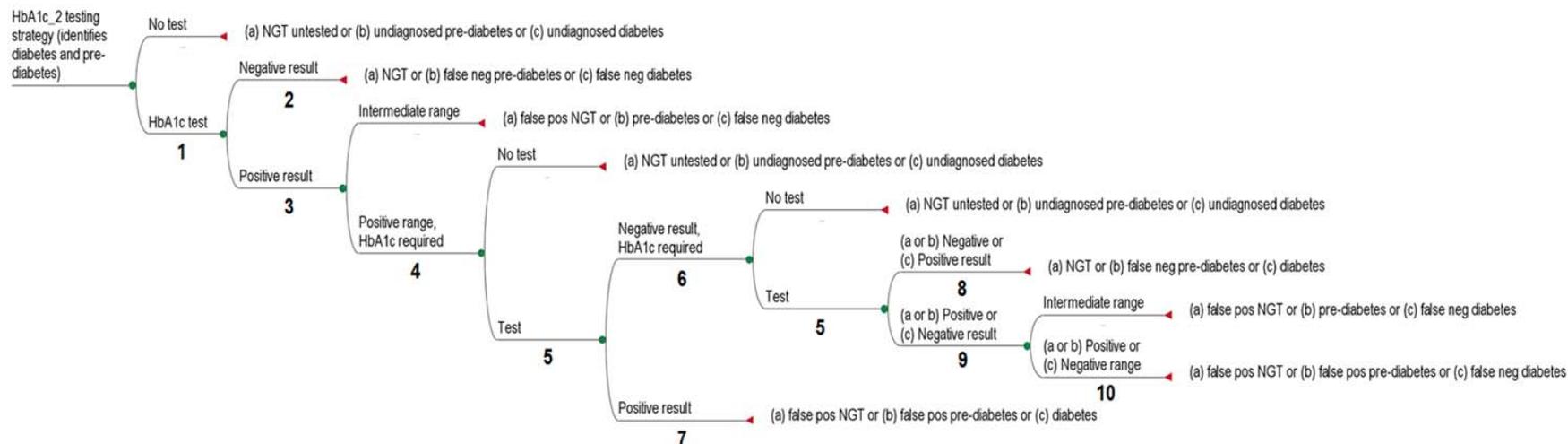
Note: Termination node is dependent on true status: (a) NGT; (b) pre-diabetes; (c) diabetes.



Normal glucose tolerance status (a)	Pre-diabetes (b)	Diabetes (c)
1 Uptake of HbA1c = 0.75	Uptake of HbA1c = 0.75	Uptake of HbA1c = 0.75
2 Specificity of HbA1c (diabetes, compared to FPG) = 0.770	Uptake of HbA1c (known pre-diabetes) = 1.0	Uptake of HbA1c (known pre-diabetes) = 1.0
3 #	#	#
4 Uptake of confirmatory HbA1c = 0.90	Uptake of confirmatory HbA1c = 0.90	Sensitivity of HbA1c (diabetes, compared to FPG) = 0.674
5 Specificity of HbA1c (diabetes, compared to OGTT) = 0.947	Uptake of HbA1c (known pre-diabetes) = 1.0	Uptake of confirmatory HbA1c = 0.90
6 #	Specificity of HbA1c (diabetes, compared to OGTT) = 0.947	Uptake of HbA1c (known pre-diabetes) = 1.0
	#	Uptake of FPG = 0.70
		Uptake of FPG (known pre-diabetes) = 1.0

Figure 24: Testing parameters in the HbA1c_1 testing strategy decision tree

FPG = fasting plasma glucose test; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test
 Note: Termination node is dependent on true status: (a) NGT; (b) pre-diabetes; (c) diabetes.



Normal glucose tolerance status (a)	Pre-diabetes (b)	Diabetes (c)
1 Uptake of HbA1c = 0.75	Uptake of HbA1c = 0.75	Uptake of HbA1c = 0.75
2 Specificity of HbA1c (diabetes/pre-diabetes, compared to FPG) = 0.783	Uptake of HbA1c (known pre-diabetes) = 1.0	Uptake of HbA1c (known pre-diabetes) = 1.0
3 #	#	#
4 Proportion of positive results in diabetes range = 0.066	Sensitivity of HbA1c (diabetes/pre-diabetes, compared to FPG) = 0.562	Sensitivity of HbA1c (diabetes/pre-diabetes, compared to FPG) = 0.562
5 Uptake of confirmatory HbA1c = 0.90	Proportion of positive results in diabetes range = 0.215	Proportion of positive results in diabetes range = 0.711
6 Specificity of HbA1c (diabetes, compared to FPG) = 0.770	Uptake of confirmatory HbA1c = 0.90	Uptake of confirmatory HbA1c = 0.90
7 #	Uptake of HbA1c (known pre-diabetes) = 1.0	Uptake of HbA1c (known pre-diabetes) = 1.0
8 Specificity of HbA1c (diabetes/pre-diabetes, compared to OGTT) = 0.821	Specificity of HbA1c (diabetes, compared to FPG) = 0.770	Sensitivity of HbA1c (diabetes, compared to FPG) = 0.674
9 #	#	Sensitivity of HbA1c (diabetes, compared to OGTT) = 0.535
10 Proportion of positive results in diabetes range = 0.066	Sensitivity of HbA1c (diabetes/pre-diabetes, compared to OGTT) = 0.362	Sensitivity of HbA1c (diabetes) = 1.0
	Proportion of positive results in diabetes range = 0.215	Proportion of negative results in NGT range = 0.072

Figure 25: Testing parameters in the HbA1c_2 testing strategy decision tree

FPG = fasting plasma glucose test; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test

Note: Termination node is dependent on true status: (a) NGT; (b) pre-diabetes; (c) diabetes.

Transition probabilities

Transition to diabetes with complications

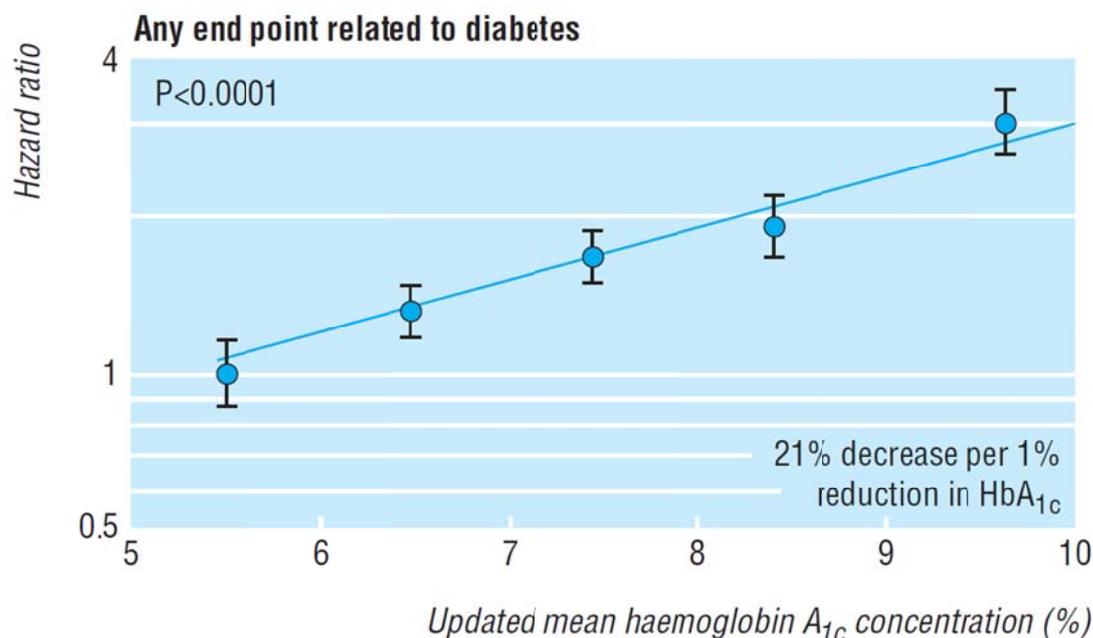


Figure 26: Hazard ratios for diabetes-related complications associated with HbA_{1c} concentration

Source: Stratton et al. (2000)

HbA_{1c} = glycated haemoglobin

Note: Hazard ratios, with 95% CIs as floating absolute risks, as estimate of association between category of updated mean HbA_{1c} concentration and any endpoint related to diabetes. Reference category (hazard ratio 1.0) is HbA_{1c} <6% with log linear scales.

Healthcare resources

Table 75: Weighted average patient episode initiation fee

Relevant MBS patient episode initiation items	Services (July 2012 – June 2013)	Weight	MBS item fee	MBS fee (outpatient)	Patient co-payment
73920	318,161	0.0155	\$2.40	\$2.05	\$0.35
73928	18,113,907	0.8797	\$5.95	\$5.10	\$0.85
73929	765,607	0.0372	\$2.40	\$2.05	\$0.35
73932	769,870	0.0374	\$10.25	\$8.75	\$1.50
73933	31,680	0.0015	\$2.40	\$2.05	\$0.35
73934	586,679	0.0285	\$17.60	\$15.00	\$2.60
73935	5,109	0.0002	\$2.40	\$2.05	\$0.35
Total	20,591,013	1.0000	\$6.25	\$5.35	\$0.90

Source: Medicare Australia (2013a)

Note: Item fees based on MBS, effective 1 July 2013.

Implications for false positive and false negative patients

Table 76: Resource use estimated for people with a false diagnosis of diabetes

Type of resource item	Natural unit of measurement	Unit cost	Source of unit cost	Quantity per annum	Total cost
GP consultation	Visit	\$36.30	MBS item 23	1	\$36.30
GP consultation	Visit	\$36.30	MBS item 2517	1	\$36.30
HbA1c	Test	\$16.80	MBS item 66551	1	\$16.80
HDL cholesterol	Test	\$11.05	MBS item 66536	1	\$11.05
Total cholesterol, triglycerides and creatinine (serum)	Test	\$11.65	MBS item 66506	1	\$11.65
Microalbuminuria (urine)	Test	\$9.70	MBS item 66500	1	\$9.70
Eye examination	Visit	\$71.00	MBS item 10915	0.5	\$35.50
Total					\$157.30

Source: based on MBS, effective 1 July 2013

Note: Resources and quantities per year based on the guidelines for the diabetes practice incentive program (Medicare Australia 2013b).

Outputs from the economic evaluation

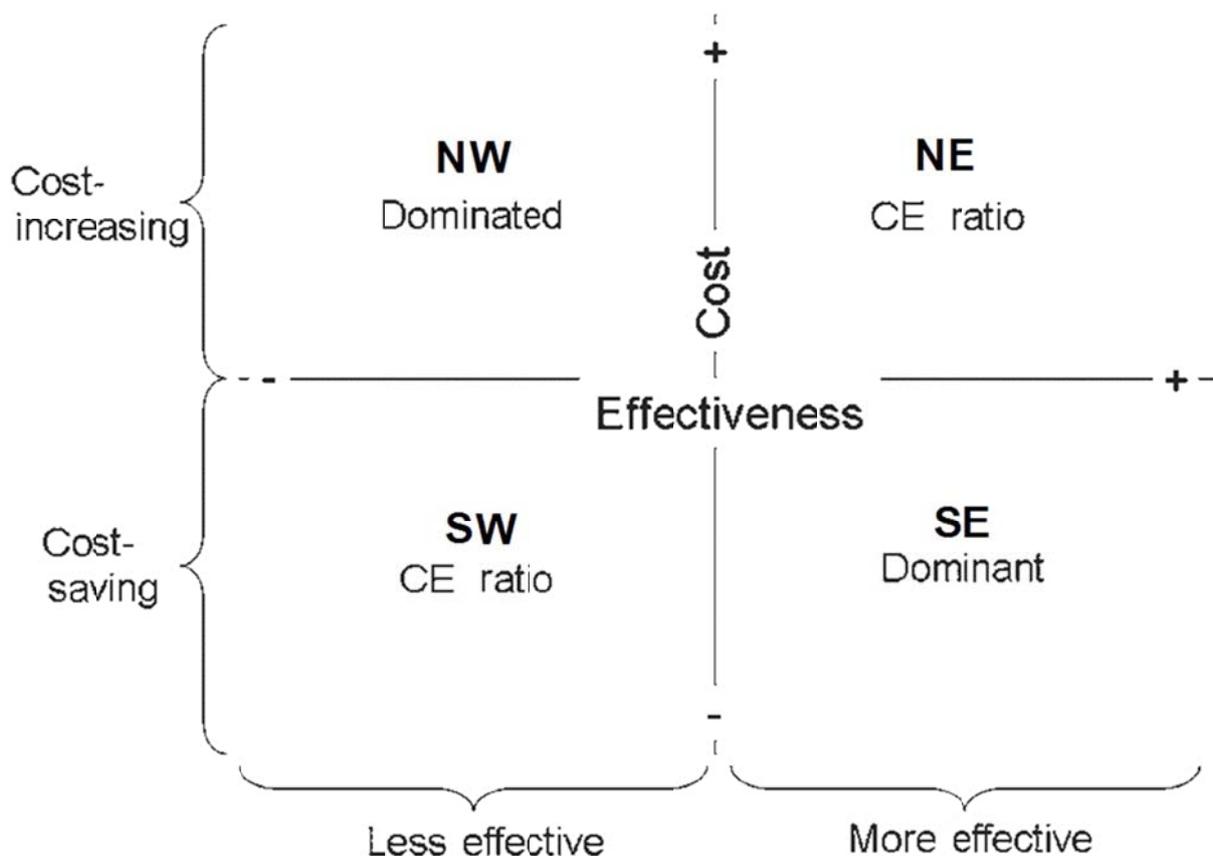


Figure 27: The cost-effectiveness plane

Source: adapted from Cohen and Reynolds (2008)

NE = north-east quadrant; NW = north-west quadrant; SE = south-east quadrant; SW = south-west quadrant

Table 77: Stepped cost-effectiveness rankings, considering all scenarios

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
Step 1					
HbA1c_1	\$8,084	-	16.2267	-	-
HbA1c_2	\$8,185	\$101	16.2420	0.0153	\$6,611
Comparator	\$8,439	\$355	16.2420	0.0000	Dominated
Step 2					
HbA1c_1	\$8,049	-	16.2175	-	-
HbA1c_2	\$8,143	\$94	16.2387	0.0212	\$4,421
Comparator	\$8,348	\$205	16.2353	-0.0034	Dominated
Step 3					
HbA1c_1	\$8,224	-	16.2015	-	-
Comparator	\$8,423	\$200	16.2340	0.3260	\$6,133
HbA1c_2	\$8,503	\$79	16.2139	-0.0202	Dominated

Comparator = FPG test followed by OGT test in patients with initial equivocal results, or confirmatory FPG test in patients with initial positive results; FPG = fasting plasma glucose; ICER = incremental cost-effectiveness ratio; OGT = oral glucose tolerance

Table 78: Incremental costs and effectiveness outcomes, by model health state, HbA1c_1 scenario

Model health state	Comparator	HbA1c_1 scenario	Increment
<i>Costs</i>			
Normal glucose tolerance	\$115.64	\$191.08	\$75.44
Undiagnosed pre-diabetes	\$435.36	\$1,528.83	\$1,093.46
Diagnosed pre-diabetes	\$1,813.44	\$349.54	-\$1,463.90
Undiagnosed diabetes	\$140.83	\$576.55	\$435.72
Diagnosed diabetes	\$2,430.64	\$1,661.94	-\$768.69
Diabetes with complications	\$3,487.47	\$3,915.78	\$428.31
Total	\$8,423.38	\$8,223.71	-\$199.67
<i>QALYs</i>			
Normal glucose tolerance	7.4097	7.4097	0.0000
Undiagnosed pre-diabetes	1.3971	4.5814	3.1843
Diagnosed pre-diabetes	4.1231	0.9388	-3.1843
Undiagnosed diabetes	0.1871	0.7532	0.5661
Diagnosed diabetes	2.2337	1.5287	-0.7050
Diabetes with complications	0.8834	0.9897	0.1063
Total	16.2340	16.2015	-0.0326

QALYs = quality-adjusted life years

Table 79: Incremental costs and effectiveness outcomes, by model health state, HbA1c_2 scenario

Model health state	Comparator	HbA1c_2 scenario	Increment
<i>Costs</i>			
Normal glucose tolerance	\$115.64	\$271.81	\$156.17
Undiagnosed pre-diabetes	\$435.36	\$693.86	\$258.50
Diagnosed pre-diabetes	\$1,813.44	\$1,392.82	-\$420.61
Undiagnosed diabetes	\$140.83	\$415.08	\$274.25
Diagnosed diabetes	\$2,430.64	\$1,971.78	-\$458.85
Diabetes with complications	\$3,487.47	\$3,757.36	\$269.89
Total	\$8,423.38	\$8,502.72	\$79.34
<i>QALYs</i>			
Normal glucose tolerance	7.4097	7.4097	0.0000
Undiagnosed pre-diabetes	1.3971	1.8333	0.4362
Diagnosed pre-diabetes	4.1231	3.6869	-0.4362
Undiagnosed diabetes	0.1871	0.5179	0.3308
Diagnosed diabetes	2.2337	1.8153	-0.4184
Diabetes with complications	0.8834	0.9508	0.0675
Total	16.2340	16.2139	-0.0202

QALYs = quality-adjusted life years

Table 80: Cost-effectiveness analysis, HbA1c_1 scenario vs HbA1c_2 scenario, step 3

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
HbA1c_1	\$8,224	-	16.2015	-	-
HbA1c_2	\$8,503	\$279	16.2139	0.0124	\$22,507

ICER = incremental cost-effectiveness ratio

Sensitivity analyses—Step 3 of the economic evaluation

Table 81: Tornado analysis of the base-case (HbA1c_1) scenario, tabulated

Variable	Description	Range tested	Lower ICER	Upper ICER	Spread	Base-case deviation	
						Lower ICER	Upper ICER
cUndiagPD	Annual cost in undiagnosed pre-diabetes	0–500.0	Dominated	\$32,674	\$43,652	279%	–433%
cDia	Annual cost in diabetes	507.0–1313.0	Dominated	\$16,375	\$20,534	168%	–167%
cUndiag_Dia	Annual cost in undiagnosed diabetes	227.0–1041.0	Dominated	\$14,480	\$16,653	135%	–136%
rr_comp_undiag	Risk of complications in undiagnosed diabetes	1.52–1.92	\$3,196	\$11,660	\$8,464	48%	–90%
cDia_comp	Annual cost in diabetes (with complications)	1836.0–3459.0	\$2,187	\$10,084	\$7,897	64%	–64%
spcHbA1c_FPG	Specificity of HbA1c (diabetes) vs FPG tests	0.839–0.948	\$2,695	\$7,602	\$4,907	56%	–24%
upFPG_kPD	Uptake of FPG test, known pre-diabetes	0.7–1.0	\$1,230	\$6,133	\$4,903	80%	0%
ini_age	Initial patient age	40.0–60.0	\$6,133	\$10,400	\$4,267	0%	–70%
snsHbA1c_FPG	Sensitivity of HbA1c (diabetes) vs FPG tests	0.589–0.749	\$4,712	\$7,712	\$3,000	23%	–26%
uDia	Annual utility in diabetes	0.8–0.85	\$6,133	\$8,188	\$2,054	0%	–33%
rIncid_PD	Increased risk of pre-diabetes in high-risk population	1.0–2.29	\$4,307	\$6,133	\$1,826	30%	0%
pUndiag_PD	Initial proportion of undiagnosed pre-diabetes	0–1.0	\$5,496	\$7,158	\$1,661	10%	–17%
upOGTT_kPD	Uptake of OGT test, known pre-diabetes	0.72–1.0	\$4,592	\$6,133	\$1,541	25%	0%
upFPG	Uptake of FPG test	0.7–1.0	\$6,133	\$7,360	\$1,227	0%	–20%
snsHbA1c_OGTT	Sensitivity of HbA1c (diabetes) vs OGT tests	0.369–0.693	\$5,608	\$6,659	\$1,051	9%	–9%
upHbA1c_conf	Uptake of confirmatory HbA1c test	0.75–0.9	\$5,276	\$6,133	\$857	14%	0%
upHbA1c	Uptake of HbA1c test	0.75–1.0	\$5,363	\$6,133	\$771	13%	0%
spcHbA1c_OGTT	Specificity of HbA1c (diabetes) vs OGT tests	0.898–0.973	\$5,666	\$6,378	\$711	8%	–4%
uUndiagDia	Annual utility in undiagnosed diabetes	0.84–0.86	\$5,840	\$6,457	\$617	5%	–5%
upOGTT_conf	Uptake of confirmatory OGT test	0.72–1.0	\$6,133	\$6,253	\$120	0%	–2%
upHbA1c_kPD	Uptake of HbA1c test, known pre-diabetes	0.75–1.0	\$6,027	\$6,133	\$106	2%	0%
upFPG_conf	Uptake of confirmatory FPG test	0.7–0.85	\$6,133	\$6,230	\$96	0%	–2%
mort_NGT	Mortality in NGT, high-risk population	1.0–1.2	\$6,132	\$6,133	\$1	0%	0%
cPD	Annual cost in diagnosed pre-diabetes	67.0–540.0	\$6,133	\$6,133	\$0	0%	0%

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Table 82: Tornado analysis of the alternative (HbA1c_2) scenario, tabulated

Variable	Description	Range tested	Lower ICER	Upper ICER	Spread	Base-case deviation	
						Lower ICER	Upper ICER
cDia	Annual cost in diabetes	507.0–1313.0	Dominated	\$5,881	\$19,683	251%	–249%
cUndiag_Dia	Annual cost in undiagnosed diabetes	227.0–1041.0	Dominated	\$3,941	\$15,715	199%	–200%
upFPG_kPD	Uptake of FPG test, known pre-diabetes	0.7–1.0	Dominated	Dominated	\$13,492	343%	0%
cDia_comp	Annual cost in diabetes (with complications)	1836.0–3459.0	Dominated	\$113	\$8,094	103%	–103%
ini_age	Initial patient age	40.0–60.0	Dominated	\$3,444	\$7,379	0%	–187%
rlncid_PD	Increased risk of pre-diabetes in high-risk population	1.0–2.29	Dominated	Dominated	\$6,812	173%	0%
cUndiagPD	Annual cost in undiagnosed pre-diabetes	0–500.0	Dominated	Dominated	\$6,439	99%	–64%
upHbA1c_kPD	Uptake of HbA1c test, known pre-diabetes	0.75–1.0	Dominated	\$837	\$4,773	0%	–121%
upHbA1c	Uptake of HbA1c test	0.75–1.0	Dominated	Dominated	\$4,590	117%	0%
upFPG	Uptake of FPG test	0.7–1.0	Dominated	Dominated	\$3,814	0%	–97%
upOGTT_kPD	Uptake of OGT test, known pre-diabetes	0.72–1.0	Dominated	Dominated	\$3,740	95%	0%
rr_comp_undiag	Risk of complications in undiagnosed diabetes	1.52–1.92	Dominated	Dominated	\$2,863	25%	–47%
spcHbA1c_pd_FPG	Specificity of HbA1c (diabetes & PD) vs FPG tests	0.747–0.815	Dominated	Dominated	\$2,353	31%	–28%
snsHbA1c_pd_FPG	Sensitivity of HbA1c (diabetes & PD) vs FPG tests	0.495–0.626	Dominated	Dominated	\$2,037	30%	–22%
upOGTT_conf	Uptake of confirmatory OGT test	0.72–1.0	Dominated	Dominated	\$1,783	0%	–45%
spcHbA1c_FPG	Specificity of HbA1c (diabetes) vs FPG tests	0.839–0.948	Dominated	Dominated	\$1,750	28%	–17%
uDia	Annual utility in diabetes	0.8–0.85	Dominated	Dominated	\$1,352	34%	0%
snsHbA1c_pd_OGTT	Sensitivity of HbA1c (diabetes & PD) vs OGT tests	0.193–0.538	Dominated	Dominated	\$1,180	15%	–15%
pUndiag_PD	Initial proportion of undiagnosed pre-diabetes	0–1.0	Dominated	Dominated	\$839	12%	–10%
upFPG_conf	Uptake of confirmatory FPG test	0.7–0.85	Dominated	Dominated	\$479	12%	0%
uUndiagDia	Annual utility in undiagnosed diabetes	0.84–0.86	Dominated	Dominated	\$404	5%	–5%
upHbA1c_conf	Uptake of confirmatory HbA1c test	0.75–0.9	Dominated	Dominated	\$232	0%	–6%
snsHbA1c_FPG	Sensitivity of HbA1c (diabetes) vs FPG tests	0.589–0.749	Dominated	Dominated	\$212	3%	–3%
spcHbA1c_pd_OGTT	Specificity of HbA1c (diabetes & PD) vs OGT tests	0.692–0.95	Dominated	Dominated	\$138	2%	–2%

Variable	Description	Range tested	Lower ICER	Upper ICER	Spread	Base-case deviation	
						Lower ICER	Upper ICER
snsHbA1c_OGTT	Sensitivity of HbA1c (diabetes) vs OGT tests	0.369–0.693	Dominated	Dominated	\$117	1%	–1%
mort_NGT	Mortality in NGT, high-risk population	1.0–1.2	Dominated	Dominated	\$41	0%	–1%
cPD	Annual cost in diagnosed pre-diabetes	67.0–540.0	Dominated	Dominated	\$0	0%	0%
spcHbA1c_OGTT	Specificity of HbA1c (diabetes) vs OGT tests	0.898–0.973	Dominated	Dominated	\$0	0%	0%

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance; PD = pre-diabetes

Sensitivity analyses—Step 2 of the economic evaluation

The results of sensitivity analyses, assuming 100% HbA1c test performance, are presented in Figure 28 and Table 83 for the HbA1c_1 testing scenario, and Figure 29 and Table 84 for HbA1c_2.

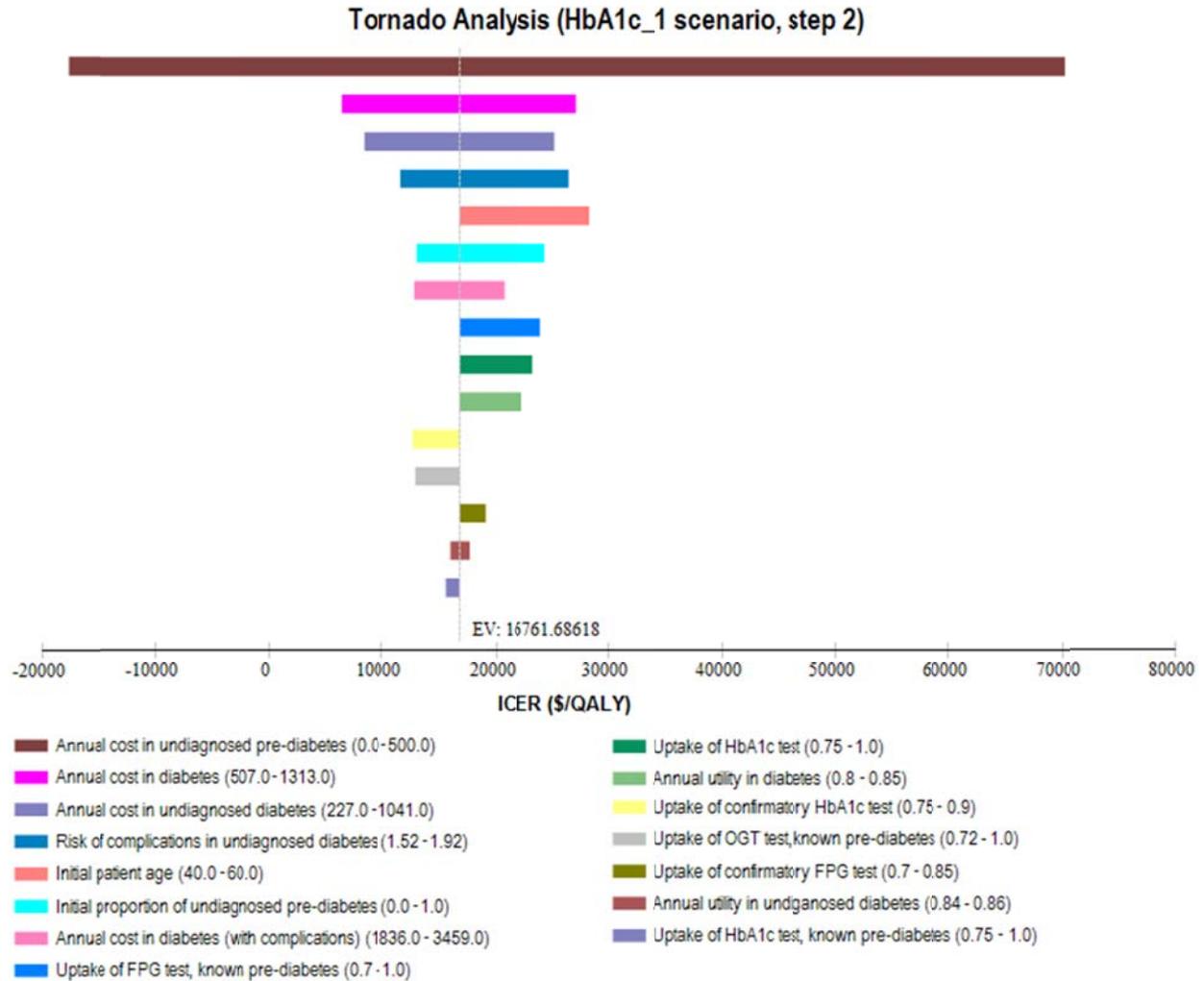


Figure 28: Tornado analysis of the base-case (HbA1c_1) scenario (Step 2)

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Table 83: Tornado analysis of the base-case (HbA1c_1) scenario (Step 2), tabulated

Variable	Description	Range tested	Lower ICER	Upper ICER	Spread	Base-case deviation	
						Lower ICER	Upper ICER
cUndiagPD	Annual cost in undiagnosed pre-diabetes	0–500.0	Dominated	\$70,232	\$87,945	–206%	319%
cDia	Annual cost in diabetes	507.0–1313.0	\$6,364	\$27,108	\$20,744	–62%	62%
cUndiag_Dia	Annual cost in undiagnosed diabetes	227.0–1041.0	\$8,341	\$25,224	\$16,883	–50%	50%
rr_comp_undiag	Risk of complications in undiagnosed diabetes	1.52–1.92	\$11,608	\$26,462	\$14,855	–31%	58%
ini_age	Initial patient age	40.0–60.0	\$16,762	\$28,265	\$11,504	0%	69%
pUndiag_PD	Initial proportion of undiagnosed pre-diabetes	0–1.0	\$13,042	\$24,366	\$11,325	–22%	45%
cDia_comp	Annual cost in diabetes (with complications)	1836.0–3459.0	\$12,839	\$20,689	\$7,850	–23%	23%
upFPG_kPD	Uptake of FPG test, known pre-diabetes	0.7–1.0	\$16,762	\$23,995	\$7,233	0%	43%
upHbA1c	Uptake of HbA1c test	0.75–1.0	\$16,762	\$23,311	\$6,549	0%	39%
uDia	Annual utility in diabetes	0.8–0.85	\$16,762	\$22,343	\$5,581	0%	33%
upHbA1c_conf	Uptake of confirmatory HbA1c test	0.75–0.9	\$12,663	\$16,762	\$4,099	–24%	0%
upOGTT_kPD	Uptake of OGT test, known pre-diabetes	0.72–1.0	\$12,916	\$16,762	\$3,846	–23%	0%
upFPG_conf	Uptake of confirmatory FPG test	0.7–0.85	\$16,762	\$19,037	\$2,275	0%	14%
uUndiagDia	Annual utility in undiagnosed diabetes	0.84–0.86	\$15,964	\$17,643	\$1,679	–5%	5%
upHbA1c_kPD	Uptake of HbA1c test, known pre-diabetes	0.75–1.0	\$15,570	\$16,762	\$1,192	–7%	0%
rIncid_PD	Increased risk of pre-diabetes in high-risk population	1.0–2.29	\$16,762	\$17,184	\$423	0%	3%
upOGTT_conf	Uptake of confirmatory OGT test	0.72–1.0	\$16,408	\$16,762	\$354	–2%	0%
upFPG	Uptake of FPG test	0.7–1.0	\$16,447	\$16,762	\$315	–2%	0%
mort_NGT	Mortality in NGT, high-risk population	1.0–1.2	\$16,754	\$16,762	\$8	0%	0%
cPD	Annual cost in diagnosed pre-diabetes	67.0–540.0	\$16,762	\$16,762	\$0	0%	0%

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

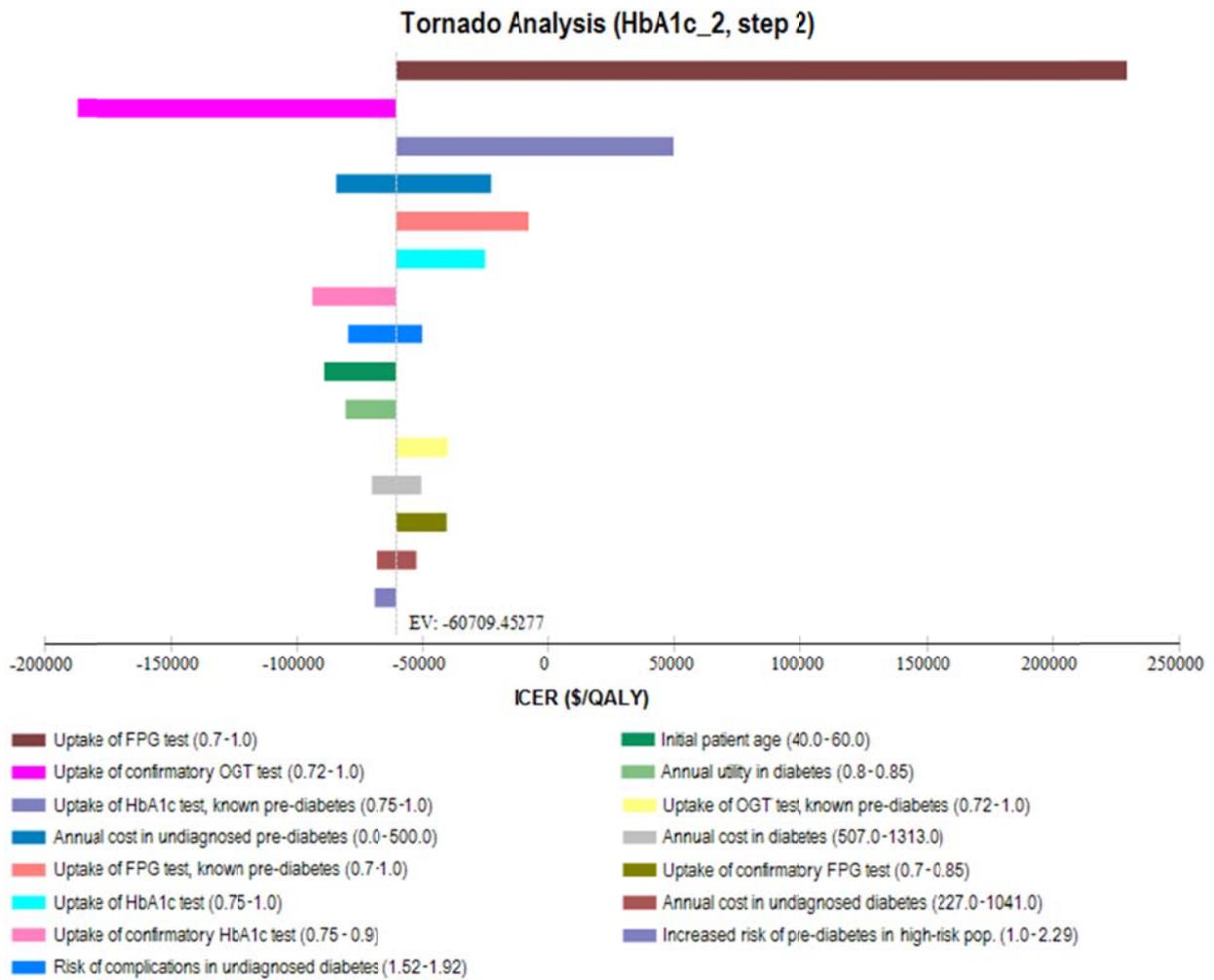


Figure 29: Tornado analysis of the alternative (HbA1c_2) scenario (Step 2)

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Table 84: Tornado analysis of the alternative (HbA1c_2) scenario (Step 2), tabulated

Variable	Description	Range tested	Lower ICER	Upper ICER	Spread	Base-case deviation	
						Lower ICER	Upper ICER
upFPG	Uptake of FPG test	0.7–1.0	Dominant	\$229,710	\$290,419	0%	478%
upOGTT_conf	Uptake of confirmatory OGT test	0.72–1.0	Dominant	Dominant	\$126,771	–209%	0%
upHbA1c_kPD	Uptake of HbA1c test, known pre-diabetes	0.75–1.0	Dominant	\$49,712	\$110,422	0%	182%
cUndiagPD	Annual cost in undiagnosed pre-diabetes	0.0–500.0	Dominant	Dominant	\$61,418	–40%	62%
upFPG_kPD	Uptake of FPG test, known pre-diabetes	0.7–1.0	Dominant	Dominant	\$53,003	0%	87%
upHbA1c	Uptake of HbA1c test	0.75–1.0	Dominant	Dominant	\$34,977	0%	58%
upHbA1c_conf	Uptake of confirmatory HbA1c test	0.75–0.9	Dominant	Dominant	\$33,484	–55%	0%
rr_comp_undiag	Risk of complications in undiagnosed diabetes	1.52–1.92	Dominant	Dominant	\$29,693	–32%	17%
ini_age	Initial patient age	40.0–60.0	Dominant	Dominant	\$28,865	–48%	0%
uDia	Annual utility in diabetes	0.8–0.85	Dominant	Dominant	\$20,458	–34%	0%
upOGTT_kPD	Uptake of OGT test, known pre-diabetes	0.72–1.0	Dominant	Dominant	\$20,295	0%	33%
cDia	Annual cost in diabetes	507.0–1313.0	Dominant	Dominant	\$20,046	–17%	16%
upFPG_conf	Uptake of confirmatory FPG test	0.7–0.85	Dominant	Dominant	\$19,945	0%	33%
cUndiag_Dia	Annual cost in undiagnosed diabetes	227.0–1041.0	Dominant	Dominant	\$16,141	–13%	13%
rlncid_PD	Increased risk of pre-diabetes in high-risk population	1.0–2.29	Dominant	Dominant	\$8,922	–15%	0%
cDia_comp	Annual cost in diabetes (with complications)	1836.0–3459.0	Dominant	Dominant	\$7,943	–7%	7%
pUndiag_PD	Initial proportion of undiagnosed pre-diabetes	0–1.0	Dominant	Dominant	\$7,672	–7%	6%
uUndiagDia	Annual utility in undiagnosed diabetes	0.84–0.86	Dominant	Dominant	\$6,136	–5%	5%
mort_NGT	Mortality in NGT, high-risk population	1.0–1.2	Dominant	Dominant	\$100	0%	0%
cPD	Annual cost in diagnosed pre-diabetes	67.0–540.0	Dominant	Dominant	\$0	0%	0%

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; NGT = normal glucose tolerance; OGT = oral glucose tolerance; PD = pre-diabetes

Additional sensitivity analysis (Table 85) was performed to incorporate the effect of LMPs in people with pre-diabetes—assuming all pre-diabetics participate in one LMP—at a cost of \$300 (AGPN 2008), which reduces the probability of progressing to diabetes by 49% (Gillies et al. 2007).

Table 85: Additional sensitivity analyses

	Cost	Incremental cost	QALYs	Incremental QALYs	ICER (\$/QALY)
Base-case (HbA1c_1)					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_1	\$8,049	-\$298 (cost saving)	16.2175	0.0178 (less effective)	\$16,762 (SW quadrant of CE plane)
<i>Lifestyle modification</i>					
Comparator	\$8,377	-	16.2526	-	-
HbA1c_1	\$8,049	-\$328 (cost saving)	16.2175	-0.0351 (less effective)	\$9,340 (SW quadrant of CE plane)
Base-case (HbA1c_2)					
Comparator	\$8,347	-	16.2353	-	-
HbA1c_2	\$8,143	-\$205 (cost saving)	16.2387	0.0034 (more effective)	Dominant (SE quadrant of CE plane)
<i>Lifestyle modification</i>					
Comparator	\$8,377	-	16.2526	-	-
HbA1c_2	\$8,170	-\$207 (cost saving)	16.2582	0.0057 (more effective)	Dominant (SE quadrant of CE plane)

QALYs = quality-adjusted life years; HbA1c = glycated haemoglobin; ICER = incremental cost-effectiveness ratio; CE = cost-effectiveness

Appendix F Additional financial information

Data sources used in the financial analysis

Table 86: Medicare statistics for items associated with tests listed in item 66500

Items associated with tests listed in item 66500	No. of services (July 2007 – June 2008)	Proportion	No. of services (July 2012 – June 2013)	Proportion
66500	666,376	5.1%	764,812	5.1%
66503	474,715	3.6%	441,987	3.0%
66506	413,076	3.1%	297,672	2.0%
66509	91,984	0.7%	76,972	0.5%
66512	75,858	0.6%	13,389,671	89.4%
66515	11,400,341	86.9%	N/A	N/A
Total	13,122,350	100%	14,971,114	100%

Source: Medicare Australia (2013a)

Table 87: Estimated ordering of initial FPG test

Initial FPG ordered	Source (2012–13 data)	Proportion used
In isolation (i.e. 1 test)	Services for item 66500	5.1%
With up to 4 other tests	Sum of services for items 66503, 66506, 66509 and 0.7% × services for item 66512	6.0%
With 5 or more other tests	99.7% × services for item 66512	88.8%

Source: Medicare Australia (2013a)

Estimating the population eligible for testing

Table 88: Diabetic and pre-diabetic population projections, 1999–00 to 2018–19 (some years omitted)

	Step	Source	1999–00	2000–01	2012–13	2013–14	2014–15	2015–16	2016–17	2017–18	2018–19
Known diabetes											
A	Estimated Australian population (aged 40 years or older)	ABS (2013b, 2013c)	8,138,026	8,349,912	10,716,769	10,927,896	11,135,359	11,340,590	11,548,414	11,760,277	11,981,565
B	Estimated mortality rate	ABS (2012)	1.47%	1.46%	1.34%	1.33%	1.32%	1.31%	1.30%	1.29%	1.28%
C	Prevalence of diabetes in 1999–00	AusDiab (Dunstan et al. 2001)	11.2%								
D	Total population with diabetes (1999–00)	A × C	915,336	-	-	-	-	-	-	-	-
E	Total population with diabetes (subsequent years)	E (or D) × (1 – B) + I (or J) × (1 – B) × H (from previous year)	-	945,753	1,303,238	1,333,932	1,364,969	1,396,383	1,428,206	1,460,466	1,493,191
Pre-diabetes											
F	Prevalence of pre-diabetes in 1999–00	AusDiab (Dunstan et al. 2001)	21.0%								
G	Incidence of pre-diabetes	AusDiab (Tanamas et al. 2013)	1.3%								
H	Incidence of diabetes in pre-diabetes	AusDiab (Tanamas et al. 2013)	2.6%								
I	Total population with pre-diabetes (1999–00)	A × F	1,712,563	-	-	-	-	-	-	-	-
J	Total population with pre-diabetes (subsequent years)	K × (1 – J) + (A – F – K) × I (from previous year)	-	1,714,494	1,877,373	1,901,375	1,926,654	1,953,098	1,980,616	2,009,187	2,038,808

NGT = normal glucose tolerance

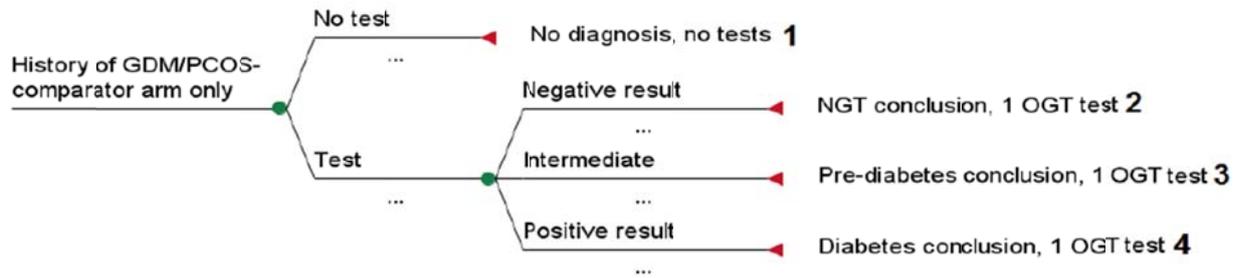
Table 89: Estimated population of women with a history of gestational diabetes or polycystic ovary syndrome eligible for OGT testing, 1999–00 to 2018–19 (some years omitted)

	Step	Source	1999–00	2000–01	2001–02	2012–13	2013–14	2014–15	2015–16	2016–17	2017–18	2018–19
A	Total number of tests ordered for women aged 15–44 years	Observed and <i>projected</i> MBS data for item 66542 (Medicare Australia 2013a)	24,556	30,327	35,364	76,580	<i>71,972</i>	<i>75,393</i>	<i>78,815</i>	<i>82,236</i>	<i>85,658</i>	<i>89,079</i>
B	Total number of tests ordered for men aged 15–44 years	Observed and <i>projected</i> MBS data for item 66542 (Medicare Australia 2013a)	7,796	9,263	10,147	18,615	<i>21,235</i>	<i>22,193</i>	<i>23,151</i>	<i>24,109</i>	<i>25,067</i>	<i>26,025</i>
C	Excess number of tests for women (observed and <i>projected</i>)	A – B	16,760	21,064	25,217	57,965	50,737	53,200	55,664	58,127	60,591	63,054
D	Estimated uptake in women with history of GDM or PCOS	Chittleborough et al. (2010)	64.7%									
E	Assuming 64.7% uptake testing, then total eligible	C / D	25,913	32,567	38,988	89,621	78,445	82,254	86,063	89,871	93,680	97,489
F	Assuming upper limit of uptake observed (75%)	Chittleborough et al. (2010)	22,347	28,085	33,623	77,287	67,649	70,934	74,218	77,503	80,787	84,072
G	Assuming lower limit of uptake observed (56.3%)	Chittleborough et al. (2010)	29,769	37,414	44,790	102,957	90,119	94,494	98,870	103,245	107,621	111,996
H	Incidence of pre-diabetes	See 'Economic evaluation' section	7.6%									
I	Incidence of diabetes	Assume as for pre-diabetes	2.6%									
J	Diabetes in GDM/PCOS population	E × I	674	847	1,014	2,330	2,040	2,139	2,238	2,337	2,436	2,535
K	Pre-diabetes in GDM/PCOS population	E × H	1,969	2,475	2,963	6,811	5,962	6,251	6,541	6,830	7,120	7,409
L	NGT in GDM/PCOS	E – J – K	23,270	29,246	35,012	80,479	70,444	73,864	77,284	80,704	84,125	87,545

GDM = gestational diabetes; NGT = normal glucose tolerance; PCOS = polycystic ovary syndrome

Note: *Figures in italics are projected estimates of use.*

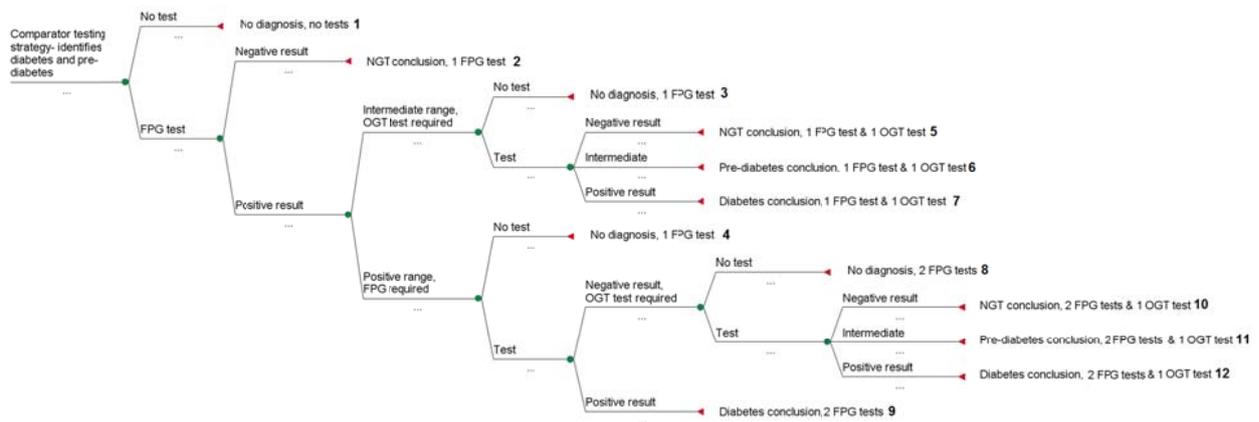
Testing outcomes



	History of GDM/PCOS		
	NGT	Pre-diabetes	Diabetes
1	35.3%	35.3%	35.3%
2	64.7%	0.0%	0.0%
3	0.0%	64.7%	0.0%
4	0.0%	0.0%	64.7%
No test	35.3%	35.3%	35.3%
1 OGT test	64.7%	64.7%	64.7%
HbA1c test	0.0%	0.0%	64.7%
No diagnosis	35.3%	35.3%	35.3%
NGT	64.7%	0.0%	0.0%
Pre-diabetes	0.0%	64.7%	0.0%
Diabetes	0.0%	0.0%	64.7%

Figure 30: Testing analytic and test outcomes in the current testing strategy (GDM/PCOS populations)

GDM = gestational diabetes; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGT = oral glucose tolerance; PCOS = polycystic ovary syndrome



	High-risk			Known pre-diabetes		
	NGT	Pre-diabetes	Diabetes	NGT	Pre-diabetes	Diabetes
1	30.0%	30.0%	30.0%	0.0%	0.0%	0.0%
2	70.0%	0.0%	0.0%	100.0%	0.0%	0.0%
3	0.0%	13.1%	11.8%	0.0%	0.0%	0.0%
4	0.0%	3.5%	4.2%	0.0%	0.0%	0.0%
5	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
6	0.0%	33.6%	0.0%	0.0%	66.7%	0.0%
7	0.0%	0.0%	30.2%	0.0%	0.0%	60.0%
8	0.0%	5.6%	0.0%	0.0%	0.0%	0.0%
9	0.0%	0.0%	23.8%	0.0%	0.0%	40.0%
10	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
11	0.0%	14.3%	0.0%	0.0%	33.3%	0.0%
12	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
No tests	30.0%	30.0%	30.0%	0.0%	0.0%	0.0%
1 FPG test	70.0%	16.6%	16.0%	100.0%	0.0%	0.0%
1 FPG test and 1 OGT test	0.0%	33.6%	30.2%	0.0%	66.7%	60.0%
2 FPG tests	0.0%	5.6%	23.8%	0.0%	0.0%	40.0%
2 FPG tests and 1 OGT test	0.0%	14.3%	0.0%	0.0%	33.3%	0.0%
HbA1c test	0.0%	0.0%	54.0%	0.0%	0.0%	100.0%
No diagnosis	30.0%	52.1%	46.0%			
NGT	70.0%	0.0%	0.0%			
Pre-diabetes	0.0%	47.9%	0.0%	100.0%	100.0%	0.0%
Diabetes	0.0%	0.0%	54.0%	0.0%	0.0%	100.0%

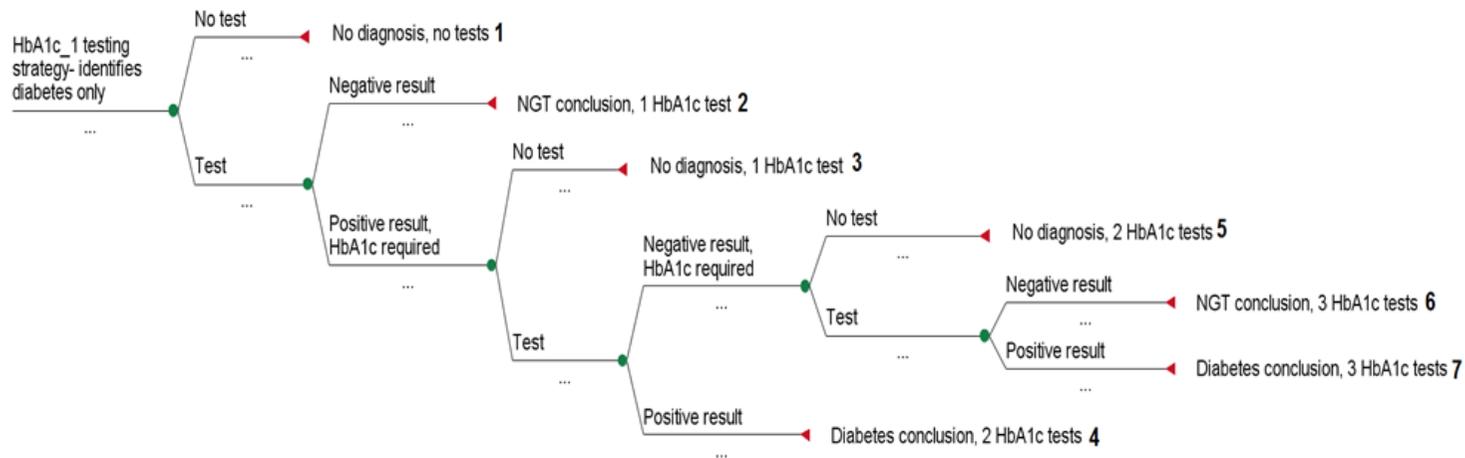
Figure 31: Testing analytic and test outcomes in the current testing strategy (high-risk and pre-diabetes populations)

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGT = oral glucose tolerance

Table 90: Diagnostic conclusions of testing, current testing strategy, 2012–13

Diagnostic conclusion	True status			Total
	NGT	Pre-diabetes	Diabetes	
Total population eligible for testing	393,152	959,193	97,789	1,469,134
No diagnosis	122,211	31,108	33,454	186,773
NGT	270,941	0	0	270,941
Pre-diabetes	0	947,085	0	947,085
Diabetes	0	0	64,335	64,335

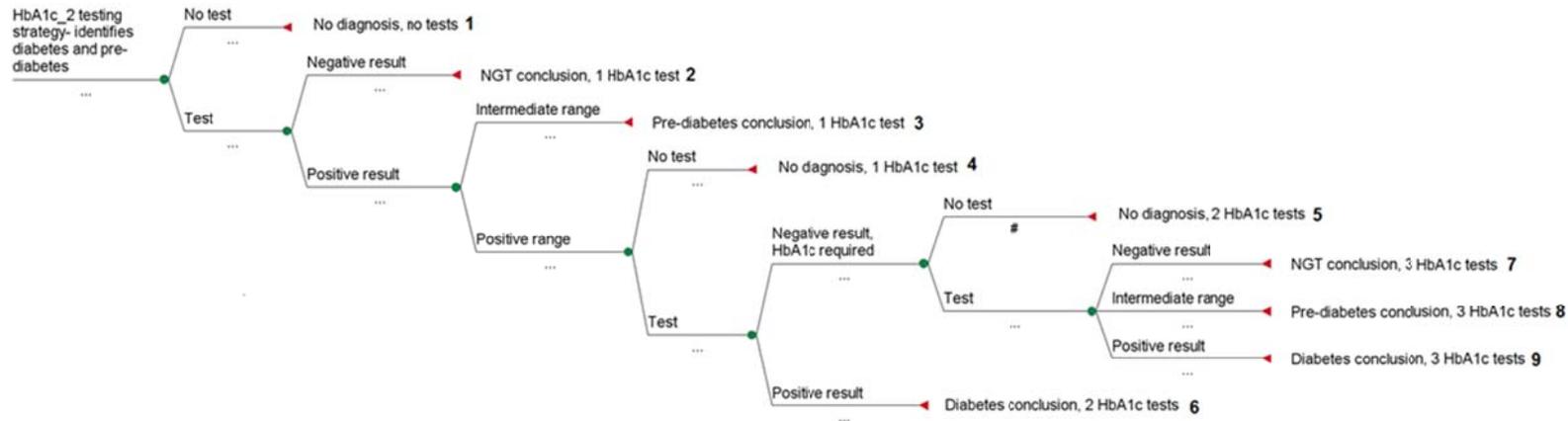
NGT = normal glucose tolerance



	High-risk		Known pre-diabetes		History of GDM/PCOS	
	NGT/pre-diabetes	Diabetes	Pre-diabetes	Diabetes	NGT/pre-diabetes	Diabetes
1	25.0%	25.0%	0.0%	0.0%	25.0%	25.0%
2	57.8%	24.5%	77.0%	32.6%	57.8%	24.5%
3	1.7%	5.1%	0.0%	0.0%	1.7%	5.1%
4	3.6%	30.7%	5.3%	45.4%	3.6%	30.7%
5	1.2%	1.5%	0.0%	0.0%	1.2%	1.5%
6	10.2%	6.2%	16.8%	10.2%	10.2%	6.2%
7	0.6%	7.1%	0.9%	11.8%	0.6%	7.1%
No tests	25.0%	25.0%	0.0%	0.0%	25.0%	25.0%
1 HbA1c test	59.5%	29.5%	77.0%	32.6%	59.5%	29.5%
2 HbA1c tests	4.8%	32.1%	5.3%	45.4%	4.8%	32.1%
3 HbA1c tests	10.8%	13.3%	17.7%	22.0%	10.8%	13.3%
No diagnosis	27.9%	31.5%			27.9%	31.5%
NGT/pre-diabetes	67.9%	30.7%	93.8%	42.8%	67.9%	30.7%
Diabetes	4.1%	37.8%	6.2%	57.2%	4.1%	37.8%

Figure 32: Testing analytic and test outcomes in the HbA1c_1 testing strategy (all populations)

GDM = gestational diabetes; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; PCOS = polycystic ovary syndrome



	High-risk			Known pre-diabetes			History of GDM/PCOS		
	NGT	Pre-diabetes	Diabetes	NGT	Pre-diabetes	Diabetes	NGT	Pre-diabetes	Diabetes
1	25.0%	25.0%	25.0%	0.0%	0.0%	0.0%	25.0%	25.0%	25.0%
2	75.0%	0.0%	0.0%	100.0%	0.0%	0.0%	75.0%	0.0%	0.0%
3	0.0%	58.9%	21.7%	0.0%	78.5%	28.9%	0.0%	58.9%	21.7%
4	0.0%	1.6%	5.3%	0.0%	0.0%	0.0%	0.0%	1.6%	5.3%
5	0.0%	1.1%	1.6%	0.0%	0.0%	0.0%	0.0%	1.1%	1.6%
6	0.0%	3.3%	32.4%	0.0%	4.9%	47.9%	0.0%	3.3%	32.4%
7	0.0%	0.0%	0.5%	0.0%	0.0%	0.8%	0.0%	0.0%	0.5%
8	0.0%	7.9%	6.1%	0.0%	13.0%	10.0%	0.0%	7.9%	6.1%
9	0.0%	2.2%	7.5%	0.0%	3.5%	12.4%	0.0%	2.2%	7.5%
No tests	25.0%	25.0%	25.0%	0.0%	0.0%	0.0%	25.0%	25.0%	25.0%
1 HbA1c test	75.0%	60.5%	27.0%	100.0%	78.5%	28.9%	75.0%	60.5%	27.0%
2 HbA1c tests	0.0%	4.4%	33.9%	0.0%	4.9%	47.9%	0.0%	4.4%	33.9%
3 HbA1c tests	0.0%	10.0%	14.1%	0.0%	16.5%	23.2%	0.0%	10.0%	14.1%
No diagnosis	25.0%	27.7%	31.9%				25.0%	27.7%	31.9%
NGT	75.0%	0.0%	0.5%				75.0%	0.0%	0.5%
Pre-diabetes	0.0%	66.8%	27.7%	100.0%	91.5%	39.7%	0.0%	66.8%	27.7%
Diabetes	0.0%	5.5%	39.9%	0.0%	8.5%	60.3%	0.0%	5.5%	39.9%

Figure 33: Testing analytic and test outcomes in the HbA1c_2 testing strategy (all populations)

GDM = gestational diabetes; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; PCOS = polycystic ovary syndrome

Use and costs of proposed testing strategy

Base-case (HbA1c_1) scenario

Table 91: Total number of tests under the base-case (HbA1c_1) testing scenario and cost implications

HbA1c_1	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,416,629	1,405,115	1,390,443	1,376,346	1,364,245
NGT in eligible population	363,372	377,456	390,960	399,254	408,558
Pre-diabetes in eligible population	973,236	954,154	932,656	912,742	893,641
Diabetes in eligible population	80,021	73,505	66,827	64,350	62,046
Patients who do not uptake any testing	118,277	121,531	123,836	126,130	128,772
Patients who uptake 1 HbA1c test	1,236,365	1,226,202	1,213,935	1,199,412	1,186,416
Patients who uptake 2 HbA1c tests	61,987	57,382	52,672	50,803	49,057
Patients who uptake 3 HbA1c tests	0	0	0	0	0
Total number of tests	1,360,339	1,340,965	1,319,278	1,301,018	1,284,530
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial HbA1c test	\$16.43	\$16.43	\$16.43	\$16.43	\$16.43
Total cost per confirmatory HbA1c test	\$55.95	\$55.95	\$55.95	\$55.95	\$55.95
Cost to the MBS	\$27,247,501	\$26,565,158	\$25,836,594	\$25,388,894	\$24,979,962
<i>Including safety net impacts</i>					
Total cost per initial HbA1c test	\$18.97	\$18.97	\$18.97	\$18.97	\$18.97
Total cost per confirmatory HbA1c test	\$59.35	\$59.35	\$59.35	\$59.35	\$59.35
Cost to the MBS ^a	\$27,504,447	\$26,817,989	\$26,084,873	\$25,633,596	\$25,221,427
Cost to patients					
Proportion bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
<i>Including safety net impacts</i>					
Cost per initial HbA1c test to the patient	\$7.77	\$7.77	\$7.77	\$7.77	\$7.77
Cost per confirmatory HbA1c test to patients	\$8.62	\$8.62	\$8.62	\$8.62	\$8.62
Total cost to patients	\$439,235	\$432,718	\$425,454	\$419,485	\$414,091

^a Assuming 7.2% of tests are eligible for safety net

HbA1c = glycated haemoglobin test; NGT = normal glucose tolerance; MBS = Medicare Benefits Schedule

Alternative (HbA1c_2) scenario

Table 92: Total number of tests under the alternative (HbA1c_2) scenario and cost implications

HbA1c_2	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,416,629	1,447,523	1,475,864	1,499,028	1,523,843
NGT in tested population	363,372	377,130	390,314	398,633	407,913
Pre-diabetes in tested population	973,236	991,387	1,008,046	1,025,217	1,042,778
Diabetes in tested population	80,021	79,006	77,504	75,178	73,152
Patients who do not uptake any testing	118,277	121,962	124,661	126,260	128,224
Patients who uptake 1 HbA1c test	1,236,365	1,264,123	1,290,631	1,313,623	1,337,699
Patients who uptake 2 HbA1c tests	61,987	61,438	60,573	59,145	57,920
Patients who uptake 3 HbA1c tests	0	0	0	0	0
Total number of tests	1,360,339	1,386,999	1,411,776	1,431,913	1,453,540
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial HbA1c test	\$16.43	\$16.43	\$16.43	\$16.43	\$16.43
Total cost per confirmatory HbA1c test	\$55.95	\$55.95	\$55.95	\$55.95	\$55.95
Cost to the MBS	\$27,247,501	\$27,642,067	\$27,980,709	\$28,198,605	\$28,457,115
<i>Including safety net impacts</i>					
Total cost per initial HbA1c test	\$18.97	\$18.97	\$18.97	\$18.97	\$18.97
Total cost per confirmatory HbA1c test	\$59.35	\$59.35	\$59.35	\$59.35	\$59.35
Cost to the MBS ^a	\$27,504,447	\$27,903,833	\$28,246,911	\$28,468,322	\$28,730,646
Cost to patients					
Proportion bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
<i>Including safety net impacts</i>					
Cost per initial HbA1c test to the patient	\$7.77	\$7.77	\$7.77	\$7.77	\$7.77
Cost per confirmatory HbA1c test to patients	\$8.62	\$8.62	\$8.62	\$8.62	\$8.62
Total cost to patients	\$439,235	\$447,719	\$455,579	\$461,916	\$468,744

^a Assuming 7.2% of tests are eligible for safety net

HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; MBS = Medicare Benefits Schedule

Changes in use and cost of current testing strategy

Table 93: Total number of tests under the current testing scenario and cost implications

Current testing	2014–15	2015–16	2016–17	2017–18	2018–19
Total no. of patients eligible for testing	1,416,629	1,435,207	1,451,004	1,463,159	1,477,361
NGT in tested population	363,372	377,264	390,568	398,856	408,134
Pre-diabetes in tested population	973,236	979,261	983,550	989,521	996,291
Diabetes in tested population	80,021	78,682	76,886	74,782	72,936

Current testing	2014–15	2015–16	2016–17	2017–18	2018–19
Patients who do not uptake any testing	146,291	150,956	154,437	156,919	159,806
Patients who uptake 1 FPG test	217,664	225,251	231,812	235,220	239,369
Patients who uptake 1 FPG & 1 OGT test	943,180	947,859	952,225	957,289	963,092
Patients who uptake 2 FPG tests	56,275	55,459	54,382	53,119	52,018
Patients who uptake 2 FPG & 1 OGT test	0	0	0	0	0
Patients who uptake 1 OGT test	53,218	55,683	58,147	60,611	63,075
Patients who uptake HbA1c testing	57,659	56,906	55,894	54,695	53,658
Total initial FPG tests	1,217,119	1,228,569	1,238,420	1,245,628	1,254,479
Total confirmatory FPG tests	56,275	55,459	54,382	53,119	52,018
Total OGT tests	996,398	1,003,541	1,010,372	1,017,900	1,026,167
Total HbA1c tests	57,659	56,906	55,894	54,695	53,658
Cost to the MBS					
<i>Excluding safety net impacts</i>					
Total cost per initial FPG test	\$2.65	\$2.65	\$2.65	\$2.65	\$2.65
Total cost per confirmatory FPG test	\$49.90	\$49.90	\$49.90	\$49.90	\$49.90
Total cost per OGT test	\$57.80	\$57.80	\$57.80	\$57.80	\$57.80
Total cost per HbA1c test	\$14.30	\$14.30	\$14.30	\$14.30	\$14.30
Cost to the MBS	\$65,534,756	\$64,481,668	\$64,455,080	\$64,846,825	\$65,199,615
<i>Including safety net impacts</i>					
Total cost per initial FPG test	\$2.79	\$2.79	\$2.79	\$2.79	\$2.79
Total cost per confirmatory FPG test	\$52.25	\$52.25	\$52.25	\$52.25	\$52.25
Total cost per OGT test	\$61.50	\$61.50	\$61.50	\$61.50	\$61.50
Total cost per HbA1c test	\$16.80	\$16.80	\$16.80	\$16.80	\$16.80
Cost to the MBS ^a	\$65,754,225	\$64,806,907	\$64,809,186	\$65,201,306	\$65,561,680
Cost to patients					
Proportion FPG tests bulk-billed	83.9%	83.9%	83.9%	83.9%	83.9%
Proportion OGT tests bulk-billed	97.1%	97.1%	97.1%	97.1%	97.1%
Proportion HbA1c tests bulk-billed	95.9%	95.9%	95.9%	95.9%	95.9%
<i>Including safety net impacts</i>					
Total cost per initial FPG test	\$0.39	\$0.39	\$0.39	\$0.39	\$0.39
Total cost per confirmatory FPG test	\$6.39	\$6.39	\$6.39	\$6.39	\$6.39
Total cost per OGT test	\$13.79	\$13.79	\$13.79	\$13.79	\$13.79
Total cost per HbA1c test	\$7.72	\$7.72	\$7.72	\$7.72	\$7.72
Total cost to patients	\$554,336	\$556,857	\$558,803	\$560,612	\$563,039

^a Assuming 7.2% of tests are eligible for safety net

FPG = fasting plasma glucose; GP = general practitioner; HbA1c = glycated haemoglobin; MBS = Medicare Benefits Schedule; OGT = oral glucose tolerance

Financial implications to the MBS

Uncertainty scenarios

Table 94: Sensitivity analyses of financial implications of base-case (HbA1c_1) scenario (including safety net implications)

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>Base-case (HbA1c_1)</i>					
Cost to the MBS of HbA1c testing	\$42,477,495	\$42,515,658	\$41,843,521	\$41,079,672	\$40,275,670
Cost to the MBS of current testing	\$81,540,611	\$80,436,591	\$80,447,963	\$80,851,395	\$81,214,961
Net cost to the MBS	-\$39,063,117	-\$37,920,933	-\$38,604,442	-\$39,771,723	-\$40,939,291
<i>Assuming all initial FPG and HbA1c tests ordered alone (base case: 5.1%)</i>					
Cost to the MBS of HbA1c testing	\$87,725,329	\$87,054,528	\$85,540,800	\$83,896,478	\$82,273,487
Cost to the MBS of current testing	\$140,585,437	\$139,004,832	\$138,121,493	\$139,013,878	\$139,798,511
Net cost to the MBS	-\$52,860,108	-\$51,950,305	-\$52,580,693	-\$55,117,400	-\$57,525,024
<i>Proportion of initial known pre-diabetes 0% (base-case: 50.1%)</i>					
Cost to the MBS of HbA1c testing	\$16,422,979	\$16,495,005	\$16,413,417	\$16,640,075	\$16,872,503
Cost to the MBS of current testing	\$11,504,426	\$13,410,104	\$16,780,905	\$20,417,267	\$23,790,748
Net cost to the MBS	\$4,918,553	\$3,084,901	-\$367,488	-\$3,777,192	-\$6,918,245
<i>Proportion of initial known pre-diabetes 100% (base-case: 50.1%)</i>					
Cost to the MBS of HbA1c testing	\$68,416,636	\$68,421,086	\$67,161,016	\$65,411,046	\$63,575,204
Cost to the MBS of current testing	\$151,266,664	\$147,166,272	\$143,833,091	\$141,017,908	\$138,384,889
Net cost to the MBS	-\$82,850,028	-\$78,745,186	-\$76,672,076	-\$75,606,863	-\$74,809,686
<i>Assuming 75% uptake in women with history of GDM/PCOS (base-case: 64.7%)</i>					
Cost to the MBS of HbA1c testing	\$42,215,379	\$42,242,396	\$41,563,999	\$40,791,497	\$39,978,503
Cost to the MBS of current testing	\$81,071,316	\$79,977,674	\$79,934,764	\$80,281,998	\$80,589,758
Net cost to the MBS	-\$38,855,937	-\$37,735,278	-\$38,370,765	-\$39,490,502	-\$40,611,255
<i>Assuming 56.3% uptake in women with history of GDM/PCOS (base-case: 64.7%)</i>					
Cost to the MBS of HbA1c testing	\$42,760,919	\$42,811,134	\$42,145,767	\$41,391,274	\$40,596,995
Cost to the MBS of current testing	\$82,048,058	\$80,932,816	\$81,002,882	\$81,467,079	\$81,890,990
Net cost to the MBS	-\$39,287,140	-\$38,121,681	-\$38,857,115	-\$40,075,806	-\$41,293,995
<i>Uptake of AUSDRISK screening (5.4%) (base-case: 14.0%)</i>					
Cost to the MBS of HbA1c testing	\$35,881,295	\$35,855,657	\$35,266,473	\$34,503,511	\$33,680,102
Cost to the MBS of current testing	\$78,082,185	\$76,639,057	\$75,966,455	\$75,405,243	\$74,894,592
Net cost to the MBS	-\$42,200,890	-\$40,783,399	-\$40,699,982	-\$40,901,732	-\$41,214,489

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>Uptake of OGT testing (41%) (base-case: 64.7–100%)</i>					
Cost to the MBS of HbA1c testing	\$42,980,756	\$42,436,144	\$41,555,541	\$40,677,342	\$39,839,273
Cost to the MBS of current testing	\$46,950,511	\$45,972,236	\$45,790,401	\$45,660,430	\$45,440,728
Net cost to the MBS	–\$3,969,754	–\$3,536,092	–\$4,234,859	–\$4,983,088	–\$5,601,455

FPG = fasting plasma glucose; GDM = history of gestational diabetes; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGT = oral glucose tolerance; PCOS = history of polycystic ovary syndrome

Table 95: Sensitivity analyses of financial implications of the alternative (HbA1c_2) scenario (including safety net implications)

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>Base-case (HbA1c_2)</i>					
Cost to the MBS of HbA1c testing	\$56,512,892	\$57,208,355	\$56,543,180	\$55,311,789	\$54,046,397
Cost to the MBS of current testing	\$81,540,611	\$80,436,591	\$80,447,963	\$80,851,395	\$81,214,961
Net cost to the MBS	–\$25,027,720	–\$23,228,236	–\$23,904,783	–\$25,539,605	–\$27,168,564
<i>Assuming all initial FPG and HbA1c tests ordered alone (base case: 5.1%)</i>					
Cost to the MBS of HbA1c testing	\$97,979,001	\$98,033,996	\$96,716,056	\$94,781,874	\$92,956,256
Cost to the MBS of current testing	\$140,585,437	\$139,004,832	\$138,121,493	\$139,013,878	\$139,798,511
Net cost to the MBS	–\$42,606,436	–\$40,970,836	–\$41,405,437	–\$44,232,004	–\$46,842,255
<i>Proportion of initial known pre- diabetes 0% (base-case: 50.1%)</i>					
Cost to the MBS of HbA1c testing	\$16,010,711	\$20,957,855	\$24,539,396	\$27,223,138	\$29,489,372
Cost to the MBS of current testing	\$11,504,426	\$13,410,104	\$16,780,905	\$20,417,267	\$23,790,748
Net cost to the MBS	\$4,506,285	\$7,547,751	\$7,758,491	\$6,805,871	\$5,698,624
<i>Proportion of initial known pre- diabetes 100% (base-case: 50.1%)</i>					
Cost to the MBS of HbA1c testing	\$96,835,722	\$93,298,331	\$88,405,246	\$83,276,059	\$78,494,678
Cost to the MBS of current testing	\$151,266,664	\$147,166,272	\$143,833,091	\$141,017,908	\$138,384,889
Net cost to the MBS	–\$54,430,942	–\$53,867,941	–\$55,427,845	–\$57,741,850	–\$59,890,211
<i>Assuming 75% uptake in women with history of GDM/PCOS (base-case: 64.7%)</i>					
Cost to the MBS of HbA1c testing	\$56,303,715	\$56,961,422	\$56,266,291	\$55,008,763	\$53,718,768
Cost to the MBS of current testing	\$81,071,316	\$79,977,674	\$79,934,764	\$80,281,998	\$80,589,758
Net cost to the MBS	–\$24,767,601	–\$23,016,251	–\$23,668,473	–\$25,273,236	–\$26,870,990

	2014–15	2015–16	2016–17	2017–18	2018–19
<i>Assuming 56.3% uptake in women with history of GDM/PCOS (base-case: 64.7%)</i>					
Cost to the MBS of HbA1c testing	\$56,739,074	\$57,475,362	\$56,842,579	\$55,639,450	\$54,400,660
Cost to the MBS of current testing	\$82,048,058	\$80,932,816	\$81,002,882	\$81,467,079	\$81,890,990
Net cost to the MBS	-\$25,308,984	-\$23,457,454	-\$24,160,303	-\$25,827,629	-\$27,490,330
<i>Uptake of AUSDRISK screening (5.4%) (base-case: 14.0%)</i>					
Cost to the MBS of HbA1c testing	\$50,537,379	\$49,395,538	\$47,503,460	\$45,459,557	\$43,514,585
Cost to the MBS of current testing	\$78,082,185	\$76,639,057	\$75,966,455	\$75,405,243	\$74,894,592
Net cost to the MBS	-\$27,544,805	-\$27,243,519	-\$28,462,995	-\$29,945,686	-\$31,380,007
<i>Uptake OGT testing (41%) (base-case: 64.7–100%)</i>					
Cost to the MBS of HbA1c testing	\$56,712,348	\$56,857,568	\$56,081,749	\$54,844,616	\$53,614,038
Cost to the MBS of current testing	\$46,950,511	\$45,972,236	\$45,790,401	\$45,660,430	\$45,440,728
Net cost to the MBS	\$9,761,837	\$10,885,332	\$10,291,349	\$9,184,187	\$8,173,310

FPG = fasting plasma glucose; GDM = history of gestational diabetes; HbA1c = glycated haemoglobin; NGT = normal glucose tolerance; OGT = oral glucose tolerance; PCOS = history of polycystic ovary syndrome

Appendix G Excluded studies

Studies that may have met the inclusion criteria but were excluded from the review are listed below, with the reason for exclusion:

Data duplicated in another study

Bianchi, C, Miccoli, R, Penno, G & Del Prato, S 2011, 'The OGTT is a better tool for detection of diabetes, impaired glucose regulation and impaired insulin secretion and action than HbA1c: the GENFIEV study', *Diabetologia*, vol. 54, p. S142.

Christman, AL, Selvin, E, Lazarus, GS & Garza, LA 2011, 'Hemoglobin A1c predicts healing rate in diabetic wounds', *Journal of Investigative Dermatology*, vol. 131, p. S34.

Janghorbani, M & Amini, M 2012, 'Incidence of type 2 diabetes by HbA(1c) and OGTT: the Isfahan Diabetes Prevention Study', *Acta Diabetologica*, vol. 49, pp. S73–S79.

Ko, GTC, Chan, JCN & Cockram, CS 1999, 'Use of a paired value of fasting plasma glucose and glycated hemoglobin in predicting the likelihood of diabetes in a community', *Diabetes Care*, vol. 22, no. 11, pp. 1908–1909.

McCance, DR, Hanson, RL, Charles, MA, Jacobsson, LT, Pettitt, DJ, Bennett, PH & Knowler, WC 1995, 'Which test for diagnosing diabetes?', *Diabetes Care*, vol. 18, no. 7, pp. 1042–1044.

Schnedl, WJ, Lahousen, T, Wallner, SJ, Krause, R & Lipp, RW 2005, 'Silent hemoglobin variants and determination of HbA1c with the high-resolution program of the HPLC HA-8160 hemoglobin analyzer', *Clinical Biochemistry*, vol. 38, no. 1, pp. 88–91.

Schnedl, WJ, Reisinger, EC, Lipp, RW, Krejs, GJ & Hopmeier, P 1995, 'Hemoglobin variants recently detected in Austria', *Annals of Hematology*, vol. 71, no. 4, pp. 185–187.

WHO 2011, 'Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus', *Diabetes Research and Clinical Practice*, vol. 93, no. 3, pp. 299–309.

Not in English, and not of a higher level of evidence than the English language literature

Buck, C, Thon, A, Wolf, A, Kohne, E & Holl, RW 2000, 'Diagnostik des Diabetes mellitus bei Mukoviszidose (CF) Stellenwert von Blutzucker, HbA1c und oralem Glukosetoleranztest', *Monatsschrift Kinderheilkunde*, vol. 148, no. 7, pp. 698–701.

Haoming, T, Jinzhong, L & Xiangxun, Z 1990, 'Glycosylated hemoglobin in the diagnosis of diabetes mellitus', *Journal of West China University of Medical Sciences*, vol. 21, no. 2, pp. 197–200.

Haupt, A, Fritsche, A, Haring, HU & Gallwitz, B 2007, 'Hereditary sphaerocytosis: difficult metabolic monitoring by falsely low HbA1c levels', *Diabetologie und Stoffwechsel*, vol. 2, no. 6, pp. 370–371.

Imanaka, S 2011, 'Epidemiological study on HbA1c level below 6.1% among community residents and follow-up study of HbA1c level: clinical significance of health examination (Japan) in the aged members from the view point of glucose metabolism', *Japanese Journal of Geriatrics*, vol. 48, no. 3, pp. 271–275.

Jimeno Mollet, J, Molist Brunet, N, Franch Nadal, J, Morato Griera, J, Otzet Gramunt, I & Pons Barro, P 2004, 'Diagnosing type 2 diabetes mellitus', *Atencion Primaria*, vol. 34, no. 5, pp. 222–228.

Meidani, M, Khorvash, F & Rajabpournikfam, MR 2012, 'The relationship between controlling HbA1c and infected diabetic foot ulcer', *Journal of Isfahan Medical School*, vol. 30, no. 174.

Munera-Jaramillo, MI, Restrepo-Lozada, MA, Gomez-Bahamon, LM, Mesa-Suarez, DR & Ramirez-Puerta, BS 2011, 'Glycosylated haemoglobin A1c compared to fasting plasma glucose in outpatients referred to a medical laboratory', *Revista de Salud Publica*, vol. 13, no. 6, pp. 980–989.

Robert, JJ, Grasset, E, de Montalembert, M, Chevenne, D, Deschamps, I, Boitard, C & Lenoir, G 1992, 'Research of factors for glucose intolerance in mucoviscidosis', *Archives Françaises de Pédiatrie*, vol. 49, no. 1, pp. 17–22.

Unable to extract data

Abadie, JM & Koelsch, AA 2008, 'Performance of the Roche second generation hemoglobin A1c immunoassay in the presence of Hb-S or Hb-C traits', *Annals of Clinical and Laboratory Science*, vol. 38, no. 1, pp. 31–36.

Adegbenro, SA, Dada, OA, Olanrewaju, DM & Fafunso, MA 1991, 'Glycosylated hemoglobin levels in children with protein-energy malnutrition', *Annals of Tropical Paediatrics*, vol. 11, no. 4, pp. 337–341.

Alves, C, Lima, DS, Cardeal, M & Santana, A 2010, 'Low prevalence of glucose intolerance in racially mixed children with cystic fibrosis', *Pediatric Diabetes*, vol. 11, no. 7, pp. 493–497.

Bennett, CM, Guo, M & Dharmage, SC 2007, 'HbA1c as a screening tool for detection of type 2 diabetes: a systematic review', *Diabetic Medicine*, vol. 24, no. 4, pp. 333–343.

Bobbert, T, Mai, K, Fischer-Rosinsky, A, Pfeiffer, AF & Spranger, J 2010, 'A1c is associated with intima-media thickness in individuals with normal glucose tolerance', *Diabetes Care*, vol. 33, no. 1, pp. 203–204.

Carta, M, Dall'Olio, G & Soffiati, G 1997, 'Determination of HbA1c in the presence of haemoglobin variants: comparison of three HPLC techniques', *European Journal of Clinical Chemistry and Clinical Biochemistry*, vol. 35, no. 12, pp. 923–925.

Cederberg, H, Saukkonen, T, Laakso, M, Jokelainen, J, Härkönen, P, Timonen, M, Keinänen-Kiukaanniemi, S & Rajala, U 2010, 'Postchallenge glucose, A1c, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: a 10-year prospective cohort study', *Diabetes Care*, vol. 33, no. 9, pp. 2077–2083.

Christiansen, R, Rasmussen, LM, Nybo, H, Steenstrup, T & Nybo, M 2012, 'The relationship between HbA1c and fasting plasma glucose in patients with increased plasma liver enzyme

measurements', *Diabetic Medicine*, vol. 29, no. 6, pp. 742–747.

Costa, B, Barrio, F, Cabre, JJ, Pinol, JL, Cos, FX, Sole, C, Bolibar, B, Castell, C, Lindstrom, J, Barengo, N & Tuomilehto, J 2011, 'Shifting from glucose diagnostic criteria to the new HbA1c criteria would have a profound impact on prevalence of diabetes among a high-risk Spanish population', *Diabetic Medicine*, vol. 28, no. 10, pp. 1234–1237.

Dix, D, Cohen, P, Kingsley, S, Senkbeil, J & Sexton, K 1979, 'Glycohemoglobin and glucose tolerance tests compared as indicator of borderline diabetes', *Clinical Chemistry*, vol. 25, no. 6, pp. 877–879.

Eberentz-Lhomme, C, Ducrocq, R & Intrator, S 1984, 'Haemoglobinopathies, malaria, and other interferences with HbA1 assessment', *Diabete et Metabolisme*, vol. 10, no. 5, pp. 304–310.

Eberentz-Lhomme, C, Ducrocq, R & Intrator, S 1984, 'Haemoglobinopathies: a pitfall in the assessment of glycosylated haemoglobin by ion-exchange chromatography', *Diabetologia*, vol. 27, no. 6, pp. 596–598.

Edelman, D, Olsen, MK, Dudley, TK, Harris, AC & Oddone, EZ 2004, 'Utility of hemoglobin A1c in predicting diabetes risk', *Journal of General Internal Medicine*, vol. 19, no. 12, pp. 1175–1180.

Fan, HQ, Tang, W, Wang, ZX, Wang, SJ, Qin, YH, Fu, Q, Gao, Y, Sun, M, Zhang, M, Zhou, HW & Yang, T 2013, 'Association of serum uric acid with 2-hour postload glucose in Chinese with impaired fasting plasma glucose and/or HbA1c', *PLoS One*, vol. 8, no. 7, e67759.

Garagorri, JM, Rodriguez, G, Ros, L & Sanchez, A 2001, 'Early detection of impaired glucose tolerance in patients with cystic fibrosis and predisposition factors', *Journal of Pediatric Endocrinology & Metabolism*, vol. 14, no. 1, pp. 53–60.

Getaneh, A, Andres, R, Brillon, DJ & Findley, SE 2011, 'Hemoglobin A1c criterion for diabetes diagnosis among Hispanic and non-Hispanic populations', *Endocrine Practice*, vol. 17, no. 2, pp. 210–217.

Goode, KM, John, J, Rigby, AS, Kilpatrick, ES, Atkin, SL, Bragadeesh, T, Clark, AL & Cleland, JGF 2009, 'Elevated glycated haemoglobin is a strong predictor of mortality in patients with left ventricular systolic dysfunction who are not receiving treatment for diabetes mellitus', *Heart*, vol. 95, no. 11, pp. 917–923.

Higgins, TN, Tran, D, Cembrowski, GS, Shalapay, C, Steele, P & Wiley, C 2011, 'Is HbA(1c) a good screening test for diabetes mellitus?', *Clinical Biochemistry*, vol. 44, no. 17–18, pp. 1469–1472.

Ito, S, Ogishima, H, Kondo, Y, Sugihara, M, Hayashi, T, Chino, Y, Goto, D, Matsumoto, I & Sumida, T 2013, 'Early diagnosis and treatment of steroid-induced diabetes mellitus in patients with rheumatoid arthritis and other connective tissue diseases', *Modern Rheumatology*, pp. 1–8.

Li, P, Jiang, R, Li, L, Li, L, Wang, Z, Li, X & Liu, C 2012, 'Diagnostic performance of hemoglobin A1c for prediabetes and association with cardiometabolic risk factors in Chinese adolescents without diabetes', *Journal of Investigative Medicine*, vol. 60, no. 6, pp. 888–894.

Lorenzo-Medina, M, De La Iglesia, S, Ropero, P, Navarro-Romero, M, Martn-Alfaro, R & Guindeo-Casass, C 2012, 'Interference of hemoglobin (Hb) Las Palmas with HPLC measurement of HbA1c in 87 patients', *Clinical Chemistry and Laboratory Medicine*, vol. 50, no. 2, pp. 403–405.

Matsushita, K, Blecker, S, Pazin-Filho, A, Bertoni, A, Chang, PP, Coresh, J & Selvin, E 2010, 'The association of hemoglobin A1c with incident heart failure among people without diabetes: the atherosclerosis risk in communities study', *Diabetes*, vol. 59, no. 8, pp. 2020–2026.

Mortada, R, Comerford, K, James Kallail, K & Karakas, SE 2013, 'Utility of hemoglobin-A1C in non-diabetic women with polycystic ovary syndrome', *Endocrine Practice*, vol. 19, no. 2, pp. 284–289.

Mukai, N, Doi, Y, Ninomiya, T, Hata, J, Hirakawa, Y, Fukuhara, M, Iwase, M & Kiyohara, Y 2012, 'Cut-off values of fasting and post-load plasma glucose and HbA1c for predicting type 2 diabetes in community-dwelling Japanese subjects: the Hisayama Study', *Diabetic Medicine*, vol. 29, no. 1, pp. 99–106.

Mulkerrin, EC, Arnold, JD, Dewar, R, Sykes, D, Rees, A & Pathy, MS 1992, 'Glycosylated haemoglobin in the diagnosis of diabetes mellitus in elderly people', *Age and Ageing*, vol. 21, no. 3, pp. 175–177.

Murros, K, Fogelholm, R, Kettunen, S, Vuorela, AL & Valve, J 1992, 'Blood-glucose, glycosylated hemoglobin, and outcome of ischemic brain infarction', *Journal of the Neurological Sciences*, vol. 111, no. 1, pp. 59–64.

Nakao, J, Orimo, H & Ito, H 1980, 'Classification of glucose intolerance in the aged based on hemoglobin A1', *Tohoku Journal of Experimental Medicine*, vol. 132, no. 3, pp. 305–312.

Pai, JK, Cahill, LE, Hu, FB, Rexrode, KM, Manson, JE & Rimm, EB 2013, 'Hemoglobin A1c is associated with increased risk of incident coronary heart disease among apparently healthy, nondiabetic men and women', *Journal of the American Heart Association*, vol. 2, no. 2, e000077.

Paisooksantivatana, K, Kongsomgan, A, Banyatsuppasin, W & Khupulsup, K 2009, 'Influence of hemoglobin E on measurement of hemoglobin A1c by immunoassays', *Diabetes Research and Clinical Practice*, vol. 83, no. 3, pp. e84–e85.

Pajunen, P, Peltonen, M, Eriksson, JG, Ilanne-Parikka, P, Aunola, S, Keinanen-Kiukaanniemi, S, Uusitupa, M, Tuomilehto, J & Lindstrom, J 2011, 'HbA1c in diagnosing and predicting type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study', *Diabetic Medicine*, vol. 28, no. 1, pp. 36–42.

Park, S, Barrett-Connor, E, Wingard, DL, Shan, J & Edelstein, S 1996, 'GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes: the Rancho Bernardo Study', *Diabetes Care*, vol. 19, no. 5, pp. 450–456.

Polage, C, Little, RR, Rohlifing, CL, Cole, TG & Roberts, WL 2004, 'Effects of beta thalassemia minor on results of six glycosylated hemoglobin methods', *Clinica Chimica Acta*, vol. 350, nos 1–2, pp. 123–128.

Qiao, Q, Dekker, JM, de Vegt, F, Nijpels, G, Nissinen, A, Stehouwer, CD, Bouter, LM, Heine, RJ & Tuomilehto, J 2004, 'Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbA1c', *Journal of Clinical Epidemiology*, vol. 57, no. 6, pp. 590–596.

Roberts, WL, McCraw, M & Cook, CB 1998, 'Effects of sickle cell trait and hemoglobin C trait on determinations of HbA(1c) by an immunoassay method', *Diabetes Care*, vol. 21, no. 6, pp. 983–986.

Santiago, JV, Davis, JE & Fisher, F 1978, 'Hemoglobin A1c levels in a diabetes detection program', *Journal of Clinical Endocrinology and Metabolism*, vol. 47, no. 3, pp. 578–580.

Schnedl, WJ, Reisinger, EC, Lipp, RW, Krejs, GJ & Hopmeier, P 1995, 'Hemoglobin-variants recently detected in Austria', *Annals of Hematology*, vol. 71, no. 4, pp. 185–187.

Sentell, TL, He, GZ, Gregg, EW & Schillinger, D 2012, 'Racial/ethnic variation in prevalence estimates for United States prediabetes under alternative 2010 American Diabetes Association criteria: 1988–2008', *Ethnicity & Disease*, vol. 22, no. 4, pp. 451–458.

Sheu, WH, Lee, W & Chen, Y 2004, 'Combined use of fasting glucose and hemoglobin A1c levels in screening for new type 2 diabetes mellitus in elderly men: TCVGHAGE', *Journal of the American Geriatrics Society*, vol. 52, no. 10, pp. 1777–1778.

Sikaris, K 2009, 'The correlation of hemoglobin A1c to blood glucose', *Journal of Diabetes Science and Technology*, vol. 3, no. 3, pp. 429–438.

Smaldone, A 2008, 'Evidence-based clinical decision making – glycemic control and hemoglobinopathy: when A1c may not be reliable', *Diabetes Spectrum*, vol. 21, no. 1, pp. 46–49.

Solomon, MP, Wilson, DC, Corey, M, Kalnins, D, Zielenski, J, Tsui, LC, Pencharz, P, Durie, P & Swezey, NB 2003, 'Glucose intolerance in children with cystic fibrosis', *Journal of Pediatrics*, vol. 142, no. 2, pp. 128–132.

Street, ME, Spaggiari, C, Ziveri, MA, Rossi, M, Volta, C, Viani, I, Grzincich, GL, Sartori, C, Zanzucchi, M, Raia, V, Terzi, C, Pisi, G, Zanetti, E, Boguszewski, MC, Kamoi, TO & Bernasconi, S 2012, 'Insulin production and resistance in cystic fibrosis: effect of age, disease activity, and genotype', *Journal of Endocrinological Investigation*, vol. 35, no. 3, pp. 246–253.

Tavintharan, S, Chew, LS & Heng, DM 2000, 'A rational alternative for the diagnosis of diabetes mellitus in high risk individuals', *Annals of the Academy of Medicine, Singapore*, vol. 29, no. 2, pp. 213–218.

Temelkova-Kurktschiev, TS, Koehler, C, Henkel, E, Leonhardt, W, Fuecker, K & Hanefeld, M 2000, 'Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA(1c) level', *Diabetes Care*, vol. 23, no. 12, pp. 1830–1834.

Tsai, LY, Tsai, SM, Lin, MN & Liu, SF 2001, 'Effect of hemoglobin variants (HbJ, HbG, and HbE) on HbA1c values as measured by cation-exchange HPLC (Diamat)', *Clinical Chemistry*,

vol. 47, no. 4, pp. 756–758.

Tzamaloukas, AH 1996, 'Interpreting glycosylated hemoglobin in diabetic patients on peritoneal dialysis', *Advances in peritoneal dialysis. Conference on Peritoneal Dialysis*, vol. 12, pp. 171–175.

Valentine, NA, Alhawassi, TM, Roberts, GW, Vora, PP, Stranks, SN & Doogue, MP 2011, 'Detecting undiagnosed diabetes using glycated haemoglobin: an automated screening test in hospitalised patients', *Medical Journal of Australia*, vol. 194, no. 5, p. 243.

Veloso, AG, Siersma, V, Heldgaard, PE & Olivarius, ND 2013, 'Patients newly diagnosed with clinical type 2 diabetes mellitus but presenting with HbA(1c) within normal range: 19-year mortality and clinical outcomes', *Primary Care Diabetes*, vol. 7, no. 1, pp. 33–38.

Unable to retrieve data within time limit

Augustin, L, Kendall, CWC, Mirrahimi, A, Chiavaroli, L, Blanco, S & Jenkins, DJA 2012, 'Does lowering glycated hemoglobin reduce hypogonadism in type 2 diabetic men with low PSA levels on low glycemic index diets?', *FASEB Journal*, vol. 26.

Dong, XL, Liu, Y, Sun, Y, Sun, C, Fu, FM, Wang, SL & Chen, L 2011, 'Comparison of HbA1c and OGTT criteria to diagnose diabetes among Chinese', *Experimental and Clinical Endocrinology & Diabetes*, vol. 119, no. 6, pp. 366–369.

Hamwi, A, Schweiger, CR, Veitl, M & Schmid, R 1995, 'Quantitative measurement of HbA(1c) by an immunoturbidimetric assay compared to a standard HPLC method', *American Journal of Clinical Pathology*, vol. 104, no. 1, pp. 89–95.

Mostafa, SA, Khunti, K, Srinivasan, BT, Webb, D & Davies, MJ 2011, 'Detecting type 2 diabetes and impaired glucose regulation using glycated hemoglobin in different populations', *Diabetes Management*, vol. 1, no. 1, pp. 77–97.

References

- Ahmad, J & Rafat, D 2013, 'HbA1c and iron deficiency: A review', *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, vol. 7, no. 2, pp. 118-122.
- Al-Fadhli, SM, Ahmad, AA & Al-Jafer, HA 2001, 'Effect of sickle cell trait and beta-Thalassemia minor on determinations of HbA1c by an immunoassay method', *Saudi Medical Journal*, vol. 22, no. 8, Aug, pp. 686-689.
- Alqahtani, N, Khan, WAG, Alhumaidi, MH & Ahmed, YAAR 2013, 'Use of glycated hemoglobin in the diagnosis of diabetes mellitus and pre-diabetes and role of fasting plasma glucose, oral glucose tolerance test', *International Journal of Preventive Medicine*, vol. 4, no. 9, pp. 1025-1029.
- Ama, V, Kengne, AP, Nansseu, NJR, Nouthe, B & Sobngwi, E 2012, 'Would sickle cell trait influence the metabolic control in sub-Saharan individuals with type 2 diabetes?', *Diabetic Medicine*, vol. 29, no. 9, pp. e334-e337.
- American Diabetes Association 2010, 'Diagnosis and classification of diabetes mellitus', *Diabetes Care*, vol. 33 Suppl 1, Jan, pp. S62-69.
- Araneta, MR, Grandinetti, A & Chang, HK 2010, 'A1C and Diabetes Diagnosis Among Filipino Americans, Japanese Americans, and Native Hawaiians', *Diabetes Care*, vol. 33, no. 12, pp. 2626-2628.
- Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, Fourth Edition edn, Blackwell Science, Oxford.
- Australian Bureau of Statistics (ABS) 2010, *Table 1.2: Persons 15 years and over, Use of health services for own health in the last 12 months, by age and sex, Chapter 1: Use of health services, 4839.0.55.001 - Health Services: Patient Experiences in Australia, 2009* Commonwealth of Australia, Canberra, viewed 22 Aug 2013, <<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4839.0.55.0012009>>.
- 2012, *Table 2.9: Death rates, Summary, Australia-2001 to 2011 in 3302.0 - Deaths, Australia, 2011*, Commonwealth of Australia, Canberra, viewed 22 Aug 2013, <<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.02011?OpenDocument>>.
- 2013a, *Table 11: Prevalence of diabetes (fasting plasma glucose), 4364.0.55.005 - Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12*, Commonwealth of Australia, Canberra, viewed 22 Aug 2013, <<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.0.55.0052011-12?OpenDocument>>.
- 2013b, *Table 59: Estimated Resident Population By Single Year Of Age, Australia, 3101.0 - Australian Demographic Statistics, Mar 2013*, Commonwealth of Australia, Canberra, viewed 22 Aug 2013, <<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Mar%202013?OpenDocument>>.
- 2013c, *Table A9: Population projections, By age and sex, Australia - Series A , 3222.0 - Population Projections, Australia, 2012 (base) to 2101*, Commonwealth of Australia, Canberra, viewed 22 Aug 2013, <<http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3222.02012%20%28base%29%20to%202101?OpenDocument>>.

Australian Diabetes Society & Australasian Diabetes in Pregnancy Society 2009, *Life after gestational diabetes (GDM)*, Diabetes Australia, viewed 20 December 2013, <<http://www.ndss.com.au/PageFiles/13947/Life%20after%20GDM.pdf>>.

Australian General Practice Network 2008, *Type 2 Diabetes Risk Evaluation – Lifestyle Modification Programs. Operational Guidelines*, Manuka, <http://newsletters.gpql.com.au/content/Document/CEO%20Update%2027%20-%2018%20August%2008/20080619_pro_LMP%20Operational%20Guidelines%20_2_.pdf>.

Bae, JC, Suh, S, Jin, SM, Kim, SW, Hur, KY, Kim, JH, Min, YK, Lee, MS, Lee, MK, Jeon, WS, Lee, WY & Kim, KW 2013, 'Hemoglobin A1c values are affected by hemoglobin level and gender in non-anemic Koreans', *Journal of Diabetes Investigation*.

Baral, N, Koner, BC, Karki, P, Ramaprasad, C, Lamsal, M & Koirala, S 2000, 'Evaluation of new WHO diagnostic criteria for diabetes on the prevalence of abnormal glucose tolerance in a heterogeneous Nepali population--the implications of measuring glycated hemoglobin', *Singapore medical journal*, vol. 41, no. 6, pp. 264-267.

Bertram, MY, Lim, SS, Barendregt, JJ & Vos, T 2010, 'Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care', *Diabetologia*, vol. 53, no. 5, May, pp. 875-881.

Bianchi, C, Miccoli, R, Bonadonna, RC, Giorgino, F, Frontoni, S, Faloia, E, Marchesini, G, Dolci, MA, Cavalot, F, Cavallo, GM, Leonetti, F, Del Prato, S & Investigators 2012, 'Pathogenetic Mechanisms and Cardiovascular Risk: Differences between HbA1c and oral glucose tolerance test for the diagnosis of glucose tolerance', *Diabetes Care*, vol. 35, no. 12, December 1, 2012, pp. 2607-2612.

Bleyer, AJ, Vidya, S, Sujata, L, Russell, GB, Akinnifesi, D, Hire, D, Shihabi, Z, Knovich, MA, Daeihagh, P, Calles, J & Freedman, BI 2010, 'The impact of sickle cell trait on glycated haemoglobin in diabetes mellitus', *Diabetic Medicine*, vol. 27, no. 9, Sep, pp. 1012-1016.

Camargo, JL & Gross, JL 2004, 'Conditions associated with very low values of glycohaemoglobin measured by an HPLC method', *J Clin Pathol*, vol. 57, no. 4, pp. 346-349.

Cavagnoli, G, Comerlato, J, Comerlato, C, Renz, PB, Gross, JL & Camargo, JL 2011, 'HbA(1c) measurement for the diagnosis of diabetes: is it enough?', *Diabetic Medicine*, vol. 28, no. 1, Jan, pp. 31-35.

Centers for Disease Control 2007, *National Health and Nutrition Examination Survey: OGTT procedures manual*, CDC, USA.

Chen, L, Magliano, DJ, Balkau, B, Colagiuri, S, Zimmet, PZ, Tonkin, AM, Mitchell, P, Phillips, PJ & Shaw, JE 2010, 'AUSDRISK: an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures', *Med J Aust*, vol. 192, no. 4, Feb 15, pp. 197-202.

Chittleborough, CR, Baldock, KL, Taylor, AW, Hague, WM, Willson, T, Martin, W, Wood, J & Phillips, PJ 2010, 'Long-term follow-up of women with gestational diabetes mellitus: the South Australian Gestational Diabetes Mellitus Recall Register', *Aust N Z J Obstet Gynaecol*, vol. 50, no. 2, Apr, pp. 127-131.

Choudhary, A, Giardina, P, Antal, Z & Vogiatzi, M 2013, 'Unreliable oral glucose tolerance test and haemoglobin A1C in beta thalassaemia major - a case for continuous glucose monitoring?', *British Journal of Haematology*, vol. 162, no. 1, pp. 132-135.

Cohen, DJ & Reynolds, MR 2008, 'Interpreting the results of cost-effectiveness studies', *J Am Coll Cardiol*, vol. 52, no. 25, Dec 16, pp. 2119-2126.

- Colagiuri, S, Colagiuri, R, Conway, B, Grainger, D & Davey, P 2003, *DiabCo\$t Australia: Assessing the burden of Type 2 Diabetes in Australia*, Canberra.
- Colagiuri, S, Davies, D, Girgis, S & Colagiuri, R 2009, *National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes*, Diabetes Australia and NHMRC, Canberra.
- Colagiuri, S, Dickinson, S, Girgis, S & Colagiuri, R 2009, *National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes*, Diabetes Australia and NHMRC, Canberra.
- Colagiuri, S, Hussain, Z, Zimmet, P, Cameron, A & Shaw, J 2004, 'Screening for type 2 diabetes and impaired glucose metabolism: the Australian experience', *Diabetes Care*, vol. 27, no. 2, pp. 367-371.
- Colagiuri, S, Lee, CM, Wong, TY, Balkau, B, Shaw, JE & Borch-Johnsen, K 2011, 'Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes', *Diabetes Care*, vol. 34, no. 1, Jan, pp. 145-150.
- Cosson, E, Hamo-Tchatchouang, E, Banu, I, Nguyen, MT, Chiheb, S, Ba, H & Valensi, P 2010, 'A large proportion of prediabetes and diabetes goes undiagnosed when only fasting plasma glucose and/or HbA1c are measured in overweight or obese patients', *Diabetes Metab*, vol. 36, no. 4, Sep, pp. 312-318.
- Cosson, E, Nguyen, MT, Hamo-Tchatchouang, E, Banu, I, Chiheb, S, Charnaux, N & Valensi, P 2011, 'What would be the outcome if the American Diabetes Association recommendations of 2010 had been followed in our practice in 1998-2006?', *Diabetic Medicine*, vol. 28, no. 5, pp. 567-574.
- d'Emden, MC, Shaw, JE, Colman, PG, Colagiuri, S, Twigg, SM, Jones, GR, Goodall, I, Schneider, HG & Cheung, NW 2012, 'The role of HbA1c in the diagnosis of diabetes mellitus in Australia', *Med J Aust*, vol. 197, no. 4, Aug 20, pp. 220-221.
- De Boer, MJ, Miedema, K & Casparie, AF 1980, 'Glycosylated haemoglobin in renal failure', *Diabetologia*, vol. 18, no. 6, //, pp. 437-440.
- De Luca, F, Arrigo, T, Conti Nibali, S, Sferlazzas, C, Gigante, A, Di Cesare, E & Cucinotta, D 1991, 'Insulin secretion, glycosylated haemoglobin and islet cell antibodies in cystic fibrosis children and adolescents with different degrees of glucose tolerance', *Hormone and Metabolic Research*, vol. 23, no. 10, pp. 495-498.
- De Marchi, S, Cecchin, E, Basile, A, Donadon, W, Lippi, U, Quaia, P & Tesio, F 1983, 'More on the Increase of Hemoglobin Ai in Chronic Renal Failure: The Role of Acidosis', *Nephron*, vol. 35, no. 1, pp. 49-53.
- Deeks, JJ 2001, 'Systematic reviews of evaluations of diagnostic and screening tests', in M Egger, G Davey Smith & DG Altman (eds), *Systematic reviews in healthcare: meta-analysis in context*, Second edn, BMJ Publishing Group, London, pp. 248-282.
- Diabetes Australia 2008, *Type 2 diabetes in children and adolescents: information sheet*, viewed 17/12/2013 2013, <http://www.diabetesaustralia.com.au/Documents/NDSS/Resources/Diabetes_Information_Sheets/TYPE-2-IN-CHILDREN-ADOLS-2008.pdf>.
- Doerr, R, Hoffmann, U, Otter, W, Heinemann, L, Hunger-Battefeld, W, Kulzer, B, Klinge, A, Ludwig, V, Amann-Zalan, I, Sturm, D, Tschoepe, D, Spitzer, SG, Stumpf, J, Lohmann, T & Schnell, O 2011, 'Oral glucose tolerance test and HbA1c for diagnosis of diabetes in patients undergoing coronary angiography the Silent Diabetes Study', *Diabetologia*, vol. 54, no. 11, pp. 2923-2930.
- Du, TT, Yin, P, Zhang, JH, Zhang, D, Shi, W & Yu, XF 2013, 'Comparison of the performance of HbA1c and fasting plasma glucose in identifying dysglycaemic status in Chinese high-risk

subjects', *Clinical and Experimental Pharmacology and Physiology*, vol. 40, no. 2, Feb, pp. 63-68.

Dunstan, D, Zimmet, P, Welborn, T, Sicree, R, Armstrong, T, Atkins, R, Cameron, A, Shaw, J, Chadban, S & on behalf of the AusDiab Steering Committee 2001, *Diabetes & Associated Disorders in Australia - 2000. The Accelerating Epidemic. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab)*, Melbourne.

Eckhardt, BJ, Holzman, RS, Kwan, CK, Baghdadi, J & Aberg, JA 2012, 'Glycated Hemoglobin A(1c) as Screening for Diabetes Mellitus in HIV-Infected Individuals', *Aids Patient Care and Stds*, vol. 26, no. 4, Apr, pp. 197-201.

Engelgau, MM, Thompson, TJ, Herman, WH, Boyle, JP, Aubert, RE, Kenny, SJ, Badran, A, Sous, ES & Ali, MA 1997, 'Comparison of fasting and 2-hour glucose and HbA1c, levels for diagnosing diabetes: diagnostic criteria and performance revisited', *Diabetes Care*, vol. 20, no. 5, pp. 785-791.

Exebio, JC, Zarini, GG, Vaccaro, JA, Exebio, C & Huffman, FG 2012, 'Use of hemoglobin A1C to detect haitian-Americans with undiagnosed type 2 diabetes', *Arquivos Brasileiros De Endocrinologia E Metabologia*, vol. 56, no. 7, pp. 449-455.

Fitzgerald, DB, Kent, BD, Garvey, JF, Russell, A, Nolan, G & McNicholas, WT 2012, 'Screening for diabetes mellitus in patients with OSAS: A case for glycosylated haemoglobin', *European Respiratory Journal*, vol. 40, no. 1, pp. 273-274.

Ford, ES, Cowie, CC, Li, CY, Handelsman, Y & Bloomgarden, ZT 2011, 'Iron-deficiency anemia, non-iron-deficiency anemia and HbA1c among adults in the US', *Journal of Diabetes*, vol. 3, no. 1, Mar, pp. 67-73.

Gianchandani, RY, Saberi, S, Zrull, CA, Patil, PV, Jha, L, Kling-Colson, SC, Gandia, KG, DuBois, EC, Plunkett, CD, Bodnar, TW & Pop-Busui, R 2011, 'Evaluation of Hemoglobin A1c Criteria to Assess Preoperative Diabetes Risk in Cardiac Surgery Patients', *Diabetes Technology & Therapeutics*, vol. 13, no. 12, Dec, pp. 1249-1254.

Gillies, CL, Abrams, KR, Lambert, PC, Cooper, NJ, Sutton, AJ, Hsu, RT & Khunti, K 2007, 'Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis', *BMJ*, vol. 334, no. 7588, Feb 10, p. 299.

Gillies, CL, Lambert, PC, Abrams, KR, Sutton, AJ, Cooper, NJ, Hsu, RT, Davies, MJ & Khunti, K 2008, 'Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis', *BMJ*, vol. 336, no. 7654, May 24, pp. 1180-1185.

Gomyo, M, Sakane, N, Kamae, I, Sato, S, Suzuki, K, Tominaga, M, Kawazu, S, Yoshinaga, H, Tsushita, K, Sato, J, Sato, Y, Tsujii, S, Yoshida, T, Seino, Y, Usui, T, Nanjo, K, Hirata, M, Kotani, K, Hososako, A, Kiyohara, Y & Kuzuya, H 2004, 'Effects of sex, age and BMI on screening tests for impaired glucose tolerance', *Diabetes Research and Clinical Practice*, vol. 64, no. 2, May, pp. 129-136.

Hajat, C, Harrison, O & Al Siksek, Z 2011, 'Diagnostic Testing for Diabetes Using HbA(1c) in the Abu Dhabi Population', *Diabetes Care*, vol. 34, no. 11, Nov, pp. 2400-2402.

Hanna, FWF, Green, J, Issa, BG, Tahrani, AA & Fryer, AA 2012, 'Limitations of glycosylated haemoglobin (HbA1c) in diabetes screening', *Practical Diabetes*, vol. 29, no. 1, 2012 Jan-Feb, pp. 29-31.

Hardikar, PS, Joshi, SM, Bhat, DS, Raut, DA, Katre, PA, Lubree, HG, Jere, A, Pandit, AN, Fall, CHD & Yajnik, CS 2012, 'Spuriously High Prevalence of Prediabetes Diagnosed by HbA(1c) in

Young Indians Partly Explained by Hematological Factors and Iron Deficiency Anemia', *Diabetes Care*, vol. 35, no. 4, Apr, pp. 797-802.

Harris, MI, Klein, R, Cowie, CC, Rowland, M & Byrd-Holt, DD 1998, 'Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes?: a U.S. population study', *Diabetes Care*, vol. 21, no. 8, pp. 1230-1235.

Hayes, AJ, Leal, J, Gray, AM, Holman, RR & Clarke, PM 2013, 'UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82', *Diabetologia*, vol. 56, no. 9, Sep, pp. 1925-1933.

Hjellestad, ID, Astor, MC, Nilsen, RM, Softeland, E & Jonung, T 2013, 'HbA(1c) versus oral glucose tolerance test as a method to diagnose diabetes mellitus in vascular surgery patients', *Cardiovascular Diabetology*, vol. 12, May, pp. 79-79.

Holman, RR, Paul, SK, Bethel, MA, Matthews, DR & Neil, HA 2008, '10-year follow-up of intensive glucose control in type 2 diabetes', *N Engl J Med*, vol. 359, no. 15, Oct 9, pp. 1577-1589.

Hu, Y, Liu, W, Chen, Y, Zhang, M, Wang, L, Zhou, H, Wu, P, Teng, X, Dong, Y, Zhou, J, Xu, H, Zheng, J, Li, S, Tao, T, Hu, Y & Jia, Y 2010, 'Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance', *Acta Diabetol*, vol. 47, no. 3, Sep, pp. 231-236.

Hutchinson, MS, Joakimsen, RM, Njolstad, I, Schirmer, H, Figenschau, Y, Svartberg, J & Jorde, R 2013, 'Effects of Age and Sex on Estimated Diabetes Prevalence Using Different Diagnostic Criteria: The Tromso OGTT Study', *International Journal of Endocrinology*, pp. 13475-13475.

Icks, A, Haastert, B, Gandjour, A, John, J, Lowel, H, Holle, R, Giani, G & Rathmann, W 2004, 'Cost-effectiveness analysis of different screening procedures for type 2 diabetes: the KORA Survey 2000', *Diabetes Care*, vol. 27, no. 9, Sep, pp. 2120-2128.

Janus, ED, Best, JD, Davis-Lameloise, N, Philpot, B, Hernan, A, Bennett, CM, O'Reilly, S, Carter, R, Vartiainen, E, Dunbar, JA & Melbourne Diabetes Prevention Study research, g 2012, 'Scaling-up from an implementation trial to state-wide coverage: results from the preliminary Melbourne Diabetes Prevention Study', *Trials*, vol. 13, p. 152.

Jean Hailes Foundation for Women's Health 2011, *Evidence-based guideline for the assessment and management of polycystic ovary syndrome*, Melbourne.

Jesudason, DR, Dunstan, K, Leong, D & Wittert, GA 2003, 'Macrovascular risk and diagnostic criteria for type 2 diabetes - Implications for the use of FPG and HbA(1c) for cost-effective screening', *Diabetes Care*, vol. 26, no. 2, Feb, pp. 485-490.

Jun, DW, Kim, HJ, Bae, JH & Lee, OY 2011, 'The Clinical Significance of HbA1c as a Predictive Factor for Abnormal Postprandial Glucose Metabolism in NAFLD Patients with an Elevated Liver Chemistry', *Hepato-Gastroenterology*, vol. 58, no. 109, Jul-Aug, pp. 1274-1279.

Khoo, J, Tay, TL, Foo, JP, Tan, E, Soh, SB, Chen, R, Au, V, Ng, BJM & Cho, LW 2012, 'Sensitivity of A1C to diagnose diabetes is decreased in high-risk older Southeast Asians', *Journal of Diabetes and Its Complications*, vol. 26, no. 2, Mar-Apr, pp. 99-101.

Kinnaird, KE & Sauerwein, TJ 2010, 'Lack of correlation between 1,5-anhydroglucitol assay and oral glucose tolerance test in patients with cystic fibrosis', *Endocr Pract*, vol. 16, no. 2, Mar-Apr, pp. 167-170.

Ko, GT, Chan, JC, Yeung, VT, Chow, CC, Tsang, LW, Li, JK, So, WY, Wai, HP & Cockram, CS 1998, 'Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects', *Diabetes Care*, vol. 21, no. 8, Aug, pp. 1221-1225.

Ko, GTC, Chan, JCN & Cockram, CS 1998, 'Supplement to the use of a paired value of fasting plasma glucose and glycated hemoglobin in predicting the likelihood of having diabetes [6]', *Diabetes Care*, vol. 21, no. 11, pp. 2032-2033.

Koethe, SM, Zielinski, J & Perry, BW 1999, 'Glycohemoglobin results in samples with C or S trait measured on the Bio-Rad Diamat and Variant Express [3]', *Clinical Chemistry*, vol. 45, no. 11, p. 2041.

Kramer, CK, Araneta, MR & Barrett-Connor, E 2010, 'A1C and diabetes diagnosis: The Rancho Bernardo Study', *Diabetes Care*, vol. 33, no. 1, pp. 101-103.

Kumaravel, B, Bachmann, MO, Murray, N, Dhatariya, K, Fenech, M, John, WG, Scarpello, TJ & Sampson, MJ 2012, 'Use of haemoglobin A1c to detect impaired fasting glucose or Type 2 diabetes in a United Kingdom community based population', *Diabetes Res Clin Pract*, vol. 96, no. 2, May, pp. 211-216.

Kumapatla, S, Aravindalochanan, V, Rajan, R, Viswanathan, V & Kapur, A 2013, 'Evaluation of performance of A1c and FPG tests for screening newly diagnosed diabetes defined by an OGTT among tuberculosis patients-A study from India', *Diabetes Research and Clinical Practice*, vol. 102, no. 1, pp. 60-64.

Laatikainen, T, Dunbar, JA, Chapman, A, Kilkkinen, A, Vartiainen, E, Heistaro, S, Philpot, B, Absetz, P, Bunker, S, O'Neil, A, Reddy, P, Best, JD & Janus, ED 2007, 'Prevention of type 2 diabetes by lifestyle intervention in an Australian primary health care setting: Greater Green Triangle (GGT) Diabetes Prevention Project', *BMC Public Health*, vol. 7, p. 249.

Lavery, I & Ingram, P 2005, 'Venepuncture: best practice', *Nurs Stand*, vol. 19, no. 49, Aug 17-23, pp. 55-65; quiz 66.

Lawrence, JM, Bennett, P, Young, A & Robinson, AM 2001, 'Screening for diabetes in general practice: cross sectional population study', *BMJ*, vol. 323, no. 7312, Sep 8, pp. 548-551.

Lee, CM, Colagiuri, R, Magliano, DJ, Cameron, AJ, Shaw, J, Zimmet, P & Colagiuri, S 2013, 'The cost of diabetes in adults in Australia', *Diabetes Res Clin Pract*, vol. 99, no. 3, Mar, pp. 385-390.

Lee, H, Oh, JY, Sung, YA, Kim, DJ, Kim, SH, Kim, SG, Moon, S, Park, IB, Rhee, EJ, Chung, CH, Kim, BJ & Ku, BJ 2013, 'Optimal hemoglobin A1(C) Cutoff Value for Diagnosing type 2 diabetes mellitus in Korean adults', *Diabetes Research and Clinical Practice*, vol. 99, no. 2, Feb, pp. 231-236.

Lee, HS, Park, HK & Hwang, JS 2012, 'HbA1c and glucose intolerance in obese children and adolescents', *Diabetic Medicine*, vol. 29, no. 7, Jul, pp. E102-E105.

Lee, JM, Wu, EL, Tarini, B, Herman, WH & Yoon, E 2011, 'Diagnosis of Diabetes using Hemoglobin A1c: Should Recommendations in Adults Be Extrapolated to Adolescents?', *Journal of Pediatrics*, vol. 158, no. 6, Jun, pp. 947-U237.

Lee, SC, Wang, LH, Tsai, SM, Fang, HY & Tsai, LY 2011, 'Effects of the Hb E, Hb H and Hb G-Taichung variants on HbA1c values by the Bio-Rad variantTM II turbo analyzer', *Clinical Biochemistry*, vol. 44, no. 16, pp. 1338-1342.

Lerchbaum, E, Schwetz, V, Giuliani, A & Obermayer-Pietsch, B 2013, 'Assessment of glucose metabolism in polycystic ovary syndrome: HbA1c or fasting glucose compared with the oral

glucose tolerance test as a screening method', *Human Reproduction*, vol. 28, no. 9, pp. 2537-2544.

Liberati, A, Altman, DG, Tetzlaff, J, Mulrow, C, Gotzsche, PC, Ioannidis, JP, Clarke, M, Devereaux, PJ, Kleijnen, J & Moher, D 2009, 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration', *PLoS Med*, vol. 6, no. 7, Jul 21, p. e1000100.

Liberopoulos, EN, Florentin, M, Kei, A, Mountzouri, E, Agouridis, A & Elisaf, MS 2010, 'Comparison of Hemoglobin A(1c) and Fasting Glucose Criteria to Diagnose Diabetes Among People With Metabolic Syndrome and Fasting Glucose Above 100 mg/dL (5.5 mmol/L)', *Journal of Clinical Hypertension*, vol. 12, no. 7, Jul, pp. 543-548.

Lin, Y, Xu, Y, Chen, G, Huang, B, Chen, Z, Yao, L & Chen, Z 2012, 'Glycated hemoglobin, diabetes mellitus, and cardiovascular risk in a cross-sectional study among She Chinese population', *J Endocrinol Invest*, vol. 35, no. 1, Jan, pp. 35-41.

Lindholm, B & Karlander, SG 1986, 'Glucose tolerance in patients undergoing continuous ambulatory peritoneal dialysis', *Acta Medica Scandinavica*, vol. 220, no. 5, //, pp. 477-483.

Lorenzo-Medina, M, De-La-Iglesia, S, Ropero, P, Martin-Alfaro, R & Quintana-Hidalgo, L 2012, 'Interference of hemoglobin D on measurements of hemoglobin A1c by the high-performance liquid chromatography HA-8160 in 27 patients', *Journal of diabetes science and technology*, vol. 6, no. 5, pp. 1235-1237.

Lorenzo-Medina, M, De-La-Iglesia, S, Ropero, P, Nogueira-Salgueiro, P & Martin-Aguila, A 2013, 'Interference of hemoglobin (Hb) N-Baltimore on measurement of HbA 1c using the HA-8160 HPLC method', *Clinical Chemistry and Laboratory Medicine*, vol. 51, no. 2, pp. e13-e15.

Lu, ZX, Walker, KZ, O'Dea, K, Sikaris, KA & Shaw, JE 2010, 'A1C for Screening and Diagnosis of Type 2 Diabetes in Routine Clinical Practice', *Diabetes Care*, vol. 33, no. 4, pp. 817-819.

Magni, A, Borgo, G, Schinella, M & Mastella, G 1996, 'Screening tests for glucose metabolism abnormalities in cystic fibrosis', *European Journal of Laboratory Medicine*, vol. 4, no. 1, pp. 6-10.

Magnussen, LV, Mumm, H, Andersen, M & Glintborg, D 2011, 'Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome', *Fertility and Sterility*, vol. 96, no. 5, Nov, pp. 1275-1280.

Manley, S, Nightingale, P, Stratton, I, Sikaris, K, Smith, J, Cramb, R & Gough, S 2010, 'Diagnosis of diabetes: HbA1c versus WHO criteria', *Diabetes & Primary Care*, vol. 12, no. 2, p. 87.

Manley, SE, Sikaris, KA, Lu, ZX, Nightingale, PG, Stratton, IM, Round, RA, Baskar, V, Gough, SC & Smith, JM 2009, 'Validation of an algorithm combining haemoglobin A(1c) and fasting plasma glucose for diagnosis of diabetes mellitus in UK and Australian populations', *Diabet Med*, vol. 26, no. 2, Feb, pp. 115-121.

Marini, MA, Succurro, E, Arturi, F, Ruffo, MF, Andreozzi, F, Sciacqua, A, Lauro, R, Hribal, ML, Perticone, F & Sesti, G 2012, 'Comparison of A1C, fasting and 2-h post-load plasma glucose criteria to diagnose diabetes in Italian Caucasians', *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 22, no. 7, pp. 561-566.

Marini, MA, Succurro, E, Castaldo, E, Cufone, S, Arturi, F, Sciacqua, A, Lauro, R, Hribal, ML, Perticone, F & Sesti, G 2012, 'Cardiometabolic Risk Profiles and Carotid Atherosclerosis in Individuals With Prediabetes Identified by Fasting Glucose, Postchallenge Glucose, and Hemoglobin A(1c) Criteria', *Diabetes Care*, vol. 35, no. 5, May, pp. 1144-1149.

Massin, P, Lange, C, Tichet, J, Vol, S, Erginay, A, Cailleau, M, Eschwege, E & Balkau, B 2011, 'Hemoglobin A1c and fasting plasma glucose levels as predictors of retinopathy at 10 years: The French DESIR study', *Archives of Ophthalmology*, vol. 129, no. 2, pp. 188-195.

McCance, DR, Hanson, RL, Charles, MA, Jacobsson, LT, Pettitt, DJ, Bennett, PH & Knowler, WC 1994, 'Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes', *BMJ (Clinical research ed.)*, vol. 308, no. 6940, pp. 1323-1328, <<http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/582/CN-00102582/frame.html>>.

Medicare Australia 2010, *Original and Extended Medicare Safety Nets by electorate (based on patient enrolment postcode) 2010 Calendar Year (year of service)*, Australian Government, Department of Human Services,, viewed 20 Dec 2013, <<http://www.medicareaustralia.gov.au/forms/medicare-safety-net-stats.pdf>>.

— 2013a, *Medicare Australia Statistics, Medicare Item Reports.*, Australian Government, Department of Human Services,, viewed 10 Sep 2013, <https://www.medicareaustralia.gov.au/statistics/mbs_item.shtml>.

— 2013b, *Practice Incentives Program. Diabetes Incentive Guidelines—October 2013*, Australian Government, Department of Human Services, viewed 18 Oct 2013, <<http://www.medicareaustralia.gov.au/provider/incentives/pip/files/9520.1308.pdf>>.

Merlin, T, Lehman, S, Hiller, JE & Ryan, P 2013, 'The "linked evidence approach" to assess medical tests: a critical analysis', *Int J Technol Assess Health Care*, vol. 29, no. 3, Jul, pp. 343-350.

Merlin, T, Weston, A & Toohar, R 2009, 'Extending an evidence hierarchy to include topics other than treatment: revising the Australian "levels of evidence"', *BMC Med Res Methodol*, vol. 9, p. 34.

Miyazaki, M, Kubo, M, Kiyohara, Y, Okubo, K, Nakamura, H, Fujisawa, K, Hata, Y, Tokunaga, S, Iida, M, Nose, Y & Ishibashi, T 2004, 'Comparison of diagnostic methods for diabetes mellitus based on prevalence of retinopathy in a Japanese population: The Hisayama study', *Diabetologia*, vol. 47, no. 8, pp. 1411-1415.

Mongia, SK, Little, RR, Rohfing, CL, Hanson, S, Roberts, RF, Owen, WE, D'Costa, MA, Reyes, CA, Luzzi, VI & Roberts, WL 2008, 'Effects of hemoglobin C and S traits on the results of 14 commercial glycated hemoglobin assays', *American Journal of Clinical Pathology*, vol. 130, no. 1, Jul, pp. 136-140.

Mortaz, S, Wessman, C, Duncan, R, Gray, R & Badawi, A 2012, 'Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: a Markov model simulation', *Clinicoecon Outcomes Res*, vol. 4, pp. 91-97.

Mostafa, SA, Davies, MJ, Webb, D, Gray, LJ, Srinivasan, BT, Jarvis, J & Khunti, K 2010, 'The potential impact of using glycated haemoglobin as the preferred diagnostic tool for detecting Type 2 diabetes mellitus', *Diabetic Medicine*, vol. 27, no. 7, Jul, pp. 762-769.

Mostafa, SA, Khunti, K, Kilpatrick, ES, Webb, D, Srinivasan, BT, Gray, LJ & Davies, MJ 2013, 'Diagnostic performance of using one-or two-HbA_{1c} cut-point strategies to detect undiagnosed type 2 diabetes and impaired glucose regulation within a multi-ethnic population', *Diabetes & Vascular Disease Research*, vol. 10, no. 1, Jan, pp. 84-92.

Mostafa, SA, Khunti, K, Srinivasan, BT, Webb, D, Gray, LJ & Davies, MJ 2010, 'The potential impact and optimal cut-points of using glycated haemoglobin, HbA_{1c}, to detect people with

impaired glucose regulation in a UK multi-ethnic cohort', *Diabetes Research and Clinical Practice*, vol. 90, no. 1, Oct, pp. 100-108.

Moutet, JP, Pileire, B, Bangou, J, Ragoucy, C, Kangambega, P & Donnet, JP 1988, 'The assays of glycosylated proteins in haemoglobinopathies and their use in screening for diabetes mellitus', *The West Indian medical journal*, vol. 37, no. 1, pp. 36-40.

MSAC 2005, *Guidelines for the assessment of diagnostic technologies*, Medical Services Advisory Committee, Commonwealth of Australia, Canberra, ACT.

Nakanishi, T, Miyazaki, A, Iguchi, K & Shimizu, A 2000, 'Effect of hemoglobin variants on routine glycohemoglobin measurements assessed by a mass spectrometric method', *Clinical Chemistry*, vol. 46, no. 10, pp. 1689-1692.

Nakao, T, Matsumoto, H, Okada, T, Han, M, Hidaka, H, Yoshino, M, Shino, T, Yamada, C & Nagaoka, Y 1998, 'Influence of erythropoietin treatment on hemoglobin A(1c) levels in patients with chronic renal failure on hemodialysis', *Internal Medicine*, vol. 37, no. 10, //, pp. 826-830.

Nathan, DM & The International Expert Committee 2009, 'International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes', *Diabetes Care*, vol. 32, no. 7, pp. 1327-1334.

National Health and Medical Research Council 1999, *A guide to the development, implementation and evaluation of clinical practice guidelines*, National Health and Medical Research Council, Canberra, Australia.

Ng, JM, Jennings, PE, Laboi, P & Jayagopal, V 2008, 'Erythropoietin treatment significantly alters measured glycated haemoglobin (HbA1c)', *Diabetic Medicine*, vol. 25, no. 2, pp. 239-240.

NHMRC 2000, *How to use the evidence: assessment and application of scientific evidence*, Handbook series on preparing clinical practice guidelines, National Health and Medical Research Council, Canberra.

— 2008, *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Stage 2 consultation.*, National Health and Medical Research Council, Australian Government, viewed 11/03/08, <www.nhmrc.gov.au/consult/index.htm>.

Nowicka, P, Santoro, N, Liu, HB, Lartaud, D, Shaw, MM, Goldberg, R, Guandalini, C, Savoye, M, Rose, P & Caprio, S 2011, 'Utility of Hemoglobin A(1c) for Diagnosing Prediabetes and Diabetes in Obese Children and Adolescents', *Diabetes Care*, vol. 34, no. 6, Jun, pp. 1306-1311.

Ogawa, E, Urakami, T, Suzuki, J, Yoshida, A, Takahashi, S & Mugishima, H 2012, 'Usefulness of HbA1c to diagnose diabetes among Japanese children detected by a urine glucose screening program in the Tokyo Metropolitan Area', *Endocrine Journal*, vol. 59, no. 6, Jun, pp. 465-471.

Ohwovoriole, AE, Kutu, JA & Johnson, TO 1984, 'Influence of methodology on glycosylated hemoglobin values in Nigerian subjects with sickle cell hemoglobinopathy', *Annals of Clinical and Laboratory Science*, vol. 14, no. 4, pp. 265-269.

Peter, A, Fritsche, A, Stefan, N, Heni, M, Haring, HU & Schleicher, E 2011, 'Diagnostic Value of Hemoglobin A1c for Type 2 Diabetes Mellitus in a Population at Risk', *Experimental and Clinical Endocrinology & Diabetes*, vol. 119, no. 4, Apr, pp. 234-237.

- Piras, G, Carluccio, A, Coe, A, Domke, I, Miravalles, E & Naji, A 1993, 'Monitoring of HbA(1c) in patients with thalassemia and sickle cell disease', *Klinisches Labor*, vol. 39, no. 12, pp. 1033-1037.
- Rathmann, W, Kowall, B, Tamayo, T, Giani, G, Holle, R, Thorand, B, Heier, M, Huth, C & Meisinger, C 2012, 'Hemoglobin A1c and glucose criteria identify different subjects as having type 2 diabetes in middle-aged and older populations: The KORA S4/F4 Study', *Annals of Medicine*, vol. 44, no. 2, Mar, pp. 170-177.
- Reid, HL, Famodu, AA, Photiades, DP & Osamo, ON 1992, 'GLYCOSYLATED HEMOGLOBIN HBA1C AND HBS1C IN NONDIABETIC NIGERIANS', *Tropical and Geographical Medicine*, vol. 44, no. 1-2, Jan-Apr, pp. 126-130.
- Roberts, WL, De, BK, Brown, D, Hanbury, CM, Hoyer, JD, John, WG, Lambert, TL, Lundell, RB, Rohlfing, C & Little, RR 2002, 'Effects of hemoglobin C and S traits on eight glycohemoglobin methods', *Clinical Chemistry*, vol. 48, no. 2, pp. 383-385.
- Robertson, DA, Tunbridge, FK, John, WG, Home, PD & Alberti, KG 1992, 'Diagnostic confusion in diabetes with persistence of fetal haemoglobin', *BMJ*, vol. 305, no. 6854, Sep 12, pp. 635-637.
- Rowley, KG, Daniel, M & O'Dea, K 2005, 'Screening for diabetes in Indigenous populations using glycated haemoglobin: sensitivity, specificity, post-test likelihood and risk of disease', *Diabetic Medicine*, vol. 22, no. 7, Jul, pp. 833-839.
- Rutter, CM & Gatsonis, CA 2001, 'A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations', *Stat Med*, vol. 20, no. 19, Oct 15, pp. 2865-2884.
- Sabatar, J, Quereda, C, Herrera, I, Pascual, J, Villafruela, JJ & Ortuno, J 1991, 'Nonenzymatic glycosylation of hemoglobin and total plasmatic proteins in end-stage renal disease', *American Journal of Nephrology*, vol. 11, no. 1, //, pp. 37-43.
- Saiedullah, M, Rahman, MR & Khan, MAH 2011, 'Inequity of diagnosis of diabetes by plasma glucose and HbA1c', *Bangladesh Journal of Medical Science*, vol. 10, no. 4, pp. 284-286.
- Santos-Rey, K, Fernandez-Riejos, P, Mateo, J, Sanchez-Margalet, V & Goberna, R 2010, 'Glycated hemoglobin vs. the oral glucose tolerance test for the exclusion of impaired glucose tolerance in high-risk individuals', *Clinical Chemistry and Laboratory Medicine*, vol. 48, no. 12, Dec, pp. 1719-1722.
- Scales, K 2008, 'A practical guide to venepuncture and blood sampling', *Nurs Stand*, vol. 22, no. 29, Mar 26-Apr 1, pp. 29-36.
- Schaufler, TM & Wolff, M 2010, 'Cost effectiveness of preventive screening programmes for type 2 diabetes mellitus in Germany', *Appl Health Econ Health Policy*, vol. 8, no. 3, pp. 191-202.
- Schnedl, WJ, Krause, R, Halwachs-Baumann, G, Trinker, M, Lipp, RW & Krejs, GJ 2000, 'Evaluation of HbA1c determination methods in patients with hemoglobinopathies', *Diabetes Care*, vol. 23, no. 3, pp. 339-344.
- Schnedl, WJ, Krause, R, Wallner, SJ, Piswanger-Soelkner, C & Lipp, RW 2008, 'Effect of silent hemoglobin variants on A1C measurement with the IFCC reference method and 6 routine methods', *Clinica Chimica Acta*, vol. 398, no. 1-2, pp. 161-162.
- Schnedl, WJ, Lahousen, T, Krause, R, Wallner, SJ, Piswanger-Soelkner, C & Lipp, RW 2007, 'Evaluation of conditions associated with glycated hemoglobin values below the reference range', *Clin Lab*, vol. 53, no. 3-4, pp. 179-181.

Schnedl, WJ, Lahousen, T, Lang, T, Lipp, RW, Yonehara, S, Fukunaga, S, Imai, T & Little, RR 2004, 'Determination of glycated hemoglobin in clinically silent hemoglobin variants', *Diabetes/Metabolism Research and Reviews*, vol. 20, no. 6, pp. 460-465.

Sharma, S & Fleming, SE 2012, 'Use of HbA1C testing to diagnose pre-diabetes in high risk African American children: A comparison with fasting glucose and HOMA-IR', *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, vol. 6, no. 3, pp. 157-162.

Snehalatha, C, Ramachandran, A, Satyavani, K & Vijay, V 2000, 'Limitations of glycosylated haemoglobin as an index of glucose intolerance', *Diabetes Research and Clinical Practice*, vol. 47, no. 2, Feb, pp. 129-133.

Somani, BL, Arora, MM, Datta, SK, Negi, R & Gupta, A 2013, 'Prevalence of unsuspected glucose intolerance in coronary artery disease (CAD) patients: Importance of HbA1c', *Medical Journal Armed Forces India*.

Stata Corporation 2011, *Intercooled Stata 12.0 for Windows*, Stata Corporation, College City, Texas, <<http://www.stata.com/company/>>.

Stratton, IM, Adler, AI, Neil, HA, Matthews, DR, Manley, SE, Cull, CA, Hadden, D, Turner, RC & Holman, RR 2000, 'Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study', *BMJ*, vol. 321, no. 7258, Aug 12, pp. 405-412.

Stutchfield, PR, O'Halloran, S & Teale, JD 1987, 'Glycosylated haemoglobin and glucose intolerance in cystic fibrosis', *Archives of Disease in Childhood*, vol. 62, no. 8, pp. 805-810.

Tanaka, Y, Atsumi, Y, Matsuoka, K, Mokubo, A, Asahina, T, Hosokawa, K, Shimada, S, Matsunaga, H, Takagi, M, Ogawa, O, Onuma, T & Kawamori, R 2001, 'Usefulness of stable HbA(1c) for supportive marker to diagnose diabetes mellitus in Japanese subjects', *Diabetes Research and Clinical Practice*, vol. 53, no. 1, Jul, pp. 41-45.

Tanamas, SK, Magliano, DJ, Lynch, B, Sethi, P, Willenberg, L, Polkinghorne, KR, Chadban, S, Dunstan, D & Shaw, JE 2013, *AusDiab 2012. The Australian Diabetes, Obesity and Lifestyle Study*, Melbourne.

Tankova, T, Chakarova, N, Dakovska, L & Atanassova, I 2012, 'Assessment of HbA1c as a diagnostic tool in diabetes and prediabetes', *Acta Diabetologica*, vol. 49, no. 5, Oct, pp. 371-378.

Tapp, RJ, Tikellis, G, Wong, TY, Harper, CA, Zimmet, PZ & Shaw, JE 2008, 'Longitudinal association of glucose metabolism with retinopathy: results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study', *Diabetes Care*, vol. 31, no. 7, Jul, pp. 1349-1354.

Tatar, E, Kircelli, F, Demirci, MS, Turan, MN, Gungor, O, Asci, G, Ozkahya, M, Ok, E, Hoscokun, C & Toz, H 2013, 'Pre-transplant HbA1c level as an early marker for new-onset diabetes after renal transplantation', *International Urology and Nephrology*, vol. 45, no. 1, Feb, pp. 251-258.

Therapeutic Goods Administration 2012, *The regulatory requirements for in-house IVDs in Australia*, Australia Government Department of Health and Ageing, Canberra, Australia.

UK Prospective Diabetes Study (UKPDS) Group 1991, 'UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance', *Diabetologia*, vol. 34, no. 12, Dec, pp. 877-890.

Valderhaug, TG, Jenssen, T, Hartmann, A, Midtvedt, K, Holdaas, H, Reisæter, AV & Hjelmæsæth, J 2009, 'Fasting plasma glucose and glycosylated hemoglobin in the screening

for diabetes mellitus after renal transplantation', *Transplantation*, vol. 88, no. 3, //, pp. 429-434.

Vlaar, EMA, Admiraal, WM, Busschers, WB, Holleman, F, Nierkens, V, Middelkoop, BJC, Stronks, K & van Valkengoed, IGM 2013, 'Screening South Asians for type 2 diabetes and prediabetes: (1) comparing oral glucose tolerance and haemoglobin A1c test results and (2) comparing the two sets of metabolic profiles of individuals diagnosed with these two tests', *BMC Endocrine Disorders*, p. 8.

Wang, H, Shara, NM, Lee, ET, Devereux, R, Calhoun, D, de Simone, G, Umans, JG & Howard, BV 2011, 'Hemoglobin A(1c), Fasting Glucose, and Cardiovascular Risk in a Population With High Prevalence of Diabetes The Strong Heart Study', *Diabetes Care*, vol. 34, no. 9, Sep, pp. 1952-1958.

Wang, JS, Lee, IT, Lee, WJ, Lin, SY, Fu, CP, Ting, CT, Lee, WL, Liang, KW & Sheu, WHH 2013, 'Performance of HbA1c and fasting plasma glucose in screening for diabetes in patients undergoing coronary angiography', *Diabetes Care*, vol. 36, no. 5, pp. 1138-1140.

Wang, W, Lee, ET, Howard, BV, Fabsitz, RR, Devereux, RB & Welty, TK 2011, 'Fasting plasma glucose and hemoglobin a1c in identifying and predicting diabetes: the strong heart study', *Diabetes Care*, vol. 34, no. 2, pp. 363-368.

Waugh, N, Royle, P, Craigie, I, Ho, V, Pandit, L, Ewings, P, Adler, A, Helms, P & Sheldon, C 2012, 'Screening for cystic fibrosis-related diabetes: a systematic review', *Health Technology Assessment*, vol. 16, no. 24, pp. 1-180.

Weykamp, CW, Martina, WV, Van der Dijs, FPL, Penders, TJ, Van der Slik, W & Muskiet, FAJ 1994, 'Hemoglobins S and C: Reference values for glycohemoglobin in heterozygous, doubleheterozygous and homozygous subjects, as established by 13 methods', *Clinica Chimica Acta*, vol. 231, no. 2, pp. 161-171.

Whiting, PF, Rutjes, AW, Westwood, ME, Mallett, S, Deeks, JJ, Reitsma, JB, Leeflang, MM, Sterne, JA & Bossuyt, PM 2011, 'QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies', *Ann Intern Med*, vol. 155, no. 8, Oct 18, pp. 529-536.

WHO 2011, 'Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus', no. WHO reference number: WHO/NMH/CHP/CPM/11.1.

Wong, KC, Brown, AM & Li, SC 2011, 'AUSDRISK - application in general practice', *Aust Fam Physician*, vol. 40, no. 7, Jul, pp. 524-526.

Wong, TY, Klein, R, Islam, FM, Cotch, MF, Folsom, AR, Klein, BE, Sharrett, AR & Shea, S 2006, 'Diabetic retinopathy in a multi-ethnic cohort in the United States', *Am J Ophthalmol*, vol. 141, no. 3, Mar, pp. 446-455.

World Health Organisation 2011, *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: abbreviated report of a WHO consultation*, World Health Organisation, Geneva.

Yang, L, Shen, X, Yan, S, Yuan, X, Lu, J & Wei, W 2013, 'HbA1c in the diagnosis of diabetes and abnormal glucose tolerance in patients with Graves' hyperthyroidism', *Diabetes Research and Clinical Practice*, vol. 101, no. 1, //, pp. 28-34.

Yesiltepe Mutlu, G, Ozsu, E, Mine Cizmecioglu, F & Hatun, S 2013, 'Can HbA1c and one-hour glucose concentration in standard OGTT be used for evaluation of glucose homeostasis in childhood?', *JCRPE Journal of Clinical Research in Pediatric Endocrinology*, vol. 5, no. 2, pp. 80-84.

Young, TK & Krahn, J 1988, 'Comparison of screening methods in a diabetes prevalence survey among northern Indians', *Clinical and Investigative Medicine*, vol. 11, no. 5, pp. 380-385.

Yung, B, Kemp, M, Hooper, J & Hodson, ME 1999, 'Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria', *Thorax*, vol. 54, no. 1, Jan, pp. 40-43.

Zhu, Y, Williams, LM & Horne, BD 2010, 'Disparity in estimated average glucose due to different hemoglobin A1c methods and hemoglobin S trait', *Clinical Chemistry and Laboratory Medicine*, vol. 48, no. 4, pp. 571-572.