National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes

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For the:
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Diabetes Australia Guideline Development Consortium

The Diabetes Australia Guideline Development Consortium comprises Diabetes Australia; Australian Diabetes Society; the Australian Diabetes Educators' Association; the Royal Australian College of General Practitioners; and The Diabetes Unit, Menzies Centre for Health Policy, The University of Sydney.

A link to the guideline can be found on the Diabetes Australia website:
www.diabetesaustralia.com.au/For-Health-Professionals/Diabetes-National-Guidelines/

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is Australia's leading funding body for health and medical research. The NHMRC also provides the government, health professionals and the community with expert and independent advice on a range of issues that directly affect the health and well being of all Australians.

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A link to the guideline can be found on the National Health and Medical Research Council website: www.nhmrc.gov.au/publications.

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the beset evidence available at the time of development.

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Glossary of Acronyms

ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
AIHW	Australian Institute of Health and Welfare
ANDIAB	Australian National Diabetes Information Audit and Benchmarking
ARB	Angiotensin receptor blocker
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
AUSDRISK	Australian Type 2 Diabetes Risk Assessment Tool
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CBG	Capillary blood glucose
CDC	Centers for Disease Control and Prevention
CVD	Cardiovascular disease
DALY	Disability adjusted life year
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HR	Hazard ratio
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low density lipoprotein
NHMRC	National Health and Medical Research Council
NNS	Number needed to screen
NPV	Negative predictive value
OGTT	Oral glucose tolerance test
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PCOS	Polycystic ovary syndrome
POC	Point of care
PPV	Positive predictive value
QALY	Quality adjusted life year
RBG	Random blood glucose
RCT	Randomised controlled trial
ROC	Receiver operator characteristic
RPG	Random plasma glucose
SES	Socio-economic status
WHO	World Health Organisation
WHR	Waist to hip ratio

Case Detection and Diagnosis
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Guideline for Case Detection and Diagnosis

Introduction

Aim of the Guideline

This Guideline addresses the topic of case detection and diagnosis of undiagnosed type 2 diabetes in asymptomatic non-pregnant adults. It targets all categories of clinicians but will have particular relevance to primary care physicians.

Methods

The methods used to identify and critically appraise the evidence to formulate the guideline recommendations are described in detail in the *Overview of Guideline Development Process and Methods* (Appendix 4*)*.

Guideline Format

Questions identified by the Expert Advisory Group (EAG) for case detection and diagnosis of type 2 diabetes are shown on the next page.

Each of these issues is addressed in a separate section in a format presenting:

- ***Recommendation(s)***
- ***Practice Point (s) –*** including experts' consensus in absence of gradable evidence
- ***Evidence Statements –*** supporting the recommendations
- ***Background –*** to issues for the guideline
- ***Evidence –*** detailing and interpreting the key findings
- ***Evidence tables –*** summarising the evidence ratings for the articles reviewed

For all issues combined, supporting material appears at the end of the guideline topic and includes:

- ***Evidence references***
- ***Search Strategy and Yield Tables*** documenting the identification of evidence sources

Questions for Case Detection and Diagnosis

The following questions have been addressed in the preparation of the guidelines

1. Is case detection and diagnosis of type 2 diabetes worthwhile?
2. How should case detection and diagnostic testing for type 2 diabetes be performed?
3. How often should testing be performed?
4. What are the socio-economic implications for case detection and diagnosis of type 2 diabetes?

Summary of Recommendations and Practice Points

Recommendations

- Identify and treat type 2 diabetes at a stage before clinical presentation in order to reduce morbidity from long term complications (Grade C)

- A three-step case detection and diagnosis procedure is recommended for detecting people with undiagnosed type 2 diabetes (Grade B):
    1. Initial risk assessment determined using a risk assessment tool or risk factors commonly associated with undiagnosed type 2 diabetes
    2. Measurement of fasting plasma glucose
    3. An oral glucose tolerance test performed in all people with an equivocal result – FPG of 5.5-6.9 mmol/L, or random plasma glucose of 5.5-11.0 mmol/L.

- Periodic re-testing for undiagnosed type 2 diabetes is recommended according to the following schedule (Grade C):
    - Each year for people with impaired glucose tolerance or impaired fasting glucose
    - Every 3 years for all other people

- Screening for undiagnosed type 2 diabetes in high risk individuals should be an integral component of a diabetes prevention program (Grade C)

Practice Points

- The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) should be used to assess risk of undiagnosed diabetes
- Risk assessment should begin at age 40 and from age 18 in Aboriginal and Torres Strait Islanders*
- An AUSDRISK score ≥ 12 is recommended when the primary purpose of risk assessment is to detect undiagnosed type 2 diabetes.
- The following should proceed to Step 2 of the case detection and diagnosis procedure and do not need assessment with the AUSDRISK:
  - 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)
  - people on antipsychotic medication
- Laboratory testing is preferred but point of care testing using capillary blood can be used for the screening step
- Random plasma glucose may be used if collection of a fasting sample is considered impractical
- Proceeding directly from risk assessment to an oral glucose tolerance test may be considered if the intermediate step is considered impractical
- The 2006 WHO/IDF criteria should be used to diagnose diabetes
- The diagnosis of type 2 diabetes requires two positive laboratory blood tests on separate days unless the plasma glucose is unequivocally elevated in the presence of acute metabolic decompensation or obvious symptoms
- All people with identified risk factors for type 2 diabetes who have a negative screening test are at risk of cardiovascular disease and the future development of type 2 diabetes, and should be given appropriate advice on risk factor reduction
- Socio-economic factors should be considered when developing programs for screening for undiagnosed type 2 diabetes

* It should be noted that the AUSDRISK may overestimate risk in those less than 25 years of age and underestimate risk in Aboriginal and Torres Strait Islanders

Section 1: Why Detect Type 2 Diabetes

Question

Is case detection and diagnosis of type 2 diabetes worthwhile?

Recommendation

Identify and treat type 2 diabetes at a stage before clinical presentation in order to reduce morbidity from long term complications (Grade C)

Evidence Statements

- Type 2 diabetes is a common, serious and costly health problem
  Evidence Level IV
- Undiagnosed type 2 diabetes is common and is not a benign condition
  Evidence Level II
- Detection and management of screen-detected diabetes may improve outcomes
  Evidence Level II
- Case detection and diagnosis of type 2 diabetes has a favourable risk:benefit ratio
  Evidence Level II

Background – Why Detect Type 2 Diabetes

The Australian national prevalence study, AusDiab (the Australian Diabetes, Obesity and Lifestyle Study), showed that type 2 diabetes affects 7.4% of the Australian population in people aged 25 years or older and that there is one undiagnosed for every diagnosed person with type 2 diabetes (2002). Diabetes, both diagnosed and undiagnosed, is a major independent risk factor for cardiovascular disease (CVD), blindness, renal failure and lower limb amputation. Many people with type 2 diabetes have the disease for a number of years before it becomes clinically apparent. Nearly 80% of people with undiagnosed type 2 diabetes have readily identifiable risk factors (Cowie et al, 1994) and over 90% visit a doctor (predominantly a general practitioner) each year (ABS, 1997a). Case detection in the primary health care setting provides an opportunity to identify the estimated 500,000 Australians (ABS, 1997b; Dunstan et al, 2002) with undiagnosed type 2 diabetes.

This section discusses and evaluates the merits of case detection and diagnosis of undiagnosed type 2 diabetes in non-pregnant adults.

Case detection can be justified if a disease represents an important health problem, is present at a high enough prevalence (within the total or a specific target population), has a relatively long asymptomatic phase, and interventions are available which have a proven beneficial effect on clinically meaningful outcomes. Furthermore, the test for the disease must be safe, acceptable to the target population and have adequate sensitivity and specificity. Ideally any case detection program should be assessed in randomised controlled trials (RCTs) measuring health outcomes and costs in screened and unscreened populations. In the absence of such information, case finding is considered worthwhile if all or most of the above requirements are fulfilled.

Type 2 diabetes is both a disease entity and a risk factor for other disease, predominantly cardiovascular and cerebrovascular disease. Consequently, both aspects should be considered in evaluating recommendations for active case detection of undiagnosed type 2 diabetes.

Screening for type 2 diabetes in asymptomatic individuals has been proposed as one strategy for decreasing the diabetes burden (WHO, 2003). To date, there have been no RCTs on the effects of early intervention in people with screen-detected diabetes. One study, the ADDITION study, is in progress and is examining cardiovascular and microvascular outcomes of intensive compared with conventional treatment in people with screen-detected diabetes and is due to report in late 2009 (Lauritzen et al, 2000).

In the absence of such information, a number of organisations have considered and made recommendations about screening for type 2 diabetes.

The World Health Organisation (WHO) proposed a number of factors which should be considered in determining whether screening should be performed (WHO, 2003) including:

- prevalence of undiagnosed type 2 diabetes, which is the most important epidemiological consideration
- health system capacity, in particular the capacity of the system to carry out screening, follow-up and diagnostic testing and its capacity to manage effectively the newly detected cases of diabetes and to implement effective prevention in those who, though not confirmed to have diabetes at the time, are at high risk of its future development

- population considerations including the acceptability of the screening program to those invited to attend and the psychosocial impact of each screening outcome – positive and negative
- economic considerations including the cost of early detection to the health system and to the individual, the extra costs of treatment following early detection and the relative cost effectiveness of early detection compared with that of improving the care of clinically detected (as opposed to screen-detected) cases

The main recommendation from this report was that health authorities and professional organisations should formulate policies concerning screening for type 2 diabetes even if the policy is that screening is not currently to be advocated.

In the 2005 Global Guideline for Type 2 Diabetes the International Diabetes Federation (IDF) does not recommend universal screening for undiagnosed diabetes (IDF, 2005). Instead the decision on whether to screen for undiagnosed diabetes should be based on the prevalence of undiagnosed diabetes in the population and the resources available for screening and subsequent treatment. Screening programs should assess risk factors for diabetes to target high-risk individuals, and follow WHO guidelines to diagnose diabetes.

The US Preventive Services Task Force (USPSTF), recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (BP) (either treated or untreated) greater than 135/80 mmHg (grade B recommendation) (USPSTF, 2008). However, the USPSTF found insufficient evidence to assess the balance of benefits and harms of routine screening for type 2 diabetes in asymptomatic adults with BP of 135/80 mmHg or lower (grade I statement).

The American Diabetes Association (ADA) does not recommend community screening for type 2 diabetes, even in high-risk populations (ADA, 2004b) on the basis of a lack of evidence that mass screening is a cost-effective approach to reduce morbidity and mortality associated with type 2 diabetes, and that the potential harms of screening are not well known. However the ADA recommends screening of high risk adults (ADA, 2008).

The Canadian Task Force on Preventive Health care concluded that there is fair evidence to recommend screening for type 2 diabetes in adults with hypertension or hyperlipidaemia to prevent cardiovascular events and death (grade B recommendation) (Feig et al, 2005).

Evidence – Why Detect Type 2 Diabetes

- **Type 2 diabetes is a common, serious and costly health problem *(Evidence Level IV)***

Diabetes was estimated to effect 246 million people worldwide (6.0% of the population) in 2007, with 380 million people (7.3% of the population) expected to have diabetes in the year 2025 (IDF, 2006). The estimated cost of treatment and prevention of diabetes and its complications worldwide in 2007 was US$232 billion, which is expected to rise to US$302.5 billion in 2025. Diabetes was responsible for an estimated 3.8 million deaths globally (~6% of total world mortality) in adults 20-79 years old in 2007. Over two-thirds of the deaths attributable to diabetes occur in developing countries. Worldwide, approximately 50% of all people with diabetes were undiagnosed.

Several studies have examined the prevalence of diabetes in Australia. These studies have given fairly consistent results when the method of ascertaining diabetes is taken into consideration.

The AusDiab study showed that 7.4% of the Australian population aged 25 years and over have type 2 diabetes (known and newly diagnosed), and an additional 16.4% have impaired fasting glucose (IFG) (5.8%) or impaired glucose tolerance (IGT) (10.6%) (Dunstan et al, 2002).

Based on self-reported data, the 2004-05 National Health Survey (NHS) estimated that 700,000 Australians (3.6% of the population) had diagnosed diabetes (ABS, 2006a). This represents a more than doubling of prevalence of diagnosed diabetes between 1989-90 and 2004-05 from 1.3% to 3.6%, largely due to an increase in type 2 diabetes (AIHW, 2008) which represented 83% of self-reported cases of diagnosed diabetes (ABS, 2006a).

The NorthWest Adelaide Health Study conducted two separate examinations – 4,060 adults aged 18 and over examined between 2000 and 2003 and 3,178 of the same adults examined between 2004 and 2006. Based on fasting plasma glucose (FPG) measurement or self-report the prevalence of diabetes was 6.6% and 7.2%, respectively. Overall, 2.1% of the cohort who did not have diabetes in the first examination had diabetes in the second examination (North West Adelaide Health Study, 2007). Data from the first examination indicated that there was 1 person with undiagnosed diabetes for every 5 to 6 people with known diabetes (Grant et al, 2005).

In a Victorian population of 4,744 subjects aged 40 years and over, the prevalence of self-reported diabetes between the years 1992-1996 was 5.1% (McKay et al, 2000).

Indigenous Australians have a higher prevalence of diabetes. In 2,626 Australian Aboriginal people aged 15-94 years the prevalence of diabetes, adjusted for age and BMI, was 14.2% among men and 15.2% among women (Daniel et al, 2002).

Recent figures based on self-report data from the National Aboriginal and Torres Strait Islander Health Survey indicate that the prevalence of diabetes (including high sugar levels) was 6% in 2004-05 (ABS, 2006b). After adjusting for age, Indigenous Australians were 3.4 times more likely than non-Indigenous Australians to report some form of diabetes.

Data from 777 Indigenous Australians aged 15-64 years participating in the Diabetes and Related conditions in Urban Indigenous people in the Darwin region (DRUID) study indicate a prevalence of diabetes of 17% in this population (Cunningham et al, 2008). The majority (68%) of these subjects with diabetes had been previously diagnosed by a health professional.

Type 2 diabetes is a serious health problem in Australia which results in premature death and major irreversible long term complications including myocardial infarction, stroke, retinopathy and blindness, renal disease requiring dialysis or transplantation, neuropathy, foot ulcer, amputation, and erectile dysfunction. In 2004 diabetes was among the top ten leading causes of death, being the direct cause of 2.7% of deaths in Australia and being associated with another 6% of deaths (ABS, 2006a). CVD is the major cause of death in people with diabetes, accounting for approximately 50% of all fatalities (IDF, 2006).

The Australian Institute of Health and Welfare (AIHW) report, *Diabetes: Australian Facts 2008* (AIHW, 2008), stated that diabetes accounted for 5.5% of the total burden of disease in Australia in 2003, 92% of which was due to type 2 diabetes (Begg et al, 2007). Approximately 85% of the total diabetes burden was due to the diabetes itself, regardless of complications. When the contribution of diabetes to the related complications of stroke and heart disease was taken into account it was responsible for 8.3% of the total disease burden. Data from the 2004-05 NHS indicates that 20% of people with diabetes reported having heart, stroke or vascular disease (ABS, 2006a). This report also indicated that individuals with diabetes were twice as likely as those without it to have a heart attack (3.0 vs. 1.5%) and four times as likely to have a stroke (9 vs. 2%). Furthermore, 14% of those who reported diabetes had an eye condition due to diabetes. Data from the 1999-2000 AusDiab study showed that approximately 22% of people with previously diagnosed type 2 diabetes and 6.2% with newly diagnosed type 2 diabetes had retinopathy (Tapp et al, 2003b). According to self-reported data from the 1999-2000 AusDiab study, approximately 6.3% of Australians aged 45 years or over with diabetes were treated for or were suffering from kidney disease. Data from the AusDiab Kidney Study reveals that the prevalence of proteinuria was over 4 times higher in those with diabetes compared with those without diabetes (8.7% vs. 1.9%, $p < 0.001$) (Chadban et al, 2003). AusDiab data indicate evidence of albuminuria in 18% of people with newly diagnosed diabetes (Tapp et al, 2004).

Recent Australian National Diabetes Information Audit and Benchmarking (ANDIAB) data show that among people attending diabetes clinics, 31% had microalbuminuria and 10% had macroalbuminuria (NADC, 2007). In 1999-2000 ~10% of people with newly diagnosed diabetes had clinical signs of neuropathy. In 2004-05 there were 3,394 lower limb amputations among people with diabetes (70% were for males). In 1999-2000 approximately 30% of males with diabetes reported suffering from impotence (AIHW, 2008).

Diabetes and its related complications incur considerable health care costs. In 2004-05 the direct health-care expenditure on diabetes was $907 million (of which type 2 diabetes accounted for 81% at $733 million), accounting for 1.7% of the total allocatable recurrent health expenditure for that year (AIHW, 2008). These figures almost certainly underestimate the true cost of diabetes. The DiabCost study reported that the average total (direct plus indirect) health costs for an individual with type 2 diabetes was $5,360 per year (Colagiuri et al, 2003a). The costs per year for individuals with both macrovascular and microvascular complications was on average 2.4 times higher than for those with no complications ($9,625 vs. $4,020). Based on a diabetes prevalence of 7.4%, the total annual cost for people with type 2 diabetes in Australia was estimated to be $2.2 billion, and if the cost of carers is included this figure rises to $3.1 billion. In addition, people with type 2 diabetes receive

$5,540 per year on average in Commonwealth benefits, increasing the total annual cost of diabetes to $6 billion.

In addition to type 2 diabetes, less severe abnormalities of glucose tolerance are also associated with increased morbidity and mortality. Intermediate hyperglycaemia (IGT and IFG) defines a subgroup of the population which has glucose levels intermediate between normal values and those diagnostic of diabetes. People with intermediate hyperglycaemia are at increased risk of the future development of type 2 diabetes and also at increased risk of CVD morbidity and mortality (WHO, 2006). Intermediate hyperglycaemia is common with prevalence rates in the 1999-2000 AusDiab study of 16.4% for IGT or IFG (Dunstan et al, 2002).

- **Undiagnosed type 2 diabetes is common and is not a benign condition** ***(Evidence Level II)***

A significant proportion of the population has undiagnosed type 2 diabetes:

A number of Australian population studies show that across different ethnic groups undiagnosed type 2 diabetes is common. These studies have used different methodologies. The following studies using a standard oral glucose tolerance test (OGTT) reported the prevalence of previously undiagnosed type 2 diabetes:

- In the AusDiab study the overall prevalence of diabetes was 7.4% with 3.7% known diabetes and 3.7% newly diagnosed diabetes – i.e. one case of undiagnosed diabetes for every known case (Dunstan et al, 2002)
- In the crossroads undiagnosed diseases study (CUDS) the prevalence of diabetes in rural Victoria in 2005 was 7.3% compared with 8.9% in the Shire Capitals (Simmons et al, 2005a). Of those with diabetes, 26% were previously undiagnosed.
- Guest et al. (1992) found a prevalence of 53% previously undiagnosed diabetes among non-Aboriginal Australians in country Victoria. The ratio of undiagnosed to diagnosed cases for Aboriginal people was 0.54.
- The Busselton study in rural Western Australia reported a diabetes prevalence of 3.4%, with 2.5% known diabetes and 0.9% newly diagnosed diabetes in a cohort of 3,197 subjects aged 25 years and over (Glatthaar et al, 1985).
- Data from the DRUID study report that in a population of Indigenous Australians where the prevalence of diabetes was 17%, the proportion of undiagnosed cases of diabetes was 32% (Cunningham et al, 2008).

Two Australian studies have used FPG to diagnose diabetes and reported the following rates of previously undiagnosed type 2 diabetes:

- In the Blue Mountains Eye Study the prevalence of self-reported diabetes was 5.9% in a cohort of 3,654 people aged 49 years and over (Mitchell et al, 1998). The prevalence of undiagnosed diabetes based on the FPG was 2.2%, giving an overall prevalence of diabetes of 8.8%.
- Data from the Melbourne Collaborative Cohort Study indicate that in a cohort of 29,331 participants aged 40-69 years, the prevalence of diabetes was 2.9% in Australian-born participants, and 9.8 and 9.5% in Greek and Italian migrants, respectively (Hodge et al, 2004). The majority of these participants had previously diagnosed diabetes, with only 21, 15 and 15% of the Australian-, Greek- and Italian-born participants with diabetes, respectively, found to have newly diagnosed diabetes.

- In the NorthWest Adelaide Health study the prevalence of diabetes was 6.6% in a cohort of 4,060 adults (Grant et al, 2005). There was 1 person with undiagnosed diabetes for every 5 to 6 people with known diabetes.

Table 1: Australian diabetes prevalence data

Study	Number of participants	Age of participants (years)	Prevalence of diabetes		
			Total (%)	Known (%)	Undiagnosed (%)
DRUID Study – Cunningham et al., 2008	777 Indigenous Australians	15-64	17	11.6*	5.4
NorthWest Adelaide Health Study, 2007	4,060	18+	6.6	5.6*	1.0*
CUDS – Simmons et al., 2005a	1,454	25+	8.1	6.0	2.1
Melbourne Collaborative Cohort Study – Hodge et al., 2004	29,331	40-69	Aus: 2.9 Greek: 9.8 Italian: 9.5	2.3 8.3 8.1	0.6 1.5 1.4
AusDiab – Dunstan et al., 2002	11,247	25+	7.4	3.7	3.7
Daniel et al., 2002	2,626 Indigenous Australians	15-94	Men: 14.2 Women: 15.2	NR	NR
Blue Mountains Eye Study – Mitchell et al., 1998	3,029#	49+	8.8	6.6	2.2
Busselton Study – Glatthaar et al., 1985	3,197	25+	3.4	2.5	0.9

* extrapolated from available data
# number who had a fasting glucose measurement
NR = Not reported

Rates of undiagnosed diabetes are likely to be higher in other populations commonly represented in Australia. For example, in a study of Chinese adults aged 35 to 74 years, three out of every four people with diabetes were previously undiagnosed (Gu et al, 2003). Similarly in a study of 1,024 Tongans aged 15 years and over, the prevalence of diabetes was 15%, of whom 80% were undiagnosed (Colagiuri et al, 2002a).

Undiagnosed type 2 diabetes is not a benign condition

Type 2 diabetes detected by a case detection program is associated with increased mortality. The AusDiab study included a cohort of 10,428 participants who were followed for a median of 5.2 years. The adjusted all-cause mortality hazard ratios (HRs) and 95%CI for those with known diabetes and newly diagnosed were 2.3 (1.6-3.2) and 1.3 (0.9-2.0), respectively, compared with those with normal glucose tolerance (Barr et al, 2007). The risk of death was increased in people with IFG (HR 1.6, [95%CI 1.0-2.4]) and IGT (HR 1.5, [1.1-2.0]).

These results are similar to other studies. In the Melton Mowbray study (Croxson et al, 1994) the age and sex adjusted relative risk (RR) of death over 4.5 years compared with people with normal glucose tolerance was 5.2 (95%CI 3.2-8.5) in people with known diabetes, 3.0 (1.3-6.6) in people newly diagnosed through a detection program for type 2 diabetes and 1.7 (0.8-3.5) in people with IGT. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study included data on over 25,000 people from a range of European countries (DECODE, 1999a). Over a mean follow-up period of 7.3 years the risk of death was approximately twice as high for people with type 2 diabetes diagnosed through a

case detection program compared with people with normal glucose tolerance. Similar findings were reported in the Cardiovascular Heart Study (Barzilay et al, 1999) which included 4,515 people over age 65 years. During a mean follow-up period of 5.9 years, this study demonstrated an excess of myocardial infarction, stroke and cardiovascular death in people found to have type 2 diabetes by an OGTT screening program. These studies are consistent with the finding of previous studies - NHANES II (Harris, 1993), the Paris Prospective Study (Eschwege et al, 1985) and the Whitehall study (Jarrett and Shipley, 1988).

A meta-analysis of five prospective cohort studies of Japanese and Asian Indian origin was conducted as part of the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study to examine the cardiovascular mortality associated with screen-detected diabetes, hypertension and hypercholesterolemia (Nakagami et al, 2006). A total of 6,573 subjects without a history of CVD were followed for a mean of 5.9 years. The overall risk for CVD mortality was higher in those with screen-detected diabetes (HR 3.42, [95%CI 2.23-5.23]) than in those with hypertension (HR 1.57, [1.10-2.24]) or hypercholesterolemia (HR 1.49, [1.05-2.10]). Stratified multivariate analysis indicated that subjects with screen-detected diabetes in the presence of hypertension or hypercholesterolemia had the highest risk of CVD, comprising 78% of all CVD deaths occurring in all subjects with screen-detected diabetes.

The risk of death and major cardiovascular events associated with both newly diagnosed and previously known diabetes was assessed in a cohort of 14,703 subjects with acute myocardial infarction enrolled in the VALsartan In Acute myocardial iNfarcTion (VALIANT) Trial (Aguilar et al, 2004). At enrollment, 580 subjects (4%) had newly diagnosed diabetes, 3,400 (23%) had previously diagnosed diabetes and 10,719 (73%) had no diabetes. At one year following enrollment, compared to control subjects, people with newly diagnosed and people with previously diagnosed diabetes had similarly elevated adjusted risks of mortality (HR 1.50, [95%CI 1.21-1.85] and HR 1.43 [1.29-1.59], respectively) and cardiovascular events (HR 1.34, [1.14-1.56] and HR 1.37, [1.27-1.48], respectively).

There are some data suggesting that the effect of a diagnosis of diabetes on mortality is dependent on age. Barnett et al. (2006) performed a systematic review of observational studies reporting all-cause mortality in people with type 2 diabetes diagnosed after age 60 years. A meta-analysis of these studies revealed a combined relative risk (95%CI) of increased mortality for men diagnosed between the ages of 60 and 70 of 1.38 (1.08–1.76), and 1.13 (0.88–1.45) for men diagnosed aged 70 years or older. For women in the same age groups the combined relative risks were 1.40 (1.10–1.79) and 1.19 (0.93–1.52), respectively. These results suggest that people diagnosed over the age of 70 have a lower relative risk of premature death than those diagnosed between 60 and 70 years of age, but a slightly higher risk than non-diabetic people. Also the increased mortality associated with a diagnosis of type 2 diabetes at an older age remains lower than that reported for the general older diabetic population.

Complications are commonly present at the time of diagnosis of type 2 diabetes in both symptomatic and asymptomatic individuals. The AusDiab study found that in people with newly diagnosed diabetes the prevalence of retinopathy was 6.2% while there were no cases of proliferative diabetic retinopathy. The prevalence of peripheral neuropathy was 7% and 7% also had peripheral vascular disease (Tapp et al, 2003a). Approximately 11% of people with newly diagnosed diabetes in the AusDiab study had microalbuminuria and 2% had macroalbuminuria (Tapp et al, 2004).

Other recent studies have reported higher rates. Spijkerman et al. (2003) found retinopathy in 7.6% of people with screen-detected diabetes, impaired foot sensitivity in 48% and microalbuminuria in 17%. Macrovascular complications were also common (Spijkerman et al, 2004a). The prevalence of myocardial infarction was 13.3%, ischaemic heart disease 40% and peripheral arterial disease 10.6%.

A cohort of 135 Indigenous Australians from the DRUID study were assessed for diabetes complications, including 99 subjects with known diabetes (mean age 53 years) and 36 with newly diagnosed diabetes (mean age 47 years) (Maple-Brown et al, 2008). Among those with known diabetes, 39% had albuminuria, 21% had retinopathy, 12% had peripheral vascular disease and 9% had neuropathy. Of those with newly diagnosed diabetes, 19% had albuminuria, 14% had peripheral vascular disease, 6% had neuropathy and none had retinopathy.

Studies which have examined the relationship of diabetes complications and the diagnosis of diabetes indicate that type 2 diabetes commonly has a lengthy asymptomatic phase. Duration of diabetes is an important determinant of the prevalence of diabetic retinopathy (NHMRC, 1997). Since retinopathy is frequently found in people with newly diagnosed type 2 diabetes and the increase in prevalence plotted against duration appears to be linear, extrapolation of the line to zero prevalence of retinopathy indicates that retinopathy maybe detectable some 4-7 years before diagnosis of type 2 diabetes (Harris et al, 1992). Furthermore, it is estimated that the minimum duration of diabetes necessary for the development of retinopathy is approximately 5 years (Jarrett, 1986). Therefore, combining the time between onset of diabetes and development of retinopathy of approximately 5 years, and the interval between detectable retinopathy and clinical diagnosis of diabetes of 4-7 years, undiagnosed diabetes may exist for as long as 12 years before clinical diagnosis (Harris et al, 1992). More recent data from the AusDiab study suggest that of those subjects who developed incident newly diagnosed diabetes at 5 years follow-up, 11.9% had retinopathy at baseline compared with 5.6% of those who did not progress to incident newly diagnosed diabetes ($p = 0.037$) (Tapp et al, 2008). After adjusting for diabetes risk factors, subjects with retinopathy at baseline were twice as likely to develop incident newly diagnosed diabetes at follow-up compared with those without retinopathy at baseline (odds ratio [OR] = 2.66, 95%CI 1.14-6.21).

A recent study estimated the delay to a physician diagnosis of type 2 diabetes and identified predictors of this delay (Samuels et al, 2006). A study population of 298 adults aged 45-64 years at baseline with incident type 2 diabetes from the Atherosclerosis Risk in Communities (ARIC) study were assessed. The subjects did not have diabetes at baseline but developed incident type 2 diabetes by the third year of follow-up (visit 2). The subjects were followed-up at 3 yearly intervals thereafter. The diagnosis of type 2 diabetes was based on self-report, physician diagnosis, or fasting or non-fasting plasma glucose. The median delay from onset of type 2 diabetes to physician diagnosis was 2.4 years. Approximately 7% of incident cases remained undiagnosed for at least 7.5 years after onset. Compared to those with promptly diagnosed incident type 2 diabetes, individuals with delayed diagnosis were significantly more likely to be obese before onset ($p = 0.003$), and had a slower rise in fasting hyperglycaemia ($p = 0.04$).

- **Detection and management of screen-detected diabetes may improve outcomes *(Evidence Level II)***

It is well established that improving metabolic control in people with newly diagnosed type 2 diabetes improves outcomes. The United Kingdom Prospective Diabetes Study (UKPDS) included 5,102 people with newly diagnosed type 2 diabetes. Over a median follow-up period of 10 years, the intensively treated group showed a 12% lower risk of any diabetes related end point ($p = 0.029$), a 25% reduction in microvascular end points ($p = 0.0099$), and a 16% reduction in myocardial infarction which just failed to reach significance ($p = 0.052$) (UKPDS, 1998b).

People with newly diagnosed diabetes have an unfavourable cardiovascular risk profile. The ADDITION study identified 3,233 people aged 40-69 years with screen-detected diabetes (Sandbaek et al, 2008). In these subjects their estimated median 10 year coronary heart disease risk was 21% in men, 11% in women and 16% overall. At diagnosis, 73% had high BP (≥ 140/90 mmHg), of whom 58% were not on antihypertensive medication. Even in those subjects receiving hypertensive therapy, 67% did not meet the treatment goal of a BP of 140/90 mmHg. Seventy per cent had cholesterol levels above 5.0 mmol/L, of which 91% were not being treated with lipid-lowering drugs. Of those receiving lipid-lowering therapy, 41% were not meeting the treatment goal of a cholesterol level lower than 5.0 mmol/L. It is therefore evident that individuals with type 2 diabetes detected by screening have an elevated risk of coronary heart disease that is potentially modifiable by intensification of treatment.

At diagnosis, people with diabetes detected by screening have relatively low HbA1c levels but already have a cardiovascular risk profile similar to that of people with established diabetes (Spijkerman et al, 2002a). In particular, ~70% had hypertension and high total cholesterol (> 5.0 mmol/L), ~33% had high triglycerides (> 3.0 mmol/L) or low HDL cholesterol levels (< 1.0 mmol/L in men and < 1.1 mmol/L in women), and 40% were obese (BMI ≥ 30 kg/m^2). Slightly lower levels of hypertension (48%) and high triglycerides (24%) were found in newly diagnosed people with diabetes in an opportunistic screening study (Leiter et al, 2001). Identifying undiagnosed diabetes should prompt earlier, more aggressive or more appropriate treatment of these other CVD risk factors (Goyder and Irwig, 1998).

However it remains unclear whether detection of undiagnosed diabetes through screening programs improves outcomes. To date there have been no randomised trials which have addressed this question. On such study is currently underway. The ADDITION study has recruited and randomised 3,057 people with screen-detected diabetes to a standard care arm and an intensive treatment arm. Individuals are being followed for 5 years with the primary outcomes being occurrence of CVD and mortality. The study is due to report its findings in late 2009 (Lauritzen et al, 2000).

Case control studies have also addressed this issue. Schellhase et al. (2003) used a health maintenance administrative dataset to assess the impact of screening in people with diabetes and advanced diabetes complications. A 10 year retrospective examination of records suggested that diabetes detected through screening was associated with a 13% reduction in the risk of complications, compared with routine diagnosis (HR 0.87, [95%CI 0.38-1.98]); however this difference was not statistically significant.

Another case control study examined outcomes in 488 people with diabetes detected on the basis of glycosuria screening compared with people with conventionally diagnosed diabetes. Over 12 years, loss of life years compared with age and sex matched controls was 1.96 years

for screen-detected diabetes and 3.42 years in conventionally diagnosed diabetes ($p < 0.05$) (Schneider et al, 1996).

Epidemiological data have also been used to examine this issue. Colagiuri et al. (2002b) performed a post hoc analysis of the 5,102 UKPDS participants with newly diagnosed type 2 diabetes. This cohort was divided into 3 groups based on their FPG at presentation – low FPG group with FPG < 7.8 mmol/L, intermediate FPG group (FPG 7.8 to < 10 mmol/L) and high FPG group (FPG ≥ 10 mmol/L). It was estimated that the high FPG group had developed diabetes approximately 5 years earlier and the intermediate group 2-3 years earlier than the low FPG group. Over the following 10 years the high FPG group had significantly worse outcomes for all-cause mortality, diabetes-related deaths, myocardial infarction, and microvascular complications compared with the low FPG group. The intermediate FPG group had significantly increased diabetes-related deaths and myocardial infarction compared with the low FPG group. If the assumptions of differences in duration of diabetes are correct, these data support an earlier diagnosis of type 2 diabetes being associated with improved outcomes. Since most of these individuals with low FPG would be asymptomatic at diagnosis, active case detection programs would be necessary to identify them.

Attributable fractions estimates in a white male US cohort aged 45-74 years with clinically or screen-detected diabetes indicate that 20% of all-cause deaths and 36% of CVD deaths are attributable to delayed diagnosis of type 2 diabetes (Narayan et al, 1999). Furthermore, population attributable risk calculations indicate that early detection and standard therapy (assuming 100% implementation and compliance) could reduce all-cause mortality and CVD mortality by 3.5% and 7.1%, respectively. Early detection and intensive therapy could reduce all-cause mortality and CVD mortality by 5.9% and 8.6%, respectively.

Modelling has also been used to estimate the benefits of earlier diagnosis of diabetes. Using a Markov chain model Kuo et al. (1999) assessed the efficacy of screening for type 2 diabetes in Taiwan. The model estimated that the average time between asymptomatic and symptomatic phases of type 2 diabetes was 8 years and that the 10-year survival rate for people with diabetes detected during the asymptomatic phase was 79%, higher than that of symptomatic type 2 diabetes (69%).

In another study, a Markov model was used to estimate the microvascular benefits of screening for type 2 diabetes in a cohort of subjects with recent onset of diabetes (< 5 years) derived from NHANES III (Hofer et al, 2000). The benefit achieved by universal screening and improved treatment (limiting HbA1c to 9%) was a reduction of ~30,000 cases of blindness over the lifetime of the cohort. Screening alone produced 7% of the benefit, while improved treatment alone provided 65% of the benefit. Targeted screening to people with 2 or more risk factors for developing diabetes would reduce the number to be screened by 51%, whilst maintaining 75% of the benefits of universal screening.

According to a review by Harris et al. (2003), given favourable assumptions, the number needed to screen (NNS) to prevent one case of blindness using tight glycaemic control for 5 years is ~4,300. More realistic assumptions produce a NNS of 900 to prevent one CVD event using tight BP control for 5 years. This review has been updated in 2008 but since no new data on the effectiveness of these interventions were identified these figures did not change.

Testing for undiagnosed type 2 diabetes will identify people with IGT and IFG, conditions associated with increased risk of progression to diabetes and increased morbidity and premature mortality, predominantly due to cardiovascular complications (WHO, 2006).

Applying the NHMRC 2002 Case Detection and Diagnosis Guideline to the AusDiab population identifies a significant proportion of the population with either IGT or IFG (Colagiuri et al, 2004). It is now well established that progression to diabetes in these people can be prevented or delayed through lifestyle modification or with a number of pharmacological agents (Gerstein et al, 2006; Ramachandran et al, 2006; Knowler et al, 2005; Kosaka et al, 2005; Torgerson et al, 2004; Buchanan et al, 2002; Chiasson et al, 2002; Knowler et al, 2002; Tuomilehto et al, 2001; Pan et al, 1997). Therefore identification of people with IGT or IFG provides an opportunity to implement interventions to decrease the chance of developing diabetes.

- **Case detection and diagnosis of type 2 diabetes has a favourable risk:benefit ratio *(Evidence Level II)***

The case detection procedure

Section 2 of this guideline proposes opportunistic case detection to detect individuals at high risk of undiagnosed diabetes followed by measurement of plasma glucose as the initial test in people identified at high risk.

The risk assessment procedure relies on routinely collected demographic and clinical examination information. Plasma glucose measurement is a safe, easy and relatively low cost test, especially when combined with blood collection for other tests. There are well established and accepted diagnostic criteria for making a diagnosis of type 2 diabetes (WHO, 2006). The properties of the screening and diagnostic procedures are further considered in Section 2.

Potential Benefits:

The potential benefits of case detection for asymptomatic type 2 diabetes have been considered in the preceding paragraphs.

Potential Harms

- Medical

Case detection may involve additional testing depending on whether or not the test is performed along with other pathology testing. The diagnostic testing of people with a positive screening test also requires additional testing. Other medical consequences of a diagnosis of type 2 diabetes include a variety of treatments (dietary, counseling and possibly medication) and follow-up visits to health professionals. If medications are used there is the additional potential for side effects.

Case detection may also result in a false negative result and failure to appropriately treat a person who has diabetes but in whom the diagnosis is missed.

- Psycho-social

A diagnosis of type 2 diabetes has potential implications for employment and personal insurance. Treatment with certain medications, especially insulin, precludes certain forms of employment, related predominantly to the risk of hypoglycaemia and the potential for harm to self and others. Insurance premiums for people with diabetes are invariably substantially higher than in people without diabetes. However, there is little evidence that people found to have diabetes at screening experience any adverse effect of labeling (Edelman et al, 2002). In a population of 1,253 subjects aged 45-64 years there were no differences in quality of life at

baseline or 1 year after screening between people with screen-detected diabetes and those without diabetes.

Perhaps the greatest concern is the false positive result and the anxiety which this may cause in the interval between the initial screening test and the diagnostic test. A number of studies have examined this issue.

A recent review assessed the psychological impact of screening for type 2 diabetes and concluded that screening in the general population has no serious psychological side effects, and that a diagnosis of type 2 diabetes has no substantial effect on perceived health status and well-being (Adriaanse and Snoek, 2006).

A stepwise approach to screening for type 2 diabetes facilitates psychological adjustment (Eborall et al, 2007a) with perceptions changing as people progressed through the screening program. The initial screening test was viewed as unimportant and little consideration was given to outcomes. By the time individuals reached the final diagnostic test they considered that a "mild" form of type 2 diabetes was a strong possibility. Obtaining a positive result at the first two screening tests altered expectation of testing negative to an increased likelihood of testing positive for type 2 diabetes. Following diagnosis, people with screen-detected diabetes tended to downplay its importance and were confident in their ability to control it. Those with intermediate screening results were unsure about the meaning of their diagnosis, and those with negative screening results seemed unaware that they remained at high risk. People with either intermediate or negative results expressed no intention to change their lifestyle, reinforcing the need to emphasise their high risk status and the need for an appropriate strategy to control risk.

A randomised controlled study of 7,380 people aged 40-69 years in the top 25% for risk of having type 2 diabetes (Eborall et al, 2007b) showed no difference in psychological parameters (state anxiety, anxiety, depression, diabetes specific worry, and self-rated health) at 3-6 months and 12-15 months post-screening in those invited for screening and a control group which was not screened. Participants who screened positive reported significantly poorer general health, higher state anxiety, higher depression, and higher worry about diabetes than those who screened negative, although effect sizes were small. At 3-6 months after the screening process, self reported health declined across groups according to the number of tests before screening negative, with the poorest general health found in those who tested positive at the final test. This effect was not evident at 12-15 months. The more screening tests that a participant had before screening negative, the more diabetes specific worry they reported at 3-6 months and 12-15 months after the screening process. However, levels of worry were low and effect sizes small. The authors concluded that screening for type 2 diabetes has limited impact on an individual's psychological health, and that being required to return for further testing after an initial positive result has a small negative psychological impact which was not likely to be clinically significant.

In another randomised controlled study examining psychological responses to different follow-up schedules, participants who underwent a screening test for type 2 diabetes were randomly allocated to either limited follow-up, with a single questionnaire at 1 year, or to intensive follow-up, with questionnaires completed at 1, 6 and 12 months after screening (Farmer and Doll, 2005). No significant differences between the 2 groups were found in the proportion of 1 year questionnaires returned ($p = 0.08$), as well as levels of anxiety according to scores on the short form of the Spielberger State Anxiety Inventory taken at 1 year ($p = 0.13$). The limited follow-up group showed a significantly greater improvement in well-being

after 1 year according to scores on the 12-item Well-Being Questionnaire (WBQ-12). This effect however, was small and of little clinical significance. The authors concluded that there are no important adverse effects of repeated questionnaire use on response rates or psychological outcomes following screening for type 2 diabetes.

One study has assessed the impact of screening for type 2 diabetes in a cohort of 431 subjects aged 35-74 years who had a sibling with diabetes (Farmer et al, 2003). Anxiety and well-being were measured at screening and at 1 year using the Spielberger State Anxiety Inventory Short Form (SSAI-SF), the Health Anxiety Inventory (HAI) and the WBQ-12. According to the SSAI-SF results, state anxiety reduced significantly from 34.5 (95%CI 33.4-35.6) at screening to 32.3 (31.2-33.4) at 1 year ($p < 0.0001$). Mean WBQ-12 scores showed a significant improvement in well-being from 26.8 (26.0-27.4) to 27.4 (26.7-28.1) ($p = 0.008$). There was no difference in SSAI-SF or WBQ-12 scores between subjects with either a normal or an 'at risk' screening test result. A score in the upper tertile of the HAI at screening was associated with a significant increase in the level of anxiety at 1 year (adjusted OR 2.0, [95%CI 1.2-3.4], $p = 0.006$).

People with screen-detected diabetes do not experience much difficulty with their condition following diagnosis (Adriaanse and Snoek, 2006; Thoolen et al, 2006), reporting low emotional distress, low threat perceptions and high self-efficacy (Thoolen et al, 2006). However, early and intensive treatment can alter peoples' psychological outcomes, resulting in relatively greater anxiety and less self-efficacy in the first year after diagnosis (Thoolen et al, 2006). Furthermore, in those with screen-detected diabetes, perceived vulnerability is higher with longer disease duration and is positively linked with distress and number of medical complaints (Thoolen et al, 2006).

Anxiety and beliefs related to screening for type 2 diabetes were assessed in a cohort of 1,339 UK subjects aged 25-75 years at high risk of developing diabetes from the Screening those at Risk (STAR) study (Skinner et al, 2005). Forty-five per cent of subjects reported little to moderate amounts of anxiety at screening (mean 35.2 ± 11.6), as determined using the Spielberger State Anxiety Scale Short Form. Family history of diabetes, ethnic group and recruitment method had no significant effect on anxiety at screening. Emotional stability (measured using the Emotional Stability Scale of the Big Five Inventory 44) was the only trait significantly associated (negatively) with anxiety at screening ($r = -0.45$, $n = 930$, $p < 0.001$). Only 12% of subjects were of the belief that type 2 diabetes was serious, shortens life and causes complications (measured using three scales from the Diabetes Illness Representations Questionnaire), with bivariate analysis indicating that these subjects had significantly higher anxiety scores than the other subjects ($t = 1.70$, d.f. = 947, $p < 0.05$). The results of this study indicate that screening for type 2 diabetes does not cause significant anxiety.

Cost and cost-effectiveness are considered in Section 4.

Summary - Why Detect Type 2 Diabetes

The following table summaries the considerations in relation to active case detection and diagnosis of type 2 diabetes in asymptomatic non-pregnant adults.

Table 2: Does type 2 diabetes meet the criteria for case detection and diagnosis?

Criteria	Met by Diabetes
The condition: • Is a substantial health problem in the community to be screened • Has a preclinical phase during which it can be diagnosed • Has a substantial undiagnosed rate • Has an improved prognosis if treated early	 Yes Yes Yes Yes
Detection and management of preclinical disease results in improved outcomes	Insufficient data
The screening and diagnostic tests are: • Safe • Acceptable to the client population • Easy to use • Relatively low cost	 Yes Yes Yes Yes
The screening test accurately identifies a high proportion of people with early disease	Yes
The case detection and diagnosis procedures are cost effective	Probable
Potential harms • Medical • Psycho-social	 No No

Evidence Tables: Section 1

Why Detect Type 2 Diabetes

Type 2 diabetes is common, serious and costly

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Chadban et al., 2003 (Australia)	IV	Cross-sectional	High	High[+]	High
Cunningham et al., 2008 (Australia)	IV	Cross-sectional	High	High[+]	High
Daniel et al., 2002 (Australian Aboriginal)	IV	Cross-sectional	High	High[+]	High
Dunstan et al., 2002 (Australia)	IV	Cross-sectional	High	High[+]	High
McKay et al., 2000 (Australia)	IV	Cross-sectional	High	High[+]	High
Tapp et al., 2003b (Australia)	IV	Cross-sectional	High	High[+]	High
Tapp et al., 2004 (Australia)	IV	Cross-sectional	High	High[+]	High

[+] Type 2 diabetes is a common, serious and costly health problem

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Undiagnosed type 2 diabetes is common and not benign

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Aguilar et al., 2004 (International)	II	Prospective cohort	High	High^{+}	High
Barnett et al., 2006 (UK)	II	Systematic review	Medium	Low^{+}	High
Barr et al., 2007 (Australia)	II	Prospective cohort	High	Low^{+}	High
Barzilay et al., 1999 (US)	II	Prospective cohort	High	High^{+}	High
Colagiuri et al., 2002a (Tonga)	IV	Cross-sectional	High	High^{+}	Medium
Croxson et al., 1994 (UK)	II	Prospective cohort	High	High^{+}	High
Cunningham et al., 2008 (Australia)	IV	Cross-sectional	High	High^{+}	High
DECODE, 1999a (Europe)	II	Prospective cohort	Medium	High^{+}	High
Dunstan et al., 2002 (Australia)	IV	Cross-sectional	High	High^{+}	High
Eschwege et al., 1985 (France)	II	Prospective cohort	High	High^{+}	High
Glatthaar et al., 1985 (Australia)	IV	Cross-sectional	High	High^{+}	High
Gu et al., 2003 (China)	IV	Cross-sectional	High	High^{+}	Medium
Guest et al., 1992 (Australia: Europids, Aboriginal)	IV	Cross-sectional	High	High^{+}	High
Harris et al., 1992 (US, Australia)	IV	Cross-sectional	High	High^{+}	High
Hodge et al., 2004 (Australia, Greek and Italian migrants)	II	Prospective cohort	High	Low^{+}	High
Jarrett, 1986 (UK)	II	Prospective cohort	High	High^{+}	High
Jarrett and Shipley, 1988 (UK)	II	Prospective cohort	High	High^{+}	High
Maple-Brown et al., 2008 (Australia)	IV	Cross-sectional	High	High^{+}	High
Mitchell et al., 1998 (Australia)	IV	Cross-sectional	High	Medium^{+}	High
Nakagami et al., 2006 (Japanese; Asian Indian)	I	Systematic review	High	High^{+}	High
NHMRC, 1997	I	Systematic review	High	High^{+}	High
Samuels et al., 2006 (US)	II	Prospective cohort	High	High^{+}	High

Undiagnosed type 2 diabetes is common and not benign (cont.)

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Simmons et al., 2005a (Australia)	IV	Cross-sectional	Medium	Medium[+]	High
Spijkerman et al., 2003 (The Netherlands)	IV	Cross-sectional	High	High[+]	High
Spijkerman et al., 2004a (The Netherlands)	IV	Cross-sectional	High	High[+]	High
Tapp et al., 2003a (Australia)	IV	Cross-sectional	High	Medium[+]	High
Tapp et al., 2004 (Australia)	IV	Cross-sectional	High	High[+]	High

[+] Undiagnosed type 2 diabetes is common and is not a benign condition

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Detection and management of screen-detected diabetes may improve outcomes

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Colagiuri et al., 2002b (UK)	II	Prospective cohort	Medium	High[+]	High
Harris et al., 2003 (International)	I	Systematic review	High	Low[+]	High
Hofer et al., 2000 (US)	N/A	Modelling	Medium	High[+]	High
Kuo et al., 1999 (Taiwan)	N/A	Modelling	Medium	High[+]	High
Leiter et al., 2001 (Canada)	IV	Cross-sectional	Medium	High[+]	High
Sandbaek et al., 2008 (The Netherlands, UK, Denmark)	IV	Cross-sectional	High	High+	High
Schellhase et al., 2003 (US)	III-3	Case-control	High	Low[+]	High
Schneider et al., 1996 (Germany)	III-3	Case-control	Medium	Medium[+]	High
Spijkerman et al., 2002a (The Netherlands)	IV	Cross-sectional	High	High[+]	High
UKPDS, 1998b (UK)	II	RCT	High	High[+]	High

[+] Detection and management of screen-detected diabetes may improve outcomes
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect
* Cross-sectional study within an RCT

Detection and diagnosis of type 2 diabetes has a favourable risk: benefit ratio

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Eborall et al., 2007a (UK)	II	Prospective cohort	Medium	N/A	Medium
Eborall et al. 2007b (UK)	II	RCT	High	High[+]	High
Edelman et al., 2002 (US)	II	Prospective cohort	Medium	High[+]	High
Farmer and Doll, 2005 (UK)	II	RCT	Medium	High[+]	Low
Farmer et al., 2003 (UK)	II	Prospective cohort	High	High[+]	Medium
Skinner et al., 2005 (UK)	IV	Cross-sectional	High	N/A	Medium
Thoolen et al., 2006 (The Netherlands)	IV	Cross-sectional	Medium	Medium[+]	Medium

[+] Case detection and diagnosis of type 2 diabetes has a favourable risk:benefit ratio

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 2: How to Detect Type 2 Diabetes

Question

How should case detection and diagnostic testing for type 2 diabetes be performed?

Recommendation

A three-step case detection and diagnosis procedure is recommended for detecting people with undiagnosed type 2 diabetes (Grade B):

1. Initial risk assessment determined using a risk assessment tool or risk factors commonly associated with undiagnosed type 2 diabetes
2. Measurement of fasting plasma glucose
3. An oral glucose tolerance test performed in all people with an equivocal result – FPG of 5.5-6.9 mmol/L, or random plasma glucose of 5.5-11.0 mmol/L.

Practice Points

- The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) should be used to assess risk of undiagnosed diabetes
- Risk assessment should begin at age 40 and from age 18 in Aboriginal and Torres Strait Islanders*
- An AUSDRISK score ≥ 12 is recommended when the primary purpose of risk assessment is to detect undiagnosed type 2 diabetes.
- The following should proceed to Step 2 of the case detection and diagnosis procedure and do not need assessment with the AUSDRISK:
  - 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)
  - people on antipsychotic medication
- Laboratory testing is preferred but point of care testing using capillary blood can be used for the screening step
- Random plasma glucose may be used if collection of a fasting sample is considered impractical
- Proceeding directly from risk assessment to an oral glucose tolerance test may be considered if the intermediate step is considered impractical
- The 2006 WHO/IDF criteria should be used to diagnose diabetes
- The diagnosis of type 2 diabetes requires two positive laboratory blood tests on separate days unless the plasma glucose is unequivocally elevated in the presence of acute metabolic decompensation or obvious symptoms

* It should be noted that the AUSDRISK may overestimate risk in those less than 25 years of age and underestimate risk in Aboriginal and Torres Strait Islanders

Evidence Statements

- Opportunistic screening is the preferred method for case detection
  Evidence Level IV
- The majority of people with undiagnosed type 2 diabetes have readily identifiable risk factors
  Evidence Level I
- Single or multiple risk factors can be used to screen for type 2 diabetes
  Evidence Level III-2
- Risk scores are commonly used to screen for type 2 diabetes
  Evidence Level III-2
- The comparability of glucose measurement in blood is affected by a number of factors
  Evidence Level IV
- Laboratory or point of care (POC) testing can be used to measure glucose in blood
  Evidence Level III-2
- Fasting glucose measurement using a cut-point of 5.5 mmol/L performs well as a screening test for undiagnosed type 2 diabetes
  Evidence Level III-2
- Non-fasting glucose measurement can also be used to screen for undiagnosed type 2 diabetes
  Evidence Level III-2
- Measurement of glycated haemoglobin (HbA1c) is another option for screening for undiagnosed type 2 diabetes but the appropriate cut-point is uncertain
  Evidence Level III-2
- The 2006 WHO/IDF diagnostic criteria should be used to diagnose type 2 diabetes
  Evidence Level II
- A two-step screening procedure with risk assessment followed by glucose measurement in blood performs well in detecting undiagnosed type 2 diabetes
  Evidence Level III-2
- Blood testing without risk factor assessment also performs well but requires blood testing in all
  Evidence Level III-2
- General practice is the usual setting for case detection for undiagnosed type 2 diabetes
  Evidence Level IV
- A number of aids facilitate screening for undiagnosed type 2 diabetes
  Evidence Level II

Background – How to Detect Type 2 Diabetes

The diagnostic criteria for diabetes and intermittent hyperglycaemia have recently been reviewed by the WHO (2006) and are summarised in Table 3. It is imperative that when hyperglycaemia is detected in an asymptomatic individual, the diagnosis of diabetes should be confirmed on a subsequent day unless there is unequivocal hyperglycaemia.

Plasma glucose concentrations are distributed over a continuum but there is an approximate threshold separating those who are at a substantially increased risk for diabetic microvascular complications, especially retinopathy, from those who are not. However, there is no definite lower limit of normality (WHO, 2006). In view of the lack of sufficient data to accurately define normal glucose levels, the WHO (2006) recommended that the term 'normoglycaemia' be used for glucose levels associated with low risk of developing diabetes complications or CVD, that is levels below those used to define intermediate hyperglycaemia which for FPG equates with a level of ≤ 6.0 mmol/L.

Table 3: Diagnostic criteria for type 2 diabetes and intermediate hyperglycaemia

Type 2 Diabetes	
Fasting plasma glucose	≥ 7.0 mmol/L **or**
2-h plasma glucose*	≥ 11.1 mmol/L
Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	< 7.0 mmol/L **and**
2-h plasma glucose*	≥ 7.8 and < 11.1 mmol/L
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9 mmol/L **and if measured**
2-h plasma glucose*	< 7.8 mmol/L

Adapted from World Health Organization, 2006

* Venous plasma glucose 2-h after ingestion of 75g oral glucose load

* If 2-h plasma glucose is not measured, status is uncertain as type 2 diabetes or IGT cannot be excluded

Screening is the process of identifying those who are at sufficiently high risk of a disorder to warrant further investigation or action (WHO, 2001). While it is desirable to have a test that is both highly sensitive and highly specific, this is not usually possible. Therefore when choosing a cut-point a trade-off needs to be made between sensitivity and specificity, since increasing one reduces the other (WHO, 2003). This 2003 WHO report concluded that the most appropriate protocol for screening for undiagnosed type 2 diabetes in a particular setting should consider (1) the sensitivity and specificity of the screening methods available (2) the number of people who will need to be screened (3) the number of people who will need subsequent diagnostic testing (4) resource implications and (5) costs.

Screening is therefore always a balance between the complexity of the screening procedure, the performance of the screening procedure, how many people require testing, and the potential harm of missing an individual with undiagnosed diabetes. Balancing these various components is not easy and is often determined by available resources and health system priorities. These aspects should be considered when interpreting the findings of studies reviewed in this section.

The characteristics of tests for population screening for case finding and diagnosis of undiagnosed type 2 diabetes have been considered by many authors. The overall purpose of the screening test is to identify as many individuals as possible who require further testing

because they may have diabetes, and to identify people in whom the diagnosis is unlikely and therefore should not be subjected to unnecessary further testing. Wiener and Roberts (1998) propose that for this purpose, the test should pick up as many true positives as possible at the risk of including some false positives that could be eliminated by latter testing – i.e. the test should have a high sensitivity but specificity is not quite as important.

Vinicor (1999) argues that establishing a diagnosis is perhaps the most important component of medical care and that the balance between sensitivity and specificity should be determined by the perceived benefits and risks of the available treatment. Because the effectiveness of treatment of diabetes was questioned in the 70's and 80's, specificity of plasma glucose cut-points was emphasised. However, with emergence of the beneficial effects of blood glucose control in the 1990's, criteria which are more sensitive, but less specific, have been adopted.

Ultimately the choice of test will depend not only on the characteristics of the test but also on the circumstances under which it is being performed, confidence in the compliance of the individual being tested, and on availability and affordability of the different methods.

Evidence – How to Detect Type 2 Diabetes

This section considers the evidence around the approach to case detection, the case detection procedure, the screening protocol and the setting for case detection and diagnosis.

1. The approach to case detection

Different approaches can be used for case detection for people with undiagnosed diabetes. These include mass screening of the population or targeted screening of a selected sub-population based on prior knowledge of which groups are at greatest risk. The latter can be done in various settings which includes opportunistic screening of individuals in relation to other contact with the healthcare system. Often more than one approach is used for selective screening programs (Strong et al, 2005). In general, mass screening programs are not recommended whereas screening for type 2 diabetes using targeted opportunistic screening in high-risk populations has been (Borch-Johnsen et al, 2003; Wareham and Griffin, 2001).

- **Opportunistic screening is the preferred method for case detection *(Evidence Level IV)***

There is general agreement that universal screening is not justified. The largest study of this kind tested over 600,000 people in Cleveland, USA, and concluded that indiscriminate mass screening programs for diabetes were of questionable value and the focus should be directed to targeted population testing (Genuth et al, 1978; Houser et al, 1977).

Blood glucose meters have also been used for diabetes screening in the general community. Newman et al. (1994) recently examined community screening in public places using various meters and various operators. The yield of undiagnosed diabetes was considerably lower than expected from prevalence studies. The overall conclusion was that it is difficult to justify glucose-based community screening in low risk populations and the data supported the ADA white paper of abandoning glucose-based community screening.

The Netherlands component of the ADDITION study evaluated the yield of population-based screening for type 2 diabetes, using 3 or 4 step stepwise screening procedures in a cohort of 56,978 subjects aged 50-70 years (Janssen et al, 2007). The initial step involved sending individuals a risk questionnaire which they were expected to complete and then attend their primary care physician if they were at high risk. This was followed by a somewhat complex protocol of a series of blood testing depending on the result at each step. The overall yield of population-based screening was quite low, with only 1% of the population being diagnosed with new type 2 diabetes, considerably lower than expected from prevalence data for undiagnosed diabetes. There was a high drop-out rate (23%) among high-risk individuals required to undergo an OGTT. The authors suggested that opportunistic screening may be more appropriate than population-based screening.

A community based-screening procedure for diabetes using an ADA questionnaire and ADA capillary glucose criteria was conducted in a population 3,301 individuals aged 20 years and over in Michigan (Tabaei et al, 2003). Of this population, 57% were classified as at-risk based on the questionnaire, and 5% screened positive based on the capillary plasma glucose criteria. However, the screening program's overall yield of individuals with undiagnosed diabetes was <1%. Applying a multivariate logistic regression equation to this population (Tabaei and Herman, 2002), the estimated prevalence of undiagnosed diabetes was 11%, compared with the < 1% yield. The authors concluded that community-based screening was

extremely inefficient, resulted in many false positive tests, and the capillary glucose criteria likely missed a considerable proportion of individuals with undiagnosed diabetes.

In their review on screening for type 2 diabetes, Engelgau and colleagues (2000) concluded that population-based and selective screening programs in a community setting consistently suffer from low yield and poor follow-up, and thus cannot be recommended. Periodic screening of those at high-risk may be feasible as part of ongoing medical care, although more evidence is needed. It was also reported that targeted opportunistic screening of high-risk groups appears to be a cost-effective strategy.

- **The majority of people with undiagnosed type 2 diabetes have readily identifiable risk factors *(Evidence Level I)***

Most people with undiagnosed type 2 diabetes have easily identifiable risk factors which is the basis for targeted testing of high risk groups to identify undiagnosed type 2 diabetes.

The following are well established risk factors for undiagnosed type 2 diabetes:

a. Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

These conditions of intermediate hyperglycaemia are common in Australia, with AusDiab data indicating the presence of IGT and IFG in 10.6 and 5.8% of the population, respectively (Dunstan et al, 2002). Those with IGT and IFG have a significant risk of progressing to the development of diabetes, with annual incidence rates of type 2 diabetes of 3.5 and 2.6%, respectively. Therefore people with these conditions should be regularly screened for undiagnosed diabetes (WHO, 2006).

b. Gestational diabetes (GDM)

Many studies have reported that women with a previous history of gestational diabetes are at increased risk of developing type 2 diabetes.

A systematic review of 28 studies examined the incidence of type 2 diabetes following GDM (Kim et al, 2002). The cumulative incidence of type 2 diabetes ranged from 2.6-70% with a follow-up period ranging from 6 weeks to 28 years postpartum. The cumulative incidence increased substantially during the first 5 years after delivery, with a plateau appearing after 10 years.

Data from Australian women who participated in the AusDiab study or the Crossroads Undiagnosed Disease Study (CUDS) was used to study the relationship between current glucose tolerance status and self-reported history of GDM (Simmons et al, 2007). Of the 5,839 women aged 25 years and over included in this study, 4.1% reported previous GDM. Current type 2 diabetes (known or newly diagnosed) was significantly more prevalent in those with previous GDM (13%) than those without previous GDM (7%) ($p < 0.05$).

c. Age

The prevalence of type 2 diabetes increases with age and this applies to both diagnosed and undiagnosed diabetes. According to AusDiab data, in the age groups 25-34, 35-44, 45-54, 55-64, 65-74, and 75+ years the prevalence of known and undiagnosed diabetes was 0.2 and 0.1%, 1.0 and 1.4%, 3.3 and 2.9%, 6.5 and 6.6%, 9.4 and 8.5%, and 10.9 and 12.1%, respectively (Dunstan et al, 2002). The prevalence of known and undiagnosed diabetes was 3.7 and 3.7%, respectively, in those aged 25 years and above, and 4.8 and 4.6%, respectively, in those aged 40-74 years.

The DECODA study group has reported the age- and sex-specific prevalence of diabetes in 11 Asian cohorts (Qiao et al, 2003). The overall prevalence of diabetes (known and undiagnosed) increased with age, peaking at 70-89 years in Chinese and Japanese subjects, and at 60-69 years followed by a decline beyond 70 years in Indian subjects. The proportion of undiagnosed diabetes varied according to age, being highest in the youngest age group and lowest in the elderly. The proportion of undiagnosed diabetes in Chinese and Japanese men (women) combined were 0.77 (0.89), 0.59 (0.61), 0.58 (0.65), 0.55 (0.50), 0.40 (0.50), and 0.40 (0.35) and in all Indian men (women) combined were 0.65 (0.71), 0.47 (0.49), 0.44 (0.43), 0.40 (0.40), 0.39 (0.44), and 0.60 (0.60), respectively, at 30-39, 40-49, 50-59, 60-69, 70-79, and 80-89 years of age.

To assess whether any change in age at diagnosis of type 2 diabetes has occurred over time, a comparison was made between data from adults aged 20 years and over from the NHANES IV (1999-2000) and NHANES III (1988-1994) (Koopman et al, 2005). The mean age at diagnosis decreased significantly from 52 in 1988-1994 to 46 years in 1999-2000 ($p < 0.05$). The authors hypothesised several reasons for the earlier detection of type 2 diabetes: a change to diagnostic criteria; improved physician recognition of diabetes; or increased public awareness. Alternatively, a younger age at diagnosis may represent a true population trend towards earlier onset of type 2 diabetes, warranting earlier screening and case detection.

d. Specific populations

- *Aboriginal and Torres Strait Islanders*

Overall prevalence rates of type 2 diabetes of 10-30% are commonly reported. Where direct comparisons have been made with non-indigenous Australians (Guest et al, 1992), age standardised rates are 4 times higher in Aboriginal and Torres Strait Islanders. In the DRUID study of 777 indigenous Australians aged 15-64 years, the prevalence of diabetes was 17% (Cunningham et al, 2008). In another study of 332 indigenous Australians aged 15 years and over the prevalence of type 2 diabetes was 12% (Brimblecombe et al, 2006).

A recent study compared the prevalence of diabetes in 10,434 individuals aged 25-74 years from the AusDiab study and 814 Aboriginal people from 3 remote communities (Hoy et al, 2007). The prevalence of diabetes (known or newly diagnosed) across the 3 Aboriginal communities ranged from 17-30%. In comparison to AusDiab data, the age- and sex-adjusted ORs for diabetes in the Aboriginal population ranged from 5.4 to 10.0 ($p < 0.001$).

A feature of type 2 diabetes in Aboriginal and Torres Strait Islanders is its earlier age of diagnosis. Braun et al. (1996) reported rates of undiagnosed diabetes of 2.7% in young Aborigines (mean age 18.3 years) from the Kimberley Region of Western Australia.

- *People from a non-english speaking background*

Australia is a nation of immigrants and is reputed to be one of the most multi-cultural nations in the world. The overseas born population accounted for one quarter (25%) of Australia's total population in 2006-2007 (ABS, 2008).

Many populations represented in Australia have higher prevalence of diabetes and the diabetes also develops at a younger age. These include people of Chinese, Indian and Pacific Islander background. In 2004-05 the age-adjusted prevalence of diabetes was higher among persons born in Southern and Central Asia (8.7%), North Africa and the Middle East (6.6%), South East Asia (5.7%) and Southern and Eastern Europe (4.9%) compared with those born in Australia (3.3%) (ABS, 2006a).

Weight at which diabetes risk increases is dependent on ethnicity. For example in a population of 2,276 randomly selected Chinese adults aged 20-94 years in which the age- and sex-adjusted prevalence of type 2 diabetes was 9.8% (Jia et al, 2002), the prevalence of type 2 diabetes increased progressively with a BMI > 23 kg/m^2.

The Diabetes Heart and Health Survey (DHAH) examined 4,049 people aged 35-74 years to determine the prevalence of new and known diabetes by ethnic group in Auckland (Sundborn et al, 2007). The ethnic groups were divided into individuals of Maori, Pacific and European ethnicity. Of the total population sampled, 2.6% were found to have newly diagnosed diabetes and 6.7% were previously diagnosed with type 2 diabetes. The proportions of new/known diabetes according to ethnicity were 1.8/3.9% for Europeans, 3.8/12.0% for Maori, and 4.0/19.5% for Pacific people. Individuals from the Pacific ethnicity group had a significantly greater relative risk of newly diagnosed diabetes than Europeans, especially in the under 45 (RR 11.6, [95%CI 1.4-82.3], $p < 0.05$) and 45-54 year (RR 4.2, [1.9-8.7], $p < 0.001$) age groups.

e. Obesity

Obesity in adult life is a well established risk factor for prevalent undiagnosed diabetes and for the future development of type 2 diabetes, with a BMI of approximately 30 kg/m^2 or more increasing the absolute risk of type 2 diabetes by 1.8 to 2.4-fold (Baan et al, 1999a; Ruige et al, 1997; Harris et al, 1987) or by 2.4 to 19-fold relative to a normal BMI (Resnick et al, 1998; Carey et al, 1997; Ford et al, 1997; Colditz et al, 1995; Chan et al, 1994; Colditz et al, 1990; Holbrook et al, 1990) in both men and women.

The AusDiab study examined the association of BMI, waist circumference, and waist to hip ratio (WHR) with type 2 diabetes and other CVD risk factors (Dalton et al, 2003). The prevalence of obesity as defined by BMI, waist circumference and WHR was 21, 31 and 16%, respectively. When adjusted for age there was little difference between the 3 measures of obesity, with the exception of WHR being marginally superior in predicting undiagnosed type 2 diabetes in men.

The relationship between body size measurements and type 2 diabetes was investigated in a cross-sectional study of 915 Australian Aboriginal adults aged 18-74 years from a remote Aboriginal community in the Northern Territory (Wang and Hoy, 2004). A total of 16% were found to have known or newly diagnosed diabetes. The risk of type 2 diabetes increased with increasing body size. The age- and sex-adjusted ORs (95%CI) for type 2 diabetes were 2.16 (1.75-2.66), 1.80 (1.49-2.17), 1.41 (1.17-1.71), 1.81 (1.51-2.19) and 1.84 (1.50-2.24) associated with a 1 SD increase in waist circumference, BMI, weight, WHR, and hip circumference, respectively.

The prevalence of type 2 diabetes and its associated risk factors was examined in a cross-sectional study of 332 Indigenous Australians aged 15 years and over (Brimblecombe et al, 2006). The prevalence of type 2 diabetes in this population was 12%. Type 2 diabetes was strongly associated with BMI and age, with an age-adjusted OR of 24.1 (95%CI 6.0-96.5, $p < 0.001$) in those with BMI ≥ 25 kg/m^2 compared with those with a BMI < 22 kg/m^2.

f. Family history

Family history of type 2 diabetes is a recognised risk factor for type 2 diabetes in another family member. The lifetime risk of developing type 2 diabetes is estimated at 40% if one parent has type 2 diabetes (Kobberling and Tillil, 1982). Most studies have reported that the

effect is not gender specific, although there have been some exceptions with Mooy et al. (1995) reporting a positive effect only in males and Sugimori et al. (1998) only in females.

The association between abnormal glucose regulation and family history of diabetes was examined in a cross-sectional study of 7,949 Swedish adults aged 35-56 years, half of whom had a family history of diabetes (Hilding et al, 2006). A family history of diabetes had a higher OR for type 2 diabetes in men (OR 3.1, [95%CI 1.7-5.6]) than in women (OR 1.7, [1.0-3.0]).

Using 1999-2002 NHANES survey data from 3,823 participants aged 20 years and over, a high familial risk of type 2 diabetes was found to be significantly associated with undiagnosed type 2 diabetes (adjusted OR 4.6, [95%CI 1.9-11.3]) (Hariri et al, 2006a).

The effect of family history may be modified by age. Costa et al. (1998) studied 205 non-diabetic siblings of people with type 2 diabetes. In comparison with the general population, at any age group, type 2 diabetes was more common in people with a family history of type 2 diabetes.

g. Hypertension

A number of studies have shown that hypertension is associated with a 1.6 to 2.6-fold increase in the chance of an individual having undiagnosed type 2 diabetes (Baan et al, 1999a; Ruige et al, 1997; Welborn et al, 1997; Chou et al, 1994; Saad et al, 1990). Bog-Hansen et al. (1998) performed a community based study in which they investigated people with hypertension for undiagnosed type 2 diabetes and found a high rate of previously undiagnosed type 2 diabetes of 26%: 17% in people under age 70 and 31% in people aged 70 or over.

Diabetes in people with hypertension may be related to treatment. A recent review has reported results of a traditional Mantel-Haenszel meta-analysis of RCTs for each major class of antihypertensive agents versus all comparators in terms of the effect on new-onset diabetes, irrespective of dose, length of follow-up and diagnostic criteria used to diagnose diabetes (Elliott, 2005). The meta-analysis indicated that both diuretics (OR 1.25, [95%CI 1.11-1.38], $p < 0.0001$) and β-blockers (OR 1.19, [1.10-1.27], $p < 0.0001$) are significantly associated with incident diabetes in hypertensive individuals. In contrast both ACE inhibitors (OR 0.79, [0.73-0.87], $p < 0.0001$) and ARBs (OR 0.77, [0.71-0.84], $p < 0.0001$) were found to have a protective effect on incident diabetes. Calcium channel blockers had no significant effect on incident diabetes (OR 0.99, [0.93-1.06], $p = 0.80$).

Despite the epidemiological evidence, the only RCT to specifically address this issue, the Diabetes Reduction Assessment with ramipril and rosiglitazone medication (DREAM) trial in subjects with IFG or IGT, found no significant difference in the development of type 2 diabetes over 3 years follow-up between the ramipril group (18%) and the placebo group (20%) (HR for the ramipril group 0.91, [95%CI 0.81-1.03], $p = 0.15$) (Bosch et al, 2006).

h. Cardiovascular and cerebrovascular disease

Diabetes, diagnosed and undiagnosed, is common in people with cardiovascular and cerebrovascular disease.

The prevalence of undiagnosed diabetes among a population of 244 individuals (age 70.5 ± 6.9 years) with prior myocardial infarction in Germany was 12% according to 1985 WHO

criteria, and 11% according to 1997 ADA criteria (Rathmann et al, 2002). In a cohort of 3,266 people scheduled for coronary angiography the prevalence of diabetes was 32% (17% known diabetes and 15% undiagnosed diabetes) (Taubert et al, 2003).

Hashimoto et al. (2005) evaluated the association between acute coronary syndrome and glucose intolerance. At least 2 weeks after admission an OGTT was performed in a cohort of 134 Japanese patients with acute coronary syndrome (89 with acute myocardial infarction and 45 with unstable angina; mean age 60 ± 10 years) who were not previously diagnosed with diabetes and who did not have a fasting glucose concentration of ≥ 7.0mmol/L or an HbA1c level > 6.0%. The prevalence of type 2 diabetes in this population was 10%. The authors conclude that an OGTT is essential to identify previously undiagnosed diabetes among people with acute coronary syndrome.

In a cohort of 122 people with acute myocardial infarction from the Glucose tolerance in Acute Myocardial Infarction (GAMI) study the prevalence of type 2 diabetes at discharge was 34% (Wallander et al, 2008). Of these, 93% were still classified with type 2 diabetes (64%) or IGT (29%) after 12 months. The OGTT result at discharge was shown to reliably inform long-term glucometabolic state, with agreements between OGTTs at discharge and 3 and 12 months. The authors recommend an OGTT for all patients with acute myocardial infarction at discharge.

In 2006 the DANSUK study reported on the prevalence of impaired glucose metabolism in patients referred to comprehensive cardiac rehabilitation (Boas Soja et al, 2006). In a cohort of 201 subjects (mean age 62.5 ± 11.0 years) who were participating in a cardiac rehabilitation trial, 13% had undiagnosed type 2 diabetes based on an OGTT. Using an FPG test alone, 19% of these subjects would be misclassified. The authors concluded that an OGTT should therefore be routinely performed as part of the management of people undergoing cardiac rehabilitation.

A high prevalence of undiagnosed type 2 diabetes has been reported in patients with an acute myocardial infarction (Norhammar et al, 2002). Using a prospective study design, 181 subjects (mean age 63.5 ± 9.4 years) with acute myocardial infarction with no diagnosis of diabetes were recruited, of whom 164 were given an OGTT at discharge and 144 after 3 months. In total, 31% of subjects at discharge and 25% at 3 months were found to have undiagnosed type 2 diabetes, suggesting that glucose abnormalities can be detected early in the post-infarction period. However, using only FBG criteria to detect undiagnosed diabetes these proportions dropped to 10% and 13%, respectively. To verify that this finding was specific to the patients with acute myocardial infarction and not attributable to the population from which they were recruited, a separate study compared the results from these patients to a population-based control cohort. In this cohort of 185 sex- and age-matched subjects (mean age 64.4 ± 9.2 years) without previously known diabetes or CVD recruited from the general population, the prevalence of undiagnosed type 2 diabetes was much lower at 11% (Bartnik et al, 2004a). In addition, abnormal glucose metabolism (IGT and type 2 diabetes) was almost twice as common in subjects with acute myocardial infarction as in controls (35%), both at discharge (67%, OR 3.79, [95%CI 2.44-5.90], $p < 0.001$) and at 3 months (66%, OR 3.51, [2.21-5.54], $p < 0.001$).

In a study of 120 patients with suspected coronary artery disease (CAD) (mean age 58 years), according to the WHO criteria the prevalence of diabetes was found to be 11.7% (Soma and Rheeder, 2006). It was reported that most of these subjects with diabetes would not have been detected (9 out of 14) had an OGTT not been used (ADA criteria).

The prevalence of diabetes was assessed in a cohort of 4,961 people (median age 66 years) from 25 countries throughout Europe with CAD (Bartnik et al, 2004b). Type 2 diabetes had been previously diagnosed in 29% of subjects. In total, 1,920 subjects without known diabetes had an OGTT to characterise glucose metabolism, of whom 923 had acute and 997 had a stable manifestation of CAD. The prevalence of newly diagnosed diabetes was 22% in the acute CAD group and 14% in the stable CAD group.

A study by Matz and colleagues (2006) has examined the prevalence of glucose abnormalities in patients with acute stroke. In a cohort of 238 patients with acute stroke, 16% were found to have newly diagnosed type 2 diabetes based on an OGTT.

A cohort of 582 consecutive people with an acute stroke with post-stroke hyperglycaemia between 6.1 and 17 mmol/L were assessed for eligibility for the Glucose Insulin Stroke Trial – an RCT investigating the benefits of maintaining euglycaemia in people with acute stroke (Gray et al, 2004). Diabetes was already recognised in 14%, while 142 were randomised and recruited into the trial, of which 62 underwent an OGTT at 12 weeks post-stroke. It was determined that between 16 and 24% of the initial 455 people without a history of diabetes were likely to have unrecognised diabetes.

The reported prevalence of diabetes at discharge in a cohort of 106 people (median age 71 years) with acute ischaemic stroke and no history of diabetes was 46% based on an OGTT (Vancheri et al, 2005). At admission a further 29% already had a diagnosis of diabetes.

i. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age and prevalence studies suggest that 5-10% of premenopausal women have the full syndrome (Dunaif, 1995).

All studies which have examined the prevalence of undiagnosed type 2 diabetes in women with PCOS have found an increased prevalence. Legro et al. (1999) have studied 254 non-diabetic women (age 14-44 years) with PCOS and compared the findings with 80 women (age 18-40 years) without PCOS. Of the PCOS women, 7.5% had newly diagnosed type 2 diabetes and 31% had IGT, while in the control group none had diabetes and 14% had IGT. In a US cohort of 122 women (aged 14-40 years) with PCOS the reported prevalence of type 2 diabetes was 10% according to 2-hour glucose level in an OGTT, and 6% according to an FPG $\geq$ 7.0 mmol/L (Ehrmann et al, 1999). In a cohort of 121 Mediterranean women (aged 14-37 years) with PCOS the prevalence of type 2 diabetes was 2.5% (Gambineri et al, 2004).

The prevalence of undiagnosed type 2 diabetes in women with PCOS is related to weight. Legro et al. (1999) found that in PCOS women with BMI $\geq$ 27 kg/m^2, the prevalence of undiagnosed diabetes was 6.0%, whereas in PCOS women with BMI < 27 kg/m^2 the prevalence was 1.5%.

Based on a prevalence of undiagnosed type 2 diabetes of 5% in a cohort of 105 women (mean age 28.3 ± 6.8 years) with PCOS, Gagnon and Baillargeon (2007) recommend that all women with PCOS have an OGTT.

j. Smoking

A meta-analysis of 25 prospective cohort studies involving 1.2 million participants found that active smoking is associated with an increased risk of type 2 diabetes (Willi et al, 2007). The

pooled adjusted relative risk of type 2 diabetes for active smoking compared with non-smoking was 1.44 (95%CI 1.31-1.58). The risk of type 2 diabetes was greater for heavy smokers (≥ 20 cigarettes/day; RR 1.61, [95%CI 1.43-1.80]) than lighter smokers (RR 1.29, [1.13-1.48]), and lower for former smokers (RR 1.23, [1.14-1.33]) compared with active smokers (RR 1.44, [1.31-1.58]).

The issue specifically addressed here is whether smoking is associated with the presence of undiagnosed type 2 diabetes. This relationship was assessed in a cross-sectional study of a French population of 28,409 volunteers aged 20-69 years (Beziaud et al, 2004). After adjusting for age, BMI, WHR and alcohol the OR for type 2 diabetes in men was 1.49 (95%CI 1.13-1.96, p = 0.004) in current smokers and 1.31 (1.01-1.17, p = 0.03) in past smokers in comparison with non-smokers. In women, no significant association between current (OR 1.46, [95%CI 0.92-2.22], p = 0.09) or past smoking (OR 0.89, [0.54-1.39], p = 0.62) and type 2 diabetes was found. No association was found between the duration of cessation of smoking and the risk of type 2 diabetes in men or women. No dose-response relationship was found between the number of cigarettes smoked and type 2 diabetes.

In a population-based cross-sectional study of 3,128 men aged 35-56 years from Stockholm the association of cigarette smoking and type 2 diabetes was investigated (Persson et al, 2000). Fifty-two per cent of the subjects had a family history of diabetes and 1.8% were diagnosed with type 2 diabetes via an OGTT. After adjusting for age, BMI, family history of diabetes, physical activity and alcohol consumption, both current (OR 1.3, [95%CI 0.6-2.7]) and former smoking (OR 1.3, [0.7-2.7]) were associated with a non-significant increased prevalence of type 2 diabetes compared with those who had never smoked. The adjusted OR for type 2 diabetes in subjects who smoked 25 or more cigarettes per day compared with those who had never smoked was 2.6 (1.1-5.8).

k. Physical inactivity

There is a clear relationship between physical activity and the development of type 2 diabetes. A systematic review was recently conducted to evaluate the association between moderate intensity physical activity and the risk of type 2 diabetes (Jeon et al, 2007). A meta-analysis was performed for 10 prospective cohort studies with a total of 301,221 participants. Compared with being sedentary, participation in moderate intensity physical activity had a summary relative risk of 0.69 (95%CI 0.58-0.83) for type 2 diabetes. In 5 of these cohort studies that specifically investigated the role of walking, the relative risk of type 2 diabetes was 0.70 (0.58-0.84) for regular walking (usually ≥ 2.5 h/week brisk walking) compared to almost no walking.

There is less information on the relationship between physical activity and newly diagnosed diabetes. Baan and colleagues (1999b) assessed this relationship in a sample of 1,016 participants without known diabetes from the Rotterdam Study in the Netherlands aged 55-75 years. The total time spent on physical activity per week decreased with increasing glucose intolerance. Adjusted ORs for vigorous activities such as bicycling (men: 0.26, [95%CI 0.14-0.49], and women: 0.37, [0.18-0.78]), and sports (men: 0.28, [0.11-0.74]) showed an inverse association with the prevalence of newly diagnosed diabetes.

In a French elderly population (n = 2,532, aged ≥ 60 years) sport activity showed a negative independent association with the prevalence of type 2 diabetes, with a significantly lower prevalence of type 2 diabetes in those doing at least 30 minutes per day of sport compared to those doing less than 30 minutes per day (OR in men 0.61, [95%CI 0.42-0.87], p = 0.007; OR in women 0.62, [0.42-0.91], p = 0.01) (Defay et al, 2001).

A sample of 8,299 Australians aged 25 years and over from the AusDiab study were studied to examine the relationships between physical activity and television viewing and the risk of undiagnosed abnormal glucose metabolism (IFG, IGT or new type 2 diabetes) (Dunstan et al, 2004). After adjusting for known confounders (family history of diabetes, smoking and dietary covariates) and television viewing, the ORs of abnormal glucose metabolism were 0.62 (95%CI 0.41-0.96) in men and 0.71 (0.50-1.00) in women who participated in physical activity for 2.5 hours or more per week compared with those who were sedentary (0 hours per week). The adjusted ORs of abnormal glucose metabolism were 1.16 (0.79-1.70) in men (non-significant) and 1.49 (1.12-1.99) in women who watched television for more than 14 hours per week compared with those who watched 7 hours or less per week. In comparison to those who watched 14 hours of television per week or less, the risk of new type 2 diabetes was significantly increased in men (OR 2.4, [1.41-4.12]) and women (OR 2.2, [1.32-3.61]) who watched more than 14 hours per week.

The association between physical activity and type 2 diabetes was explored in a case-control study of 1,267 subjects (167 with type 2 diabetes and 1,100 controls with normal glucose tolerance) aged 20-74 years (Fulton-Kehoe et al, 2001). Subjects with recently diagnosed type 2 diabetes had significantly lower levels of physical activity than those with normal glucose tolerance. After adjusting for confounders (age, sex, ethnicity and family history of diabetes), the OR for type 2 diabetes in those subjects within the highest tertile of physical activity levels was 0.6 (95%CI 0.37-0.98) compared to those within the lowest tertile.

l. Antipsychotic medication and mental illness

Certain mental illnesses and antipsychotic medications are associated with an increase in prevalence of type 2 diabetes.

In a retrospective, chart-review study in the US, the prevalence of type 2 diabetes was determined in a cohort of 243 psychiatric inpatients aged 50-74 years with a variety of mental illnesses (Regenold et al, 2002). Diagnoses of type 2 diabetes were obtained from discharge summaries by examining for previously diagnosed type 2 diabetes or the prescription of insulin or oral hypoglycaemic medication on discharge. The overall prevalence of type 2 diabetes in the total patient group (25%) was significantly greater than the rate expected for an age-, race-, and gender-matched group in the general US population (14%) ($p < 0.003$). The reported rates of type 2 diabetes according to each mental illness were: schizoaffective disorder (50%) > bipolar I disorder (26%) > major depression (18%) = dementia (18%) > schizophrenia (13%) ($p < 0.006$), independent of the effects of age, race, gender, medication and body mass. Of these rates of type 2 diabetes, only those for schizoaffective disorder and bipolar I disorder were significantly higher than national norms.

The presence of glucose abnormalities and other metabolic risk factors was assessed in a cohort of 100 non-diabetic subjects (mean age 38.0 ±8.7 years) with schizophrenia who were treated with second generation antipsychotics for at least 6 months (De Hert et al, 2006). The prevalence of type 2 diabetes in this population was 4%.

The relationship between dysglycaemia and schizophrenia was assessed in a study of 1,123 Canadian subjects (mean age 44.4 ± 12.7 years) with schizophrenia (Voruganti et al, 2007). In total, 75% of subjects not already diagnosed with diabetes (3.5%) had FPG measured in the preceding 6 months. Based on an FPG level ≥ 7.0 mmol/, 12% were found to have diabetes.

Antipsychotic medications may contribute to this increased prevalence of diabetes. Data from a recent meta-analysis of 25 observational pharmaco-epidemiologic studies found no significant difference in the risk of developing treatment-emergent type 2 diabetes using either second-generation or first-generation antipsychotics (Citrome et al, 2007). However, there are limited data on two recent second-generation antipsychotics, aripiprazole and ziprasidone. Estimates of attributable risk for individual second-generation antipsychotics compared with first-generation antipsychotics ranged from 53 more to 46 fewer new cases of diabetes per 1,000 subjects.

A systematic review of 17 pharmaco-epidemiologic studies examined the relationship between certain atypical antipsychotics and the risk of type 2 diabetes (Ramaswamy et al, 2006). Treatment with olanzapine in people with major psychiatric illness, compared with no treatment, is associated with a significantly greater risk of new-onset diabetes. Risperidone was not associated with a greater relative risk of diabetes than conventional antipsychotics or no treatment. Of 9 studies that compared the relative risk of diabetes with risperidone and olanzapine, 6 demonstrated significantly greater risk with olanzapine, although the magnitude of this risk varies considerably across studies. Definitive conclusions could not be made for clozapine and quetiapine due to insufficient evidence. Results from the review also show that 3 out of 4 studies did not demonstrate a significant increase in risk for diabetes using atypical antipsychotics compared with conventional antipsychotics. According to these results, the authors suggest that while some atypical antipsychotics may have a lower risk of diabetes than conventional antipsychotics, others have a higher risk, and grouping them together tends to bias toward the null.

Bellantuono and colleagues conducted a review of 21 studies (9 prospective, 11 retrospective) to evaluate the risk of type 2 diabetes in people treated with different antipsychotic drugs (conventional and second-generation) (Bellantuono et al, 2004). Subjects with schizophrenia treated with different antipsychotics have an increased risk of developing type 2 diabetes than the general population. It is not currently clear, however, whether the increased risk of developing type 2 diabetes is due to the schizophrenia itself or due to the antipsychotic treatment. The authors of this study state that methodological flaws of the available data prevented them from comparing the risk of type 2 diabetes for conventional versus second-generation antipsychotics.

An Australian consensus statement of diabetes and mental health recommends that all people on antipsychotic medication should be screened for type 2 diabetes (Lambert and Chapman, 2004). It suggests that screening should be performed monthly for six months after initiating or changing antipsychotic therapy and at a minimum of twice yearly thereafter.

m. Sleep disorders

There is an association between obstructive sleep apnoea syndrome (OSAS) and type 2 diabetes (Meslier et al, 2003). In a cohort of 595 males aged 21-78 years with suspected OSAS, 494 were confirmed to have OSAS while the remaining 101 were non-apnoeic snorers. There was a high prevalence of type 2 diabetes (diagnosed by OGTT) in both OSAS subjects (30%) and non-apnoeic snorers (14%). Diabetes was previously diagnosed in 19% of OSAS subjects and 11% of non-apnoeic snorers, while undiagnosed diabetes was detected in 11% of OSAS people and 3% of non-apnoeic snorers.

The relationship between sleep-disordered breathing and glucose intolerance was assessed in a cohort of 2,656 subjects from the Sleep Heart Health Study (Punjabi et al, 2004). The prevalence of diabetic fasting glucose levels was significantly higher in subjects with a

respiratory disturbance index (RDI) of ≥15 events/hour (9%) compared with those with a RDI of < 5 events/hour (4%). Similarly, the prevalence of diabetic 2-hour glucose levels was significantly elevated in subjects with a RDI ≥ 15 events/hour (15%) compared with subjects with a RDI of < 5 events/hour (9%).

The association of sleep-disordered breathing (SDB) with type 2 diabetes was assessed in a population-based study of 1,387 participants (49.0 ± 8.3 years) in the Wisconsin Sleep Cohort (Reichmuth et al, 2005). A higher prevalence of type 2 diabetes was associated with increasing levels of SDB. The prevalence of type 2 diabetes was 15% in subjects with an apnoea-hypopnea index (AHI) ≥ 15 and 3% in those with an AHI < 5. Compared with subjects with an AHI < 5, the OR for physician-diagnosed type 2 diabetes in subjects with an AHI ≥ 15 was 2.3 (95%CI 1.28-4.11, p = 0.005), after adjusting for age, sex and body habitus (waist girth). When using a broader definition of type 2 diabetes as either FPG ≥ 7.0 mmol/L or physician-diagnosed diabetes, the adjusted OR for having type 2 diabetes in subjects with an AHI ≥ 15 compared with subjects with an AHI < 5 was 1.67 (1.04-2.67, p = 0.03).

2. Case detection procedure

Most commonly a 3-step case detection procedure for undiagnosed diabetes is used which includes:

- risk assessment
- screening blood testing
- diagnostic testing

In interpreting the findings of studies included in this section, it should be noted that the majority of published studies on screening for undiagnosed diabetes define cases of type 2 diabetes based on a single test, rather than using the confirmatory measurement required for a clinical diagnosis. This is likely to affect the yield of the different strategies for case detection and diagnosis in terms of the number of reported cases of type 2 diabetes. Approximately 75% of people with screen-detected diabetes on a single test will be confirmed to have diabetes on repeat testing (Christensen et al, 2004; Mooy et al, 1996).

In addition, different methods have been used to define diabetes including an OGTT, FPG, medication-requiring diabetes and self-report.

2.1 Risk assessment

A number of risk assessment strategies have been used which can broadly be grouped into 2 categories: single or multiple risk factors; and risk scores

2.1.1 Single or multiple risk factors

- **Single or multiple risk factors can be used to screen for type 2 diabetes *(Evidence Level III-2)***

The Australian NHMRC screening protocol for identifying undiagnosed type 2 diabetes was assessed in a population-based sample of 10,508 Australian adults (Colagiuri et al, 2004). The protocol involves an initial assessment of risk status, measurement of FPG in individuals at risk, and further testing with either FPG (if FPG ≥ 7.0 mmol/L) or OGTT (if FPG 5.5-6.9 mmol/L). In this population the protocol had a sensitivity of 80%, a specificity of 80% and a positive predictive value (PPV) of 14% for detecting undiagnosed type 2 diabetes. It was

concluded that the Australian screening protocol performed well in detecting undiagnosed diabetes in an Australian population.

Dallo and Weller (2003) evaluated the ADA recommendations for screening for undiagnosed diabetes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2002) in a representative sample of 6,515 adults 20 years and older from the US NHANES III cohort (diabetes diagnosed by FPG). Screening in the presence of one risk factor produced a sensitivity of 100%, a specificity of 18%, and required 83% of the population to be tested. Screening in the presence of two risk factors was more efficient, with a sensitivity of 98% and specificity of 42%, and 59% of the population required further testing. Since diabetes occurs at a younger age in minorities, screening white people aged 40 years and over and screening minorities aged 30 years and over resulted in a high sensitivity (95%), a specificity of 41%, but required 60% of the population to be tested.

Age is a commonly used single risk factor for screening for undiagnosed diabetes. A study in the UK assessed the ADA recommendation of universal screening for undiagnosed type 2 diabetes in general practice of all people aged 45 years and over (Lawrence et al, 2001). A cohort of 876 adults aged over 45 years from a local general practice in the UK were screened for type 2 diabetes, with an FPG screening test result $\geq$ 6.1 mmol/L warranting further diagnostic testing via an OGTT. The prevalence of diabetes was 0.2% in people with age as a single risk factor and 2.8% in people with age and one or more risk factors (hypertension, obesity and family history of diabetes). Screening all people over 45 required an estimated 120 hours of staff time, whereas screening those with risk factors in addition to age would take approximately half the time. Screening for type 2 diabetes on the basis of age alone had a very low yield compared with targeting people with multiple risk factors for diabetes.

A Canadian study of 9,042 people aged over 40 years suggested that routine screening for type 2 diabetes by family physicians is justified in people over the age of 40 in light of the finding that undiagnosed diabetes is present in 2.2% of these people (Leiter et al, 2001). Newly diagnosed glucose intolerance (IFG, IGT and probable diabetes) was found in an additional 3.5% of participants, while 16.4% had previously known diabetes. The prevalence of undiagnosed diabetes increases with age, with a minimum prevalence of 1.4% in the 40-44 and 45-49 years age ranges, and a maximum prevalence of 3.4% in those aged 65-69 years. The screening procedure involved a capillary blood glucose (CBG) measurement, which if > 5.5 mmol/L the patient returned for an FPG on another day. If the FPG was 6.1-6.9 mmol/L the patient returned for an OGTT. Several risk factors including hypertension, high triglyceride levels, heart disease, previously identified IGT and history of GDM were significantly associated with either new or known diabetes. The authors confirm their results support the ADA recommendation to screen high-risk individuals for undiagnosed type 2 diabetes.

Using family history as a risk factor to screen for undiagnosed diabetes was examined in a representative sample of the US population (3,823 subjects from the NHANES III data, aged 20 years or more, diabetes diagnosed on a single FPG) (Hariri et al, 2006a). The use of a three-tiered familial risk stratification (high, moderate, low) for diabetes screening yielded a high specificity (94%) and PPV (10%), but low sensitivity (19%) for high familial risk alone, compared with either moderate or high familial risk (specificity: 73%; PPV: 5%; sensitivity: 48%) or BMI $\geq$ 25 kg/m^2 (specificity: 38%; PPV: 4%; sensitivity: 88%). Combining high familial risk and BMI $\geq$ 25 kg/m^2 improved the specificity (97%) and PPV (13%), while the addition of age $\geq$ 45 years as a risk factor further improved PPV (21%), without reducing

specificity (96%). It was concluded that family history can be used as an initial screening risk factor for diabetes as a simple, inexpensive, reliable, and non-invasive screening tool for undiagnosed diabetes.

The use of self-reported family medical history as a screening tool for type 2 diabetes was assessed in a cohort of 4,345 US adults who participated in the 2004 *HealthStyles* mail survey by completing a questionnaire on personal and family history of diabetes, perceived risk of diabetes and practice of risk-reducing behaviours (Hariri et al, 2006b). Respondents were ranked into three familial risk levels. Using family history as a screening tool had a sensitivity of 73%, a specificity of 68%, a PPV of 22% and a negative predictive value (NPV) of 96% for detecting type 2 diabetes in this population (Hariri et al, 2006b). The combination of family history and obesity as a screening tool improved the specificity (94%) and PPV (38%), but reduced sensitivity (29%) and NPV (92%). Accordingly, the authors suggest that family history, in conjunction with obesity, may be a useful and inexpensive tool for detecting undiagnosed diabetes.

In a population of 1,353 German adults aged 55-74 years participating in the KORA Survey 2000 the prevalence of known and unknown diabetes was 9 and 10% in men, and 8 and 7% in women, respectively (Rathmann et al, 2003). Individuals with undiagnosed diabetes had higher BMI, waist circumference, SBP, triglycerides, uric acid, and lower LDL cholesterol than normoglycaemic individuals ($p < 0.01$). In men, the combination of abdominal adiposity, hypertension and parental diabetes resulted in a NNS of 2.9 (95%CI 2.0-4.6) to identify one person with undiagnosed diabetes. In women, a combination of increased triglycerides, hypertension and parental diabetes produced a NNS of 3.2 (2.2-5.1).

The performance of waist circumference, BMI, age, and random CBG measurements as screening tests for detecting undiagnosed type 2 diabetes were compared in an overweight multi-ethnic population in the UK (Featherstone and Goyder, 2007). The study population consisted of 4,343 subjects aged 40 years and over with a BMI $\geq 25 kg/m^2$ and no known diabetes. The prevalence of undiagnosed type 2 diabetes in this population was 3.8%. The area under the receiver operator characteristic (ROC) curve for detecting undiagnosed type 2 diabetes using waist circumference, BMI and age were all similar, at 0.63 (95%CI 0.59-0.68), 0.62 (0.57-0.66), and 0.61 (0.57-0.65), respectively. The performance of random CBG ≥ 6.0 mmol/L at detecting undiagnosed type 2 diabetes was significantly higher, with an area under the ROC curve of 0.73 (0.69-0.78).

2.1.2 Risk scores

- **Risk scores are commonly used to screen for type 2 diabetes *(Evidence Level III-2)***

High-risk screening strategies based on common risk factors such as age > 45 years, ethnicity and overweight/obesity may identify more than 50% of the population, bringing it close to universal screening (Borch-Johnsen et al, 2003). Therefore risk scores based on a combination of several risk factors are increasingly used as the initial step in identifying individuals at high risk of having undiagnosed diabetes.

The ADA recommends screening of all people with one or more risk factors or having symptoms of diabetes (ADA, 2008). The ADA (1993) has developed a questionnaire to numerically assess risk**,** however this questionnaire was not prospectively evaluated during its development (Herman et al, 1995). Burden and Burden (1994) did not find the questionnaire

useful in community screening in the UK suggesting that a particular difficulty was the inclusion of non-specific symptoms (e.g. fatigue and blurred vision). Ruige et al. (1997) tested this questionnaire in European populations and reported a sensitivity of 59%, specificity of 59% and PPV of 5.6% for identifying undiagnosed type 2 diabetes.

A number of studies (Baan et al, 1999a; Ruige et al, 1997; Herman et al, 1995) have assessed risk stratification as a means of identifying people with undiagnosed type 2 diabetes. Diabetes was defined by the OGTT in the whole of each population irrespective of risk status, and risk factors which most closely associated with diabetes were determined. The studies identified different sets of risk factors predictive of undiagnosed diabetes, although there were some commonalities. Despite the differences in these studies, the three methods have similar performance in identifying people with undiagnosed type 2 diabetes: sensitivity 72-78%, specificity 55-56% and PPV 6-8%. With respect to the proportion of the population who would require further testing, the risk classification trees developed by Herman et al (1995) identified 30% of the population which needed follow-up testing to establish a definitive diagnosis of diabetes. The method developed by Ruige et al (1997), when applied in Caucasian people aged 45-74, identified 45% who would require definitive blood glucose testing in order to identify 72% with undiagnosed diabetes. Neither of these studies employed an intermediate step of measuring blood glucose between application of the risk factor questionnaire and performing an OGTT. The trade off with these risk factor assessment approaches compared with universal testing is that approximately 20% of undiagnosed diabetes will be missed but the need to unnecessarily test many people is avoided.

The Danish diabetes risk score includes age, sex, BMI, known hypertension, physical activity at leisure time, and family history of diabetes (Glumer et al, 2004a). The risk score was derived from the first half of the population-based sample Inter99 study of 6,784 individuals aged 30-60 years, and was validated on the second half of this population. External validation was performed using the population from the ADDITION pilot study. The area under the ROC curve was 0.80 (95%CI 0.77-0.84) for the first half of the Inter99 population, 0.76 (0.72-0.80) for the second half, and 0.80 (0.72-0.88) for the ADDITION pilot study population. In the same populations, the sensitivity was 73, 67, and 76%, and specificity was 74, 74, and 72%, respectively. The percentage of subjects requiring subsequent testing was 28, 28, and 29%, respectively. The cardiovascular risk profile of those who were true positive was less favourable than those who were false negative, with significant differences seen in a number of categories: age (53.3 vs. 45.6 years, $p < 0.0001$), BMI (31.4 vs. 26.6 kg/m^2, $p < 0.0001$), systolic BP (151 vs. 139 mmHg, $p < 0.001$), diastolic BP (92 vs. 87 mmHg, $p < 0.001$), HDL cholesterol (1.2 vs. 1.4 mmol/L, $p < 0.0001$), and HbA1c (6.8 vs. 6.3%, $p < 0.0001$). Typical of such risk scores, 24% of individuals with previously undiagnosed diabetes will be missed using this risk score.

The performance of the Finnish Diabetes Risk Score (DRS) was tested in 1,377 individuals aged 55-75 years presenting with one or more cardiovascular risk factors in the IGLOO (Impaired Glucose Tolerance and Long-Term Outcomes Observational) study (Franciosi et al, 2005). The sensitivity, specificity, and PPV of the DRS with a cut-point of 9 in detecting undiagnosed type 2 diabetes was 86, 41, and 23% respectively, with an area under the ROC curve of 0.72 (95%CI 0.68-0.76). Using FPG alone with a cut-point of 6.1 mmol/L those values were 92, 68, and 38%, respectively, and for FPG with a cut-point of 5.6 mmol/L they were 97, 38, and 25%, respectively. Combining the DRS with an FPG measurement with a cut-point of 6.1 mmol/L produced a sensitivity, specificity, and PPV of 99, 78, and 43%, respectively. Combining the DRS with an FPG measurement with a cut-point of 5.6 mmol/L produced a sensitivity, specificity, and PPV of 100, 59, and 30%, respectively. These results

indicate that the DRS is a valid an inexpensive method for opportunistic screening for type 2 diabetes, and is a viable alternative to FPG, which may not always be readily available in general practice. Using the DRS as an initial screening strategy, followed by FPG in those at risk (DRS ≥ 9), and an OGTT in those with an FPG ≥ 5.6 mmol/L would detect 83% of cases of undiagnosed diabetes, requiring FPG measurements in 64% and an OGTT in 38%. In contrast, using FPG as an initial measurement in all subjects, followed by an OGTT in those with FPG ≥ 5.6 mmol/L would identify 92% of cases of undiagnosed diabetes, but would require 56% of the subjects to undergo an OGTT.
Several other population specific risk scores have been developed e.g. in India (Ramachandran et al, 2005), Germany (Schulze et al, 2007) and the US (Heikes et al, 2008). Although somewhat different, they share many similar risk factors.

Multivariate logistic regression equations can also be used to screen for undiagnosed diabetes. One example was developed in an Egyptian cohort of 1,032 adults (Tabaei and Herman, 2002) and included age, gender, BMI, random capillary plasma glucose and time since last meal. The equation was validated in an independent sample of 1,065 US adults with a similar age and BMI. The equation produced similar results in both the Egyptian and the US population for sensitivity (65 vs. 62%), specificity (both 96%) and PPV (67 vs. 63%). The equation, which can be applied using a programmable handheld calculator, is a simple and inexpensive method for detecting previously undiagnosed diabetes.

Another example is the Cambridge Risk Score (CRS), which is based on data routinely collected in UK primary care practices (age, gender, BMI, steroid and antihypertensive medication, family and smoking history). The CRS is used to identify individuals at risk of having undiagnosed type 2 diabetes for diagnostic testing (Griffin et al, 2000). In a cohort of 1,077 subjects aged 40-64 years the risk score had a sensitivity and specificity of 72 and 77%, respectively, with an area under the ROC curve of 0.8 (95%CI 0.68-0.91).

The CRS has been applied to the Dutch Hoorn study, using the OGTT as the gold standard (Spijkerman et al, 2002b). Of the population of 2,297 subjects aged 50-75 years, there were 113 true positive cases of undiagnosed type 2 diabetes using the risk score, which produced a sensitivity of 73% and a specificity of 52%. However, a large group (n = 1,037) screened positive using the risk score, but were not confirmed to have diabetes using the OGTT (false positive). Regardless, the risk of mortality was significantly increased in both the true positives (RR 3.40, [95%CI 2.15-5.38]) and the false positives (RR 2.62, [2.00-3.43]) compared with the true negative group.

The performance of the CRS to detect diabetes was assessed in a cohort of 1,355 patients in a semi-rural general practice in Denmark (Heldgaard and Griffin, 2006). The prevalence of type 2 diabetes in this population was 2.3%, as determined by OGTT. The risk score produced an area under the ROC curve for detecting diabetes of 0.84 (95%CI 0.76-0.92). With a cut-point of 0.246, 20% of the population would have required further testing. At this cut-point the sensitivity for detecting undiagnosed diabetes was 71%, the specificity 81%, PPV 8%, and likelihood ratio 3.77.

Barriga et al. (1996) explored the use of decision tree analysis (CART software) to develop a method of screening for IGT and type 2 diabetes. Two screening approaches were simulated: a simultaneous approach, where all risk variables were entered into CART models at once; and a serial approach, where risk variables, grouped according to effort required for data collection, were entered into CART models in stages. Using a combination of FPG > 5.7 mmol/L and age > 62.5 years or BMI > 29.7 kg/m^2, the simultaneous model achieved a

sensitivity of 91%, specificity of 55%, and PPV of 31%. In contrast, a serial approach eliminated 35% from further testing using the criteria of age < 53.5 years and BMI < 28 kg/m^2. The remainder required an FPG measurement, of which 45% required an OGTT. This serial approach resulted in a sensitivity of 85% and a specificity of 64%.

Risk assessment tools developed in one population do not necessarily perform well when applied to other populations, especially from diverse ethnic backgrounds. The DETECT-2 collaboration assessed the Rotterdam Predictive Model (RPM) which included information on age, gender, BMI, and BP treatment, in a cohort of 29,758 individuals from diverse ethnic and regional backgrounds (Northern and Southern Europe, U.S., Indian subcontinent, Asia, Australia, Pacific Islands, and Africa) (Glumer et al, 2006a). There was large variability in the performance of the risk score across the various populations with sensitivity ranging from 12-57%, specificity from 65-93%, PPV from 2-25%, and percentage of the population requiring further testing from 8-38%. The performance of the risk score was poorest in the non-Caucasian populations. The variation in performance was attributed to differences in the prevalence of components of the risk score, particularly age and BMI.

Another study examined the performance of four diabetes screening questionnaires/risk scores (Rotterdam Diabetes Study, Cambridge Risk Score, San Antonio Heart Study, and the Finnish Diabetes Risk Score) when applied to another population, the KORA survey of 1,353 participants aged 55-74 years (Rathmann et al, 2005). The area under the ROC curve for the four screening tools was 0.61 (95%CI 0.56-0.66), 0.67 (0.62-0.72, $p < 0.001$ vs. Rotterdam), 0.9 ($p < 0.01$ vs. all 3 questionnaires) and 0.65 (0.60-0.69, $p = 0.10$ vs. Rotterdam), respectively, with the prediction model developed from the San Antonio Heart Study performing best, which is not surprising since it includes a plasma glucose measure. The range of sensitivity (58-82%), specificity (39-85%) and PPVs (11-34%) across the screening tests were generally lower than values obtained in the original studies.

The Finnish Diabetes Risk Score (FINDRISC) was evaluated as a tool for screening for undiagnosed type 2 diabetes in 2,966 Finnish subjects aged 45-74 years (Saaristo et al, 2005). The risk scores includes information on age, BMI, waist circumference, physical activity, daily consumption of fruits, berries or vegetables, history of antihypertensive drug treatment, history of blood glucose, and family history of diabetes. The prevalence of screen-detected diabetes was 11.6% in men and 6.4% in women. Using the risk score for detecting undiagnosed type 2 diabetes, the area under the ROC curve was 0.72 (95%CI 0.68-0.77) in men and 0.73 (0.68-0.78) in women. Using a cut-point of 11 for identifying undiagnosed type 2 diabetes, the sensitivity, false positive rate, PPV and NPV were 66, 31, 22 and 94%, respectively, in men and 70, 39, 11 and 96%, respectively, in women. Using this cut-point the proportion of the population requiring an OGTT was 12% in men and 15% in women.

Recently an Australian Diabetes Risk Assessment Tool (AUSDRISK) for the prediction of incident diabetes has been developed (Shaw, personal communication, 2008). The AUSDRISK contains information on age, gender, ethnicity, family history of diabetes, hypertension, smoking, fruit and vegetable consumption, physical activity, and obesity. In addition to predicting future diabetes, AUSDRISK can discriminate between those who did and those who did not have undiagnosed diabetes. The risk tool performed well in terms of area under the ROC curve for detecting current undiagnosed diabetes (0.75). Using a score of ≥ 15 for identifying undiagnosed diabetes the sensitivity, specificity, and PPV were 57, 77, and 12%, respectively. Using a cut-point of ≥ 12, these values were 78, 58, and 10%, respectively. Assessing performance in the AusDiab baseline population aged ≥ 40 years, 24% had an AUSDRISK ≥ 15 and therefore required an FPG test. Of these, 56% had an FPG

of 5.5-6.9 mmol/L, resulting in 13% of the total population requiring an OGTT. In comparison, 43% of the baseline population had an AUSDRISK ≥ 12 and required an FPG test. Of these, 55% had an FPG of 5.5-6.9 mmol/L, therefore requiring an OGTT in 24% of the total population. Using a 3 step protocol with the AUSDRISK, followed by an FPG test in those at risk, and then an OGTT in those with elevated FPG, 53% of subjects with undiagnosed type 2 diabetes would be identified using an AUSDRISK cut-point of ≥ 15, whereas 71% would be identified using a cut-point of ≥ 12. Taking into consideration the balance between performance in terms of sensitivity and specificity, the percentage of the population identified as being at risk and requiring additional testing, and the overall rate of detecting diabetes, it was considered that a risk score of ≥ 12 provided the best balance of these attributes.

2.2 Screening blood test

Having identified at risk individuals using a risk assessment tool, most protocols include a screening blood test as the next step rather than proceeding directly to definitive testing for diabetes in order to identify people who require further testing.

There are several considerations in attempting to define an appropriate screening test. Case detection and diagnosis is based on some degree of hyperglycaemia but it should be remembered that this requires criteria which dichotomise a continuous variable. The separation of normal from abnormal is somewhat arbitrary and this invariably results in a less than perfect correlation between the screening and diagnostic tests.

The following issues are addressed in this section:

Measurement of glucose in blood

- technical considerations
  - comparability of results
  - laboratory vs. point of care (POC) testing
- performance in screening for type 2 diabetes
  - fasting
  - non-fasting

Measurement of glycated haemoglobin (HbA1c)

2.2.1 Measurement of glucose in blood

- **The comparability of glucose measurement in blood is affected by a number of factors *(Evidence Level IV)***

Accurate and precise measurement of glucose concentration in the circulation is essential in the diagnosis and management of diabetes. However, what is often assumed to be straightforward is not always the case, as discussed in the review by Burrin and Alberti (1990). Glucose oxidase is the standard laboratory method used to measure glucose in the circulation. The most important variables in interpreting a result for glucose in the circulation are the origin of the sample (i.e. arterial, capillary or venous), and whether the glucose is measured in plasma or whole blood. The analysis of each sample incorporates a combination of these two variables with the most common combinations being venous plasma, venous whole blood and capillary whole blood. Most laboratories measure venous plasma glucose while meters measure capillary whole blood glucose.

Measurement differences may also arise depending on the site of collection of the blood sample. Venous and capillary samples will give the same result in the fasting state but in the non-fasting state capillary will give results which are approximately 8% higher than venous samples (Burrin and Alberti, 1990). Glucose measured in plasma is approximately 11% higher than glucose measured in whole blood. However, this difference is dependent on haematocrit, increasing to 15% at a haematocrit of 0.55 and decreasing to 8% at a haematocrit of 0.30 (Fogh-Andersen et al, 1990).

A comparison has been made between venous and capillary glucose measurements for fasting, random, and 2 hour post-glucose samples (Colagiuri et al, 2003b). As shown in Table 4 the results obtained in this study regarding equivalence values for venous plasma glucose and capillary blood glucose are considerably different to those published by the WHO (1999). These results bring to light the difficulty associated with accurately equating venous and capillary glucose levels and raise doubts regarding current published equivalence values, which may produce misclassification in glucose tolerance status. Capillary glucose values were consistently lower than venous glucose values for fasting and random measurements, while they were consistently higher for the 2-hour post-load sample.

Table 4: Venous plasma glucose and capillary blood glucose equivalence values

	Venous plasma (mmol/L)	**Capillary whole blood (mmol/L)**	
		WHO, 1999	**Colagiuri et al., 2003**
Fasting	6.1	5.6	5.2
	7.0	6.1	6.1
2 h after oral glucose	7.8	7.8	8.3
	11.1	11.1	11.7
Random	5.5	4.4	4.8
	11.1	11.1	10.0

Adapted from Colagiuri et al., 2003

Stahl and colleagues (2002) conducted a study to determine whether capillary whole blood and venous plasma glucose measurements can be used interchangeably in the diagnosis of diabetes. Seven hundred and thirteen people without known diabetes were included in the analysis. On average, venous plasma glucose was 0.66 mmol/L (14%) higher than capillary whole blood glucose. For individual results, there was unpredictable variation between the two measurements which cannot be reduced by conventional formulas. The error induced by converting capillary whole blood to venous plasma glucose is so significant that it may lead to random, unpredictable misclassification of individuals and may affect the outcome of population screening. It was concluded that the two measurements are not interchangeable and that conversion of capillary whole blood to venous plasma values should not be done for diagnostic purposes, with venous plasma measurements recommended for the diagnosis of diabetes.

For this and other reasons the conversion of whole blood glucose to plasma glucose is problematic. Nevertheless, the WHO provides equivalence estimates of diagnostic values for venous plasma and capillary plasma (WHO, 2006) (Table 5) because access to laboratory glucose measurement is limited in many parts of the world which must rely on capillary POC glucose measurement.

Table 5: Conversion of non-fasting plasma venous glucose to plasma capillary glucose values (mmol/L)

Venous plasma glucose	Capillary plasma glucose
7.8	8.9
11.1	12.2

Adapted from World Health Organization, 2006
Note: Values are identical in the fasting state

The blood collection and handling procedure prior to analysis will affect the test result for plasma glucose measurement. The processing of the sample after collection is important to ensure accurate measurement of plasma glucose. This requires rapid separation of the plasma after collection (within minutes) but it is recognised that this seldom occurs. Collection into a container with glycolytic inhibitors (e.g. NaF) is only partially effective. A minimum requirement is that the sample should be placed immediately in ice-water after collection and before separating, but even so separation should be within 30min (Burrin and Alberti, 1990).

Stahl and colleagues (2001) examined the optimal conditions for sampling, additives, storage, transport and analysis for plasma glucose to minimise false-positive and false-negative results in the diagnosis of diabetes. The study reported that for accurate measurement of plasma glucose, blood should be drawn into tubes containing heparin and the antiglycolytic agent NaF and kept on ice water for a maximum of 1 hour. The sample must then be centrifuged at a minimum of 1000 x g for 10 minutes within 1 hour after sampling. The plasma will then be stable for at least 48 hours at room temperature. Alternatively, blood can be drawn in tubes containing heparin provided the plasma is separated immediately after blood drawing. The authors also reported that serum glucose is ~0.2 mmol/L lower than in plasma, and this should be taken into consideration otherwise it may result in misclassification.

- **Laboratory or point of care (POC) testing can be used to measure glucose in blood *(Evidence Level III-2)***

Near patient testing using a portable meter is convenient but raises concerns about accuracy of the test result. There have been numerous studies examining the accuracy of blood glucose meters (not reviewed here). The general conclusion is that commercially available blood glucose meters perform well in the context of self monitoring but there are concerns that they are not sufficiently accurate for screening for undiagnosed diabetes.

Most portable devices measure the glucose concentration directly in the plasma component of the blood by filtering out the red blood cells. The signal is then calibrated to produce a readout either as blood or plasma glucose. It should also be noted that many portable glucose measuring devices are still calibrated to whole blood despite the International Federation of Clinical Chemistry (IFCC) recommendation that all glucose measuring devices report in plasma values (D'Orazio et al, 2005).

Puntmann and colleagues (2003) conducted a study to compare several POC testing meters (Accutrend Sensor, Accu-Chek plus, Elite XL, HemoCue, and Omni) which measured capillary blood, with laboratory measurement of venous plasma and venous blood for diagnosing type 2 diabetes during an OGTT. At least in the fasting state, all POC testing meters tested were less reliable than laboratory measurement and were above the chosen criteria of clinical acceptability (discordance rate ≤ 5%). However, upon transforming all

meter results with a regression function to correct for bias, the discordance rates were < 5% compared with the laboratory measurement. Therefore, with appropriate recalibration, the POC testing meters tested were acceptable for detecting type 2 diabetes.

Despite these limitations, some studies have shown POC testing to be useful as part of a screening protocol for undiagnosed diabetes.

A comparison of the diagnostic validity of capillary plasma glucose and venous plasma glucose concentration using the OGTT was studied in 350 subjects (Kruijshoop et al, 2004). Across all subjects, capillary plasma glucose values were significantly higher during the OGTT than venous plasma glucose values in the fasting state (0.18 mmol/L, [95%CI 0.10-0.26]) and 2 hours after glucose intake (1.09 mmol/L, [0.87-1.32]) ($p < 0.05$). However, in the group diagnosed with type 2 diabetes ($n = 97$), capillary plasma glucose values were significantly higher than venous plasma glucose values in the fasting state (7.7 ± 1.7 vs. 7.5 ± 1.3, $p < 0.05$), but not at 2 hours post load (13.7 ± 3.9 vs. 13.1 ± 3.2). Using capillary plasma glucose to diagnose type 2 diabetes resulted in a sensitivity of 84% and a specificity of 98%. The consistency in diagnosis of subjects with type 2 diabetes between capillary and venous plasma glucose measurements was 78%. Results indicated a high correlation between capillary and venous plasma glucose concentrations (fasting $r = 0.92$, $p < 0.0001$; 2 hour post load $r = 0.83$, $p < 0.0001$). The authors suggest that a capillary plasma glucose measurement using a commercially available glucose meter is a suitable and cost-effective alternative to venous plasma glucose for the detection and diagnosis of type 2 diabetes.

- **Fasting glucose measurement using a cut-point of 5.5mmol/L performs well as a screening test for undiagnosed type 2 diabetes *(Evidence Level III-2)***

FPG is a suitable test for screening for undiagnosed type 2 diabetes due to its high sensitivity and specificity, as well as its simplicity and convenience (Harris and Eastman, 2000). Measurement of FPG can be combined with pathology testing for other reasons. The usefulness of particular levels of FPG in detecting undiagnosed diabetes has been assessed in several studies.

An FPG level of approximately 5.5 mmol/L as the cut-point defining low risk of undiagnosed type 2 diabetes is supported by a number of studies. Costa et al. (1999) examined FPG results in 616 bank employees with diabetes being tested with an OGTT and reported that an FPG ≥ 5.4 mmol/L achieved optimal sensitivity and specificity. Below this level 0.5% had undiagnosed diabetes and 3.2% IGT compared with 4% diabetes and 21% IGT above this cut-point. Bortheiry et al. (1994) reported that the best equilibrium between sensitivity and specificity for the diagnosis of diabetes was achieved at a cut-point of 5.6 mmol/L for fasting CBG in their study of 4,019 Brazilian people undergoing an OGTT. The DECODE Study Group (DECODE, 1999b) analysed data from many European studies which included a total of 29,108 people who had an OGTT. Using an FPG cut-point of > 5.5 mmol/L would identify 93% of people with diabetes and 69% of people with IGT. By comparison a cut-point for FPG of 6.1-6.9 mmol/L would identify 82% of people with diabetes and 29% of those with IGT. Larsson et al. (1995) reported that optimal sensitivity and specificity for detecting undiagnosed diabetes was achieved in their cohort of women aged 55-57 years with a fasting blood glucose (FBG) of 5.3 mmol/L – sensitivity and specificity were 77% and PPV 12%. Wiener (1995) found similar results in a small group of non-pregnant adults undergoing OGTT with an FPG of 5.5 mmol/L having a sensitivity of 89% and specificity of 59% for detecting undiagnosed diabetes. Cockram et al. (1992) reported that an FPG of 5.6 mmol/L

gave a sensitivity and specificity of 87% compared with a 2-hour plasma glucose of 11.1 mmol/L.

Two reports from Australia presented data on individuals referred for OGTT for different categories of glucose tolerance according to FPG which included a 5.5 mmol/L cut-point value (Appleton, 1999; Diamond and Meerkin, 1999) (Table 6). Approximately twice as many people with FPG between 5.5 and 6.0 mmol/L had diabetes and IGT compared with people with FPG values below 5.5 mmol/L. Similarly, Ramachandran et al. (1993) reported that only 1% of people with an FPG below 5.5 mmol/L had diabetes in an Asian Indian population from South India.

Table 6: The performance of various levels of fasting plasma glucose in detecting abnormalities of glucose tolerance

Reference	N	FPG < 5.5 mmol/L				FPG 5.5-6.0 mmol/L				FPG 6.1-6.9 mmol/L			
		Total	NGT	IGT	DM	Total	NGT	IGT	DM	Total	NGT	IGT	DM
Appleton, 1999	44,592	31%	77%	19%	3%	30%	67%	26%	7%	23%	39%	39%	22%
Diamond and Meerkin, 1999	2,341	53%	73%	23%	4%	20%	49%	40%	11%	16%	22%	34%	44%

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus
Total = % of total population within each plasma glucose range
% for NGT, IGT, DM within each plasma glucose range refer to % of total in that range

Modan and Harris (1994) compared the performance of various FPG levels in people in the USA and Israel for detecting undiagnosed type 2 diabetes. Thirty five percent of people in the USA and 19% of people from Israel with newly diagnosed diabetes had an FPG less than 6.1 mmol/L. While these authors concluded that no FPG level provided a satisfactory cut-point to use in screening for undiagnosed diabetes, an FPG of ≥ 5.55 mmol/L was more effective than other FPG levels. This level had a sensitivity of 83% and 95%, respectively, in the USA and Israel with corresponding specificities of 76% and 47%, and PPVs of 17.2% and 11.8%. Davies et al. (1993) performed a similar study in 442 people from the Isle of Ely, UK. At an FPG cut-point of 5.5 mmol/L sensitivity was 96% and specificity 28%, compared with results of 65% and 64%, respectively, with a cut-point of 6.0 mmol/L.

Another consideration favouring the selection of the lower cut-point for normality are data relating FPG to mortality. Levitan et al. (2004) performed a meta-analysis of 38 prospective studies and confirmed that hyperglycaemia in the non-diabetic range was associated with increased risk of fatal and non-fatal CVD. From 12 studies reporting FPG levels, cardiovascular events appeared to increase with increasing FPG, with a possible threshold at 5.5 mmol/L.

FPG is relatively stable, changing by a mean of 0.06 mmol/L per decade of age, whereas post challenge plasma glucose increases with age by a mean of 0.28 mmol/L (Blunt et al, 1991). Some data suggest that using FPG for screening for undiagnosed type 2 diabetes may be influenced by age. Blunt et al. (1991) compared two age groups, 50-64 and 65-79 years, and found that the sensitivity for an FPG above 5.5 mmol/L was nearly 100% for the younger age group and 75% for the older age group, while specificity was approximately 60% for both groups and PPV was 12% and 25%, respectively, reflecting the higher prevalence of diabetes in the older age group. However, this finding was not supported by two other studies. Bortheiry et al. (1994) found similar sensitivities of 84-91% and specificities of 69-76% for each decade of age from 30-70 years using a fasting CBG level of 5.6 mmol/L as a cut-point

for predicting the diagnosis of diabetes. Modan and Harris (1994) also reported similar sensitivities in their US and Israeli populations for decades of age from 40-69 years. These differences may reflect the older age group included in the Blunt et al. (1991) study, but age does not seem to be a factor affecting the properties of FPG up to age 70.

The choice of cut-point value for FPG has implications for the number of people requiring definitive testing. The Australian screening protocol for identifying undiagnosed type 2 diabetes was assessed in a population-based sample of 10,508 Australian adults (Colagiuri et al, 2004). The protocol involves an initial assessment of risk status, measurement of FPG in individuals at risk, and further testing with either FPG (if FPG ≥ 7.0 mmol/L) or OGTT (if FPG 5.5-6.9 mmol/L). In this population the protocol had a sensitivity of 80%, a specificity of 80% and a PPV of 14% for detecting undiagnosed type 2 diabetes. Increasing the FPG cut-point from 5.6 mmol/L to 6.1 mmol/L or using HbA1c instead of FPG to determine the need for an OGTT in at-risk individuals reduced sensitivity, increased specificity and PPV, and reduced the amount requiring an OGTT.

POC testing may increase compliance with screening programs. A study of a large cohort of 7,736 adults aged 50-75 years showed that a stepwise screening procedure, using a combined symptom risk questionnaire and a fasting capillary glucose measurement followed by diagnostic testing using an OGTT, is an acceptable and practical method of screening for type 2 diabetes (Spijkerman et al, 2002a). A high response rate was achieved, with a non-response rate of 11% for the diagnostic test (OGTT). This is in contrast to some programs, which use a diagnostic OGTT in those with a screening FPG ≥ 6.1 mmol/L, with a reported non-response rate for the screening FPG test of 65% (Lawrence et al, 2001).

- **Non-fasting glucose measurement can also be used to screen for undiagnosed type 2 diabetes *(Evidence Level III-2)***

Measurement of a fasting sample may be considered impractical under certain circumstances, e.g. a high chance that the individual will not comply with returning for an FPG measurement. Under such circumstances measurement of random blood glucose (RBG) may be performed. However, follow-up testing is required for a result ≥ 5.5 mmol/L. Using cut-point values above this resulted in substantially less people with undiagnosed diabetes being detected – 15% fewer with a cut-point of ≥ 6.0 mmol/L, 29% less with a cut-point of ≥ 6.5 mmol/L and 41% less with a cut-point of ≥ 7.0 mmol/L (Welborn et al, 1997).

It has been reported that in studies that excluded subjects with known diabetes, random and postprandial glucose tests performed better than fasting tests (Engelgau et al, 2000). This occurs since those with undiagnosed diabetes are reportedly more likely to meet the 2-h OGTT diagnostic criterion than the fasting criterion (Engelgau et al, 1995).

The performance of ADA recommended screening for detecting undiagnosed diabetes was evaluated in 1,471 adults aged 20 years and over (Rolka et al, 2001). The screening tests included the ADA risk questionnaire and a random CBG test (cut-points of 7.8 mmol/L and 6.7 mmol/L) using a portable meter. Each screening test was evaluated against multiple diagnostic criteria for diabetes (FSG ≥ 7.0 mmol/L, 2-h SG ≥ 11.1 mmol/L, or either). The questionnaire produced a sensitivity of 72-78% and a specificity of 50-51% across the 3 diagnostic criteria. The sensitivity and specificity for CBG ≥ 7.8 mmol/L was 56-65% and 95-96%, and for CBG ≥ 6.7 mmol/L was 75-84% and 86-90%, respectively. When the

questionnaire and a random CBG of ≥ 6.7 mmol/L were combined the sensitivity was 58-63% and specificity was 92-94%. Results indicate that lowering the CBG cut-point from 7.8 to 6.7 mmol/L may improve sensitivity whilst maintaining adequate specificity.

A recent study examined POC testing of capillary glucose in the exclusion and diagnosis of diabetes in 200 participants aged 16-65 years in remote Australia (Marley et al, 2007). The concordance between POC capillary measurements and laboratory venous glucose measurement was high ($\rho = 0.93$), with a mean difference between the two of 0.48 mmol/L. The most clinically appropriate POC thresholds values for excluding or diagnosing diabetes were determined using ROC curves. The POC capillary value for excluding diabetes was < 5.5 mmol/L (equivalent to a venous value of < 5.5 mmol/L) which had a sensitivity of 53%, specificity of 94% and PPV of 89%, and for diagnosing diabetes was ≥ 12.2 mmol/L (equivalent to a venous value of ≥ 11.1 mmol/L) which had a sensitivity of 83%, specificity of 99% and PPV of 95%. Although the glucose meters used and the degree of fasting slightly altered the results, this had no significant impact on the diagnostic utility of POC glucose measurement in this setting. The authors highlighted the difficulty of relying solely on laboratory results for the diagnosis of diabetes in remote areas, as some samples took 7 days to reach the laboratory, while on many occasions the appropriate sample did not arrive at the laboratory at all. POC capillary glucose testing is sufficiently accurate to be a useful component in the diagnosis of diabetes in remote communities throughout Australia.

2.2.2 Measurement of glycated haemoglobin (HbA1c)

- **Measurement of glycated haemoglobin (HbA1c) is another option for screening for undiagnosed diabetes but the appropriate cut-point is uncertain *(Evidence Level III-2)***

HbA1c reflects average plasma glucose over the previous 2-3 months in a single measure. HbA1c is attractive since it can be performed at any time of the day and does not require any preparation of the subject (e.g. fasting), has low intra-individual variability, and directly relates to treatment targets. These properties have made it the gold standard for assessing glycaemic control in people with diabetes and have resulted in its consideration as an option for assessing glucose tolerance in people without diagnosed diabetes.

However there are aspects of its measurement which are problematic. Standardisation to an international standard (Diabetes Control and Complications Trial [DCCT]-alignment) is essential to ensure comparability between laboratories. Furthermore, the HbA1c result is influenced by several factors including anaemia, abnormalities of haemoglobin, pregnancy and uraemia. Some of these factors may be a bigger problem in under-resourced countries due to a higher prevalence of anaemia and of haemoglobinopathies. The precise effect of these factors on the HbA1c result varies with the laboratory method used (Goldstein et al, 2004).

HbA1c, an indirect measure of average glycaemia, has been suggested and evaluated as a potential test for screening and diagnosing type 2 diabetes. With respect to screening it has been compared with FPG as part of a screening protocol. In relation to the diagnosis of diabetes, it has been proposed in the context of having a simple and single test which could replace the OGTT. This section reviews HbA1c as an option for screening for undiagnosed diabetes.

Bennett and colleagues (2007) performed a systematic review on the use of HbA1c as a screening tool for detecting type 2 diabetes. Overall, based on results from the 9 included studies, HbA1c has slightly lower sensitivity but higher specificity than FPG in detecting type 2 diabetes. In those studies using an HbA1c cut-point of ≥ 6.1% the sensitivity ranged from 78-81% and specificity from 79-84%. At an FPG cut-point of ≥ 6.1 mmol/L the sensitivity ranged from 48-64% and specificity from 94-98%. The authors concluded that HbA1c and FPG are equally effective as screening tools for type 2 diabetes. However, neither HbA1c nor FPG were effective in detecting IGT, not surprisingly, since neither test involves a glucose challenge. The cut-point for HbA1c is recommended to be either ≥ 6.1% or ≥ 6.2%, as these were found to be the optimum cut-points in most studies. Population specific cut-points should also be considered, since optimum cut-points vary with ethnicity, age, gender and the population prevalence of diabetes.

The use of HbA1c as a screening test for undiagnosed diabetes in high risk ethnic groups in New Zealand (predominantly Maori, Pacific Island people and Asians) was evaluated in a cohort of adults over 20 years of age (Ellison et al, 2005). An HbA1c level of ≥ 6.1% had a sensitivity of 94% and a specificity of 77% in detecting subjects with an FPG of ≥ 7.0 mmol/L, and a sensitivity of 90% and specificity of 73% for detecting subjects with a 2 hour post-glucose load of ≥ 11.1 mmol/L. The authors concluded that HbA1c was an appropriate test for opportunistic screening for type 2 diabetes, provided it was followed by a diagnostic OGTT.

The usefulness of HbA1c to screen for undiagnosed diabetes was compared to that of FPG in a population of 1,904 Japanese adults aged 35-89 years (Nakagami et al, 2007). In the Japanese National Diabetes Survey an HbA1c cut-point of 5.6% had a sensitivity of 57%, specificity of 95%, PPV of 44%, and NPV of 97%. Meanwhile an FPG cut-point of 6.1 mmol/L (IFG level) had a sensitivity of 64% and a specificity of 95%. The area under the ROC curve was similar for HbA1c (0.86, [95%CI 0.81-0.90]) and FPG (0.90, [0.87-0.94]). It was concluded that the measurement of HbA1c alone, with a cut-point of 5.6%, may be reasonable to screen for undiagnosed diabetes and predict vascular complications in Japan.

Martin and colleagues (2005) performed a study to assess the accuracy of POC measurements of HbA1c levels in 152 residents of a remote Aboriginal community aged 11-76 years with a high prevalence of type 2 diabetes. Mean (7.06%) and median (6.0%) values for POC capillary HbA1c and laboratory HbA1c were identical. The correlation coefficient for POC and laboratory results was 0.99 for HbA1c. The mean difference in results between POC testing and laboratory measurements was < 0.01% for HbA1c. The authors suggest that POC capillary HbA1c testing is an accurate and practical method of monitoring diabetes in a remote setting.

A report from a recent panel of the American Association of Clinical Endocrinologists (AACE) found several factors supporting the use of HbA1c for screening for diabetes (Saudek et al, 2008). The panel made several recommendations including that screening standards that prompt further testing and closer follow-up should be established, including HbA1c ≥ 6.0%.

To determine an optimal screening HbA1c level that should prompt further tests to diagnose type 2 diabetes, 4,935 subjects (aged 20+ years) from the 1999-2004 NHANES population were screened using HbA1c and given FPG tests to diagnose type 2 diabetes (Buell et al, 2007). Overall, 3.5% had undiagnosed type 2 diabetes (FPG ≥ 7.0 mmol/L). A screening

HbA1c level of 5.8% produced the highest combination of sensitivity (86%) and specificity (92%).

The use of HbA1c at various cut-points in screening for type 2 diabetes has been evaluated in 891 male Japanese subjects aged 26-80 years with known diabetes (Shirasaya et al, 1999). The prevalence of undiagnosed type 2 diabetes in this population was 4.2% according to 1980 WHO criteria. The sensitivity and specificity for detecting type 2 diabetes was 87 and 58%, respectively, at an HbA1c cut-point of 5.3%; 84 and 79%, respectively, at an HbA1c cut-point of 5.6%; and 76 and 91%, respectively, at an HbA1c cut-point of 5.9%.

2.3 Diagnostic testing

- **The 2006 WHO/IDF diagnostic criteria should be used to diagnose type 2 diabetes *(Evidence Level II)***

The WHO/IDF 2006 criteria are the international standard for diagnosing diabetes. As shown in Table 2, in an asymptomatic individual the diagnosis is based on measurement of FPG, with or without oral glucose tolerance testing (WHO, 2006).

2.3.1 The oral glucose tolerance test (OGTT)

The OGTT continues to be recommended by the WHO (2006) for the diagnosis of diabetes. Although ADA acknowledges the OGTT as a valid way to diagnose diabetes, the use of the test for diagnostic purposes in clinical practice is discouraged in favour of FPG for several reasons, including inconvenience, greater cost and less reproducibility (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Some of this variation can be minimised with attention to dietary preparation and taking care to collect the 2-h sample within 5 min of 120 min (Kaneko et al, 1998).

As reviewed in the WHO 2006 report, many studies have reported that FPG and 2-h post-glucose plasma glucose do not identify the same people as having diabetes. In the DECODE study (DECODE, 1998), of the 1,517 people with newly diagnosed diabetes, 40% met only the FPG criterion, 31% met only the 2-h plasma glucose criterion and 28% met both criteria. Therefore using only FPG will fail to diagnose approximately 30% of people with diabetes. Data from the NHANES III study cited in the 1997 ADA report show similar findings for newly diagnosed diabetes (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). This discrepancy is more obvious in an older population. Barrett-Connor and Ferrara (1998) reported that 70% of women and 48% of men aged 50-89 years had new diabetes diagnosed solely by an elevated 2-h plasma glucose. Does this matter and are there any differences in outcomes for people diagnosed on the basis of the fasting or 2-h plasma glucose or both? Many studies have documented increased rates of mortality in people with diabetes. Studies which have compared these rates in relation to diabetes diagnosed on the basis of fasting or 2-h plasma glucose have consistently shown worse outcomes in those diagnosed on the basis of the 2-h plasma glucose result.

One reason for this difference is that an FPG of 7.0 mmol/L may not be equivalent to a 2-h plasma glucose of 11.1 mmol/L, and there is a view that the current FPG level for diagnosing diabetes may be too high (Unwin et al, 2002). For example, the DECODE Study Group (DECODE, 1999b) reported that in a wide range of European populations, the FPG which predicts a 2-hour value of 11.1 mmol/L was 6.4 mmol/L in men and 5.8 mmol/L in women.

Another concern with the OGTT has been its reproducibility. This has been examined using duplicate OGTTs with a median interval of 13 days (range 1-87 days) in a cohort of 52 subjects aged 22-62 years (Schousboe et al, 2002). It was reported that the intra-individual coefficient of variation was considerably lower for FBG (7%) than for the OGTT (15%).

This issue was also examined in the Hoorn study (Mooy et al, 1996). Repeat testing with an OGTT was performed over a 2 to 6 week period and the diagnostic categories compared in 555 people without known diabetes. The reproducibility was 91% for normal glucose tolerance, 48% for IGT and 78% for diabetes. Most of the movement was in the IGT category, in which prevalence decreased from 11.5% on the first test to 5.6% on the second test, with most people moving from IGT to normal. Only one person moved from diabetes to normal glucose tolerance and that occurred between the first and second tests.

Ko et al. (1998) examined the reproducibility of the OGTT in 212 Chinese people 6 weeks apart. The overall reproducibility was 66%, with the reproducibility of normal glucose tolerance being 95%, IGT 44% and diabetes 59%. Again, most of the change related to movement in the IGT category. However, 4 subjects changed to normal from diabetes between the first and second test.

An earlier study by Eriksson and Lingarde (1990) administered a $30g/m^2$ OGTT on 2 occasions within one month to 889 men whose initial FBG was above 6.5 mmol/L. Test reproducibility was 88% for normal glucose tolerance, 31% for IGT and 45% for diabetes. Thirteen men moved from diabetes to normal and 7 from normal to diabetes between the first and second tests.

Reversion from diabetic to non-diabetic status is a recognised phenomenon. In the San Antonio Heart Study the reversion rate from diabetes, diagnosed either by the WHO 1980 criteria (which required both an elevated FPG $\geq$ 7.8 mmol/L and elevated 2-hour plasma glucose of $\geq$ 11.1 mmol/L) or the ADA 1997 criteria, to normal glucose tolerance was approximately 12% over an 8 year period. The reason for this phenomenon is unknown but is more likely to occur with lower baseline plasma glucose levels and may be related to lifestyle changes (Burke et al, 1998).

Most studies which have looked at OGTT reproducibility have noted that fewer individuals have an abnormality of glucose tolerance on the second test. Mooy et al. (1996) suggest that this might be related to stress because heart rate was lower on the second test. Another possibility is self imposed lifestyle changes between tests. However biological variation is a significant contributor. Cummings and Fraser (1988) studied 14 healthy people aged 23-48 years who each had 10 OGTTs repeated at approximately 1 week intervals. The coefficient of variation of the tests was 11%, but no individual moved from normal into either the IGT or diabetes category.

Care should be taken to perform the OGTT under standardised conditions and to assure the quality of the procedure. Factors which can interfere with the test (e.g. smoking) must be avoided.

Studies to date have all assessed OGTT reproducibility using the WHO 1985 criteria and the effect, if any, of the new diagnostic criteria of the lower FPG value combined with the 2-hour value, has not been studied. It may be that the more reproducible FPG will improve the performance of the OGTT. Also no studies have specifically examined the reproducibility of the OGTT in the diagnostically uncertain range of FPG between 5.5 and 6.9 mmol/L.

2.3.2 HbA1c as a diagnostic test for type 2 diabetes

WHO continue to recommend against HbA1c as a diagnostic criterion for diabetes on the basis of the global limitation of the assay and its lack of availability in most countries throughout the world (WHO, 2006). However this question is currently under review and it may be included as a diagnostic criterion option in the near future. This issue is outside the scope of this guideline.

2.3.3 The diagnosis of type 2 diabetes must be confirmed by re-testing

The diagnosis of diabetes has important consequences for the individual beyond health implications, e.g. insurance. Several studies cited in this review illustrate the biological variation in plasma glucose measurement. Although this is most obvious with the OGTT, FPG is also subject to intra-individual variation. It is therefore essential that the diagnosis of diabetes in an asymptomatic individual is confirmed by testing on separate days.

Repeat testing with an OGTT was performed over a 2 to 6 week period in 555 people without known diabetes participating in the Hoorn study. In total, 78% of people with screen-detected diabetes on a single test were confirmed to have diabetes on repeat testing (Mooy et al, 1996). In a Danish study performing population-based stepwise screening for undiagnosed diabetes in general practice, clinical diabetes was confirmed in 80% of subjects who had confirmatory diagnostic testing (Christensen et al, 2004).

The short-term variability in measures of FPG, 2-h glucose, and HbA1c was assessed in a population of 685 adults aged 20 years and over without diagnosed diabetes from the NHANES III survey data (Selvin et al, 2007). Two-hour glucose levels had substantially more variability (within-person coefficient of variation 16.7%) than either FPG (5.7%) or HbA1c (3.6%). The proportion of individuals with an FPG $\geq$ 7.0 mmol/L on the first test who also had a second FPG $\geq$ 7.0 mmol/L was 70%. Results were similar using the 2-h glucose cut-point of $\geq$ 11.1 mmol/L (72%). The prevalence of undiagnosed diabetes using a single FPG $\geq$ 7.0 mmol/L was 3.7%, which decreased by 24% to 2.8% when a second FPG test was used to confirm the diagnosis of diabetes. Likewise, the prevalence of undiagnosed diabetes decreased by 26%, from 9% using a single 2-h glucose test, to 6.7% when including a second test in the confirmation of diabetes.

A recent study has assessed the short-term (14 days on average) reproducibility of glucose measurements in the detection of IFG, IGT and diabetes in a high-risk screening setting using a population of 918 adults aged 40-69 years from the Danish part of the ADDITION study (Rasmussen et al, 2008). The intra-individual coefficients of variation were 7.9% for capillary FPG and 13.8% for capillary 2-h blood glucose. Twenty three per cent of individuals with IGT at the first test had diabetes at the second test, only 76% with diabetes at the first test had confirmed diabetes at the second test, and 30% with IFG and IGT had normal glucose tolerance at the second test.

Another study assessed the reproducibility (over a median of 3 months) of the diagnosis of diabetes in a cohort of 696 Caucasian women (aged 37.5 ± 5.6 years) with previous GDM (Albareda et al, 2004). Diabetes was confirmed in 60% of women overall, and in 56% of women without clinical symptoms. Excluding those diagnosed with clinical symptoms, the reproducibility at the second test was lower in those diagnosed by FPG alone (33%) or isolated post-challenge hyperglycaemia alone (40%), than in those diagnosed by both (100%).

3. Screening Protocol

- **A two-step screening procedure with risk assessment followed by glucose measurement in blood performs well in detecting undiagnosed type 2 diabetes *(Evidence Level III-2)***

In a cohort of 1,377 subjects aged 55-75 years from the IGLOO study, combining the Finnish Diabetes Risk Score (DRS) with an FPG measurement with a cut-point of 6.1 mmol/L produced a sensitivity, specificity and PPV of 99, 78, and 43%, respectively (Franciosi et al, 2005). Combining the DRS with an FPG measurement with a cut-point of 5.6 mmol/L produced a sensitivity, specificity and PPV of 100, 59, and 30%, respectively. Using the DRS as an initial screening strategy, followed by FPG in those at risk (DRS $\geq$ 9), and an OGTT in those with an FPG $\geq$ 5.6 mmol/L would detect 83% of cases of undiagnosed diabetes, requiring FPG measurements in 64% and an OGTT in 38%. In contrast, using FPG as an initial measurement in all subjects, followed by an OGTT in those with FPG $\geq$ 5.6 mmol/L would identify 92% of cases of undiagnosed diabetes, but would require 56% of the subjects to undergo an OGTT.

A recent study compared the use of a Danish diabetes stepwise screening protocol in the Inter99 population from Denmark (6,270 individuals aged 30-70 years) and the AusDiab population from Australia (7,079 individuals aged 30-70 years) (Glumer et al, 2005). The two populations had similar risk factor profiles, with slight differences in obesity, hypertension, use of antihypertensive medication, and family history of diabetes. The screening protocol consisted of initial screening using a Danish risk score followed by measurement of FPG. The overall performance of the screening protocol was similar between the Australian and Danish populations, particularly in terms of sensitivity (71 vs. 77%), PPV (6 vs. 9%), and area under the ROC curve (0.75 vs. 0.77). Slight but significant differences were found between the Australian and Danish populations in terms of specificity (70 vs. 66%, $p < 0.001$) and percentage of the population requiring further testing (31 vs. 36%, $p < 0.001$). When combining the risk score with FPG $\geq$ 6.1mmol/L, again specificity was marginally but significantly higher in the Australian population (95 vs. 93%, $p < 0.001$) and the percentage of the population requiring further testing was slightly but significantly lower (5 vs. 8%, $p < 0.001$). The authors concluded that when applied to an Australian population the Danish diabetes risk score performed well in terms of sensitivity, specificity and percentage of the population requiring further testing, and that it is suitable for detecting people at high-risk of undiagnosed diabetes.

The effectiveness of a stepwise screening strategy for detecting type 2 diabetes was studied in a Danish population of 60,926 subjects in general practice aged 40-69 years (Christensen et al, 2004). The stepwise screening program consisted of 4 steps: (1) mail-distributed self-administered risk-chart; (2) RBG and HbA1c screening tests; (3) FBG as diagnostic procedure 1 (if RBG $\geq$ 5.5 mmol/L or HbA1c $\geq$ 6.1%); (4) OGTT as diagnostic procedure 2 (if 5.6 $\leq$ FBG < 6.1 mmol/L or HbA1c $\geq$ 6.1%). Letters of invitation to participate, which included the risk-chart were sent to 60,926 individuals. Only 11,263 individuals with a high-risk risk score attended the initial screening consultation. The sensitivity of the stepwise screening strategy was calculated to be 67%. It was concluded that population-based stepwise screening for type 2 diabetes in general practice is not effective, despite reliable screening algorithms, largely due to a high dropout rate among high-risk individuals prior to entry into the program.

The Australian screening protocol for identifying undiagnosed type 2 diabetes was assessed in a population-based sample of 10,508 Australian adults (Colagiuri et al, 2004). The protocol involves an initial assessment of risk status, measurement of FPG in individuals at risk, and further testing with either FPG (if FPG ≥ 7.0 mmol/L) or OGTT (if FPG 5.5-6.9 mmol/L). In this population the protocol had a sensitivity of 80%, a specificity of 80% and a PPV of 14% for detecting undiagnosed type 2 diabetes. The protocol identified one new case of diabetes for every 32 people screened, with 43% of people screened requiring an FPG measurement, and 21% requiring an OGTT. Increasing the FPG cut-point from 5.6 mmol/L to 6.1 mmol/L or using HbA1c instead of FPG to determine the need for an OGTT in at-risk individuals reduced sensitivity, increased specificity and PPV, and reduced the amount requiring an OGTT. It was concluded that the Australian screening protocol performed well in detecting undiagnosed diabetes in an Australian population.

A recent Australian study compared the use of two different screening methods for undiagnosed type 2 diabetes in Australian community pharmacies (Krass et al, 2007). A cohort of 1,286 people were allocated to either the tick test only (TTO) or the sequential screening (SS) method, using the TTO followed by CBG testing. The proportion of the population diagnosed with type 2 diabetes was significantly higher with the SS method (1.7%) compared with the TTO method (0.2%) ($p = 0.008$).

A population of 6,917 middle-aged Swedish women were screened to evaluate a two-step screening procedure for detecting candidates for an OGTT (Lidfeldt et al, 2001). The two-step procedure included a questionnaire (past and present diseases, drug treatment, family history of diabetes) and physical examination (body weight, height, WHR, BP, RBG, and a non-fasting lipid profile), followed by a diagnostic OGTT if required. Those with a positive screening outcome underwent an OGTT (n = 2,923), as did a randomly selected control group who screened negative (n = 221). A significantly higher proportion of screen-positive women were diagnosed with diabetes (7.6%) compared with those from the screen-negative control group (1.8%) ($p < 0.001$). For predicting impaired glucose metabolism the two-step screening procedure had a sensitivity of 70%, specificity of 55%, PPV of 34% and NPV of 85%, based on findings in the control sample.

An Irish diabetes detection program has assessed the use of a 3 step screening tool in detecting undiagnosed diabetes, IFG and IGT in an opportunistic screening setting in 3,821 people aged 40 years and over attending their general practitioner (GP) (Smith et al, 2003). The 3 step screening procedure was initiated with a risk assessment questionnaire. Those without known diabetes with at least 2 or more risk factors and/or symptoms underwent a random venous plasma glucose (rVPG) test. Those with a rVPG level ≥ 5.5 mmol/L underwent an OGTT. An average of 93% of subjects returned the completed questionnaires. The prevalence of undiagnosed diabetes in this population was 2.2%. Had the OGTT not been included in the screening strategy, 14% of cases of undiagnosed diabetes would not have been detected. Raising the cut-point for the rVPG test indicating the need for OGTT to 6.5 and 7.5 mmol/L would have missed 32 and 48% of cases of undiagnosed diabetes, respectively.

A recent study has examined the use of survey and clinical data in the screening and diagnosis of type 2 diabetes (Chetty and Bruce Zellner, 2007). The study was performed in two separate populations: a cohort of 153,113 adults aged 24-83 from the Behavioural Risk Factor Surveillance System (BRFSS) and a cohort of 2,190 adults aged 40-74 from the NHANES III data. The survey included information on age, gender, race, BMI and education while the clinical test used was an FPG test. The reported area under the ROC curve was 0.68

using only survey data and 0.91 using an FPG test alone in detecting type 2 diabetes. When both the survey data and the FPG test were used in a stepwise fashion the area under the ROC curve increased to 0.93.

- **Blood testing without risk factor assessment also performs well but requires blood testing in all *(Evidence Level III-2)***

Several studies have consistently shown that laboratory blood testing performs better than a risk assessment in finding people with undiagnosed diabetes. However it should be noted that this involves all people having a blood test.

One study examined 1,899 European, Maori and Pacific Island individuals aged 40-79 years on how best to screen for undiagnosed diabetes and dysglycaemia (Simmons et al, 2005b). The area under the ROC curve for detecting undiagnosed diabetes was 0.92 (95%CI 0.89-0.95) for FBG, 0.86 (0.82-0.90) for HbA1c, 0.75 (0.69-0.80) for RBG, and 0.60 (0.55-0.66) for risk factor screening. A FPG cut-point of ≥ 5.5 mmol/L produced a sensitivity of 90%, a specificity of 63% and a PPV of 23% for detecting undiagnosed diabetes. An HbA1c cut-point of ≥ 5.3% produced a sensitivity of 83%, a specificity of 57% and a PPV of 20%. A RBG of ≥ 5.6 mmol/L resulted in sensitivity of 73%, specificity of 54% and PPV of 17%. The most effective screening test, FBG, detected 90% of new diabetes, while risk factor screening followed by FBG detected significantly fewer cases (88%), but required 9.2% less OGTTs. Risk factor screening prior to diagnostic blood testing may decrease the detection of undiagnosed diabetes compared with initial blood testing, but will decrease the number of individuals requiring blood testing.

The performance of the Finnish DRS was tested in 1,377 individuals aged 55-75 years presenting with one or more cardiovascular risk factors from the IGLOO study (Franciosi et al, 2005). The sensitivity, specificity, and PPV of the DRS in detecting undiagnosed type 2 diabetes was 86, 41, and 23% respectively. Using FPG alone with a cut-point of 6.1 mmol/L those values were 92, 68, and 38%, respectively, and for FPG with a cut-point of 5.6 mmol/L they were 97, 38, and 25% respectively.

The screening performance of random plasma glucose (RPG) was assessed in 1,139 individuals aged 18-84 years without known diabetes in the Screening for Impaired Glucose Tolerance Study (SIGT 5) (Ziemer et al, 2008). The performance of RPG was compared to age, BMI and race/ethnicity, which are screening prompts recommended by the ADA and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Subjects aged > 45 years and with a BMI > 25 kg/m^2 had a significant risk for type 2 diabetes (OR 3.44, [95%CI 1.80-6.56]). Both age > 45 years + BMI > 25 kg/m^2 and age > 45 years + BMI > 25 kg/m^2 + black race provided significant detection of diabetes (both areas under the ROC curve 0.63). However, screening using RPG alone was better (area under the ROC curve 0.81). An RPG cut-point of 7.0 mmol/L produced a sensitivity of 41%, a specificity of 93%, and a PPV of 23% for detecting type 2 diabetes.

Random capillary glucose (RCG) testing using a reflectance meter has also been studied, although there are few well designed studies which have properly addressed this question. Two studies have examined this and performed an OGTT in the whole population irrespective of the RCG result. Qiao et al. (1995) studied 1,008 people and using a cutoff level for RCG of 5.8 mmol/L achieved a sensitivity of 79% in men but only 40% in women, while specificity was 86% and 84%, respectively, for men and women. The authors

concluded that RCG is too insensitive to use for routine screening for diabetes in a general population, particularly in populations with a known low prevalence of diabetes.

Engelgau et al. (1995) performed a similar study in 828 people aged 20 years and over and found that RCG as a screening test for diabetes was significantly affected by age and the postprandial period. Compared with the OGTT, an RCG of 5.6 mmol/L achieved a sensitivity ranging from 68-74% and specificity ranging from 66-77% depending on age. The authors concluded that it might be possible to use RCG measurements for screening provided that age-specific cutoff values were also used.

4. Setting for case detection and diagnosis

- **General practice is the usual setting for case detection for undiagnosed type 2 diabetes *(Evidence Level IV)***

Primary care is generally considered the most appropriate setting for detecting new cases of previously undiagnosed diabetes. However, there is little information on current practice in relation to case detection of undiagnosed diabetes. One study assessed activities relating to early detection of type 2 diabetes in primary care in one locality in the UK (John et al, 2006). Telephone questionnaires were conducted to obtain information from 36 practices in a region of South Wales. This was combined with an analysis of biochemistry laboratory records of requests for blood glucose and OGTT tests over the previous year. Of the 36 practices, 25% had no current system for identifying those at risk of type 2 diabetes, 42% performed opportunistic screening, 8% issued invitations to be tested, while 25% did both. FBG was used as a diagnostic test in 56% of practices, while FBG or OGTT was used in 44%. HbA1c was not used by any practice as a diagnostic test. Those with a negative test result were followed up annually in 63% of practices, while the remaining practices had no formal arrangements for repeat testing. Those practices using both opportunistic screening and invitations for testing requested a significantly higher mean number of glucose tests than practices with no active identification (mean number of glucose tests requested per 100 population = 205 vs. 149), however, opportunistic screening alone was not significantly higher than no active identification (159 vs. 149).

Targeted screening of high-risk individuals identified using computerised searches of medical practice databases for age and BMI criteria, followed by measuring FPG, identified a substantial number of new cases of type 2 diabetes (Greaves et al, 2004). The NNS to detect a case of hyperglycaemia (type 2 diabetes or IFG) was between 15 and 28. The number needed to test to detect a case of type 2 diabetes was between 18 and 38. The authors concluded that this type of screening was feasible in general practice in the UK.

One study has examined the association between how well GPs know their patients and a diagnosis of type 2 diabetes (Drivsholm and de Fine Olivarius, 2006). In a cohort of 1,136 adults aged $\geq$ 40 years with newly diagnosed diabetes, GPs indicated that they knew 48% of the patients very well, 39% of the patients fairly well, and 14% of the patients not well. The results indicate that the glycaemic levels among patients whom the GP did not know well were significantly higher than those the GPs knew very well or fairly well, with regards to HbA1c ($p < 0.01$) and FPG ($p < 0.05$). The authors tentatively suggest that this reflects a late diagnosis of diabetes in patients the GPs do not know well, and that GPs should be especially aware of the possibility of undiagnosed type 2 diabetes in these patients.

An alternate setting is pharmacy. The feasibility of this approach was tested in 530 community pharmacies in Switzerland, screening a total of 93,258 people (mean age 61 years) (Hersberger et al, 2006). The sequential screening procedure, involving risk assessment, CBG measurement and targeted counselling, detected approximately 7% of participants suspected of having type 2 diabetes and 72% with at least 2 risk factors. Of all those screened, 6.4% were referred to a physician and 74% received targeted advice in relation to physical activity and nutrition based on their specific risk profile.

Another option is initial screening in a pharmacy setting followed by referral to a physician. A recent Australian study compared the use of two different screening methods for undiagnosed type 2 diabetes in Australian community pharmacies (Krass et al, 2007). A cohort of 1,286 people were allocated to either the tick test only (TTO) or the sequential screening (SS) method. Both methods involved the same initial risk assessment. The subjects with one or more risk factors in the TTO group were referred to their GP. In the SS method, subjects presenting with risk factors for diabetes were offered a CBG test, and those deemed at-risk referred to a GP. The proportion of the population diagnosed with type 2 diabetes was significantly higher with the SS method (1.7%) compared with the TTO method (0.2%) ($p = 0.008$).

Pharmacists in the US screened 888 participants with one or more risk factors for diabetes in pharmacies and non-health care settings (Snella et al, 2006). A total of 794 participants were deemed at risk using a risk factor tool and received further screening, of which 81% were referred to physicians for follow-up. Screening in the pharmacy setting resulted in significantly higher follow-up rates (45%) than screening conducted in a non-health care setting (35%) ($p = 0.02$).

The web also provides a setting for screening for diabetes. One example is the ADA Diabetes Personal Health Decisions Tool, which allows at-risk individuals to enter personal information including age, sex, height, weight, race, family history, medications, and a variety of blood values into an interactive web-based program that produces a risk profile (ADA, 2004a). The tool can be freely accessed on the ADA website and provides information about how individuals can modify their health parameters to improve their risk status.

In order to assess adherence to current ADA recommendations for type 2 diabetes screening, Ealovega and colleagues (2004) performed a retrospective study of opportunistic screening in routine clinical practice. Of the 8,286 non-diabetic subjects aged ≥ 45 years belonging to a health maintenance organisation in the US, 69% had been screened for type 2 diabetes in the previous 3 years. Screening frequency increased with age and was higher in subjects with one or more primary care visits. Women were more likely to be screened than men, and subjects with at least one risk factor for type 2 diabetes were more likely to be screened than those with none. RPG was the most commonly used screening test (95%). The overall yield of opportunistic screening was very low (0.6%) and only 38% of those with abnormal results received appropriate follow-up.

- **A number of aids facilitate screening for undiagnosed type 2 diabetes** ***(Evidence Level II)***

A recent study determined the best way to trigger diabetes screening in an opportunistic fashion when a patient attends a family physician for some other reason in a New Zealand population (Kenealy et al, 2005). It was demonstrated that patient reminders (OR 1.72,

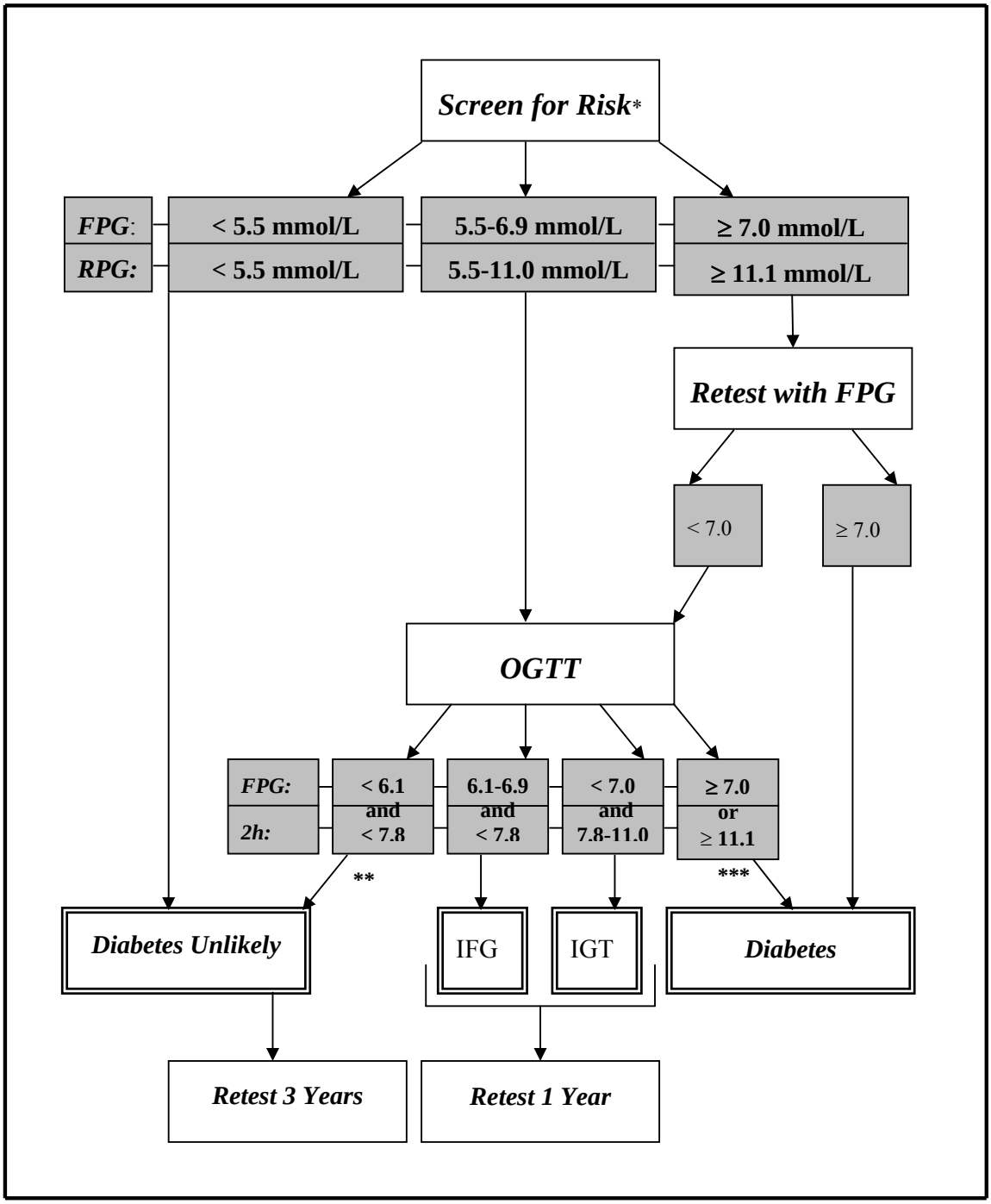
[95%CI 1.21-2.43]) and computer reminders (OR 2.55, [1.68-3.88]) to screen people for type 2 diabetes when visiting a family physician were both more effective than usual care. Computer reminders proved to be more effective than patient reminders (OR 1.49, [1.07-2.07]). The findings also indicate that patients were more likely to receive screening if they visited the family physician repeatedly, were regular patients of the practice, and if their family physician had a higher screening rate prior to the study.

A simple nurse-based prompt is effective in increasing screening and preventive services for individuals at risk for type 2 diabetes (Boltri et al, 2007a). In a population of 1,176 adults recruited from 10 primary care practices, according to a multivariate regression model a nurse-based prompt significantly increased the likelihood of receiving fasting glucose testing (OR 9.3, [95%CI 3.6-24.0]). In addition, 71% of those patients who received the nurse-based prompt had a notation of high risk for diabetes on their chart, whereas only 29% of those who did not receive the prompt had such a notation.

Similar research has found that a patient-based risk assessment prompt used in an outpatient setting may represent a simple, cost-effective method for identifying undiagnosed type 2 diabetes (Boltri et al, 2007b). In this study, a total of 511 adults completed an ADA risk assessment questionnaire, with only the intervention group (256 subjects) presenting their completed questionnaires to their physician, while those in the control group (255 subjects) gave their completed questionnaires to the research assistant. The patient-based risk assessment prompt did not significantly increase fasting glucose screening rates in the intervention group (OR 1.3, [95%CI 0.9-1.8], $p = 0.217$), possibly since those in the control group may have initiated conversations about their diabetes risk with their physician after just completing the questionnaire, thus potentially increasing screening rates among control subjects. However, according to univariate analysis, the odds of diagnosis of diabetes was significantly higher in the intervention group (OR 5.2, [1.1-24.3], $p = 0.036$), and approached significance using a multivariate analysis adjusting for other risk factors (OR 4.6, [0.9-23.2], $p = 0.063$).

A recent study assessed the value of using a GP's electronic medical record (EMR) to identify individuals at risk for undiagnosed type 2 diabetes, and to determine the feasibility of using such information to initiate screening procedures (Klein Woolthuis et al, 2007b). Eleven Dutch general practices (25 GPs) participated in the study, with an EMR-derived risk assessment performed in a total of 13,581 people aged 45-75 years without known diabetes. An EMR-based risk (hypertension, CVD, lipid metabolism disorders and/or obesity) was found in 28%. Of people without an EMR-based risk, additional risk assessment during regular consultation revealed that greater than one risk factor (mainly family history: 51% and obesity: 59%) was found in 51%. All people with an EMR-based risk and those deemed at-risk following additional risk assessment were invited for an FPG measurement, with 90% attending. It was found that 5.9% of patients with an EMR-based risk had an FPG result exceeding the cut-point for diabetes. It was concluded that in combination with additional risk assessment during consultation, the GP's EMR was a valuable tool in identifying individuals at risk of undiagnosed type 2 diabetes.

Figure 1: Testing for and diagnosing type 2 diabetes



FPG – fasting plasma glucose RPG – random plasma glucose OGTT – oral glucose tolerance test
IFG – impaired fasting glucose IGT – impaired glucose tolerance

* using AUSDRISK except in specific high risk categories

** diagnosis must be confirmed by further testing if initial FPG 5.5-6.9 mmol/L or RPG 5.5-11.0 mmol/L.

*** people with an initial plasma glucose consistent with a diagnosis of diabetes or IGT/IFG which is not confirmed on subsequent testing should be retested after 1 year and subsequent testing interval determined according to the 1 year result

Evidence Tables: Section 2

How to Detect Type 2 Diabetes

Case detection approach

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Janssen et al., 2007 (The Netherlands)	IV	Cross-sectional	High	Low[+]	Medium
Newman et al., 1994 (US)	IV	Cross-sectional	Medium	Medium[+]	Medium
Tabaei et al., 2003 (US)	IV	Cross-sectional	Medium	Low[+]	Medium

[+] Opportunistic screening is the preferred method for case detection
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Identifiable risk factors for undiagnosed type 2 diabetes

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Baan et al., 1999a (The Netherlands)	III-2	Diagnostic accuracy	Medium	Medium^{+}	High
Baan et al., 1999b (The Netherlands)	IV	Cross-sectional	High	High^{+}	High
Bartnik et al., 2004b (Europe)	IV	Cross-sectional	Medium	High^{+}	High
Bellantuono et al., 2004 (International)	I	Systematic review	Medium	Medium^{+}	High
Beziaud et al., 2004 (France)	IV	Cross-sectional	High	Medium^{+}	High
Boas-Soja et al., 2006 (Denmark)	IV	Cross-sectional	Medium	High^{+}	High
Bog-Hansen et al., 1998 (Sweden)	IV	Cross-sectional	High	High^{+}	High
Braun et al., 1996 (Australian Aboriginal)	II	Prospective cohort	Medium	High^{+}	High
Brimblecombe et al., 2006 (Australian Aboriginal)	IV	Cross-sectional	High	High^{+}	High
Carey et al., 1997 (US)	II	Prospective cohort	High	High^{+}	High
Chan et al., 1994 (US)	II	Prospective cohort	High	High^{+}	High
Citrome et al., 2007 (International)	I	Systematic review	High	Medium^{+}	High
Colditz et al., 1990 (US)	II	Prospective cohort	High	High^{+}	High
Colditz et al., 1995 (US)	II	Prospective cohort	High	High^{+}	High
Costa et al., 1998 (Spain)	IV	Cross-sectional	High	High^{+}	High
Cunningham et al., 2008 (Australia)	IV	Cross-sectional	High	High^{+}	High
Dalton et al., 2003 (Australia)	IV	Cross-sectional	High	High^{+}	High
De Hert et al., 2006 (Belgium)	IV	Cross-sectional	Medium	Low^{+}	High
Dunstan et al., 2002 (Australia)	IV	Cross-sectional	High	High^{+}	High
Dunstan et al., 2004 (Australia)	IV	Cross-sectional	High	Medium^{+}	High
Ehrmann et al., 1996 (US)	II	Prospective cohort	High	High^{+}	High
Ehrmann et al., 1999 (US)	II	Prospective cohort	Medium	High^{+}	High
Ford et al., 1997 (US)	II	Prospective cohort	High	High^{+}	High

Identifiable risk factors for undiagnosed type 2 diabetes (cont.)

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Fulton-Kehoe et al., 2001 (US)	III-3	Case-control	Medium	Medium^{+}	Medium
Gagnon and Baillargeon, 2007 (Canada)	III-2	Diagnostic accuracy	Medium	High^{+}	High
Gambineri et al., 2004 (Italy)	IV	Cross-sectional	Medium	Low^{+}	Medium
Gray et al., 2004 (UK)	II	Prospective cohort	High	High^{+}	High
Guest et al., 1992 (Australia: Aboriginal, European descent)	IV	Cross-sectional	Medium	High^{+}	High
Hariri et al., 2006a (US)	IV	Cross-sectional	High	High^{+}	High
Harris et al., 1987 (US)	IV	Cross-sectional	High	High^{+}	High
Hashimoto et al., 2005 (Japan)	IV	Cross-sectional	Medium	High^{+}	High
Hilding et al., 2006 (Sweden)	IV	Cross-sectional	High	Medium^{+}	Medium
Holbrook et al., 1990 (US)	II	Prospective cohort	High	High^{+}	High
Hoy et al., 2007 (Australian Aboriginal)	IV	Cross-sectional	High	High^{+}	High
Jeon et al., 2007 (International)	I	Systematic review	High	Medium^{+}	High
Jia et al., 2002 (China)	IV	Cross-sectional	High	High^{+}	Medium
Kim et al., 2002 (International)	I	Systematic review	Medium	High^{+}	High
Koopman et al., 2005 (US)	III-2	Retrospective cohort	Medium	Low^{+}	High
Lauruschkat et al., 2005 (German)	IV	Cross-sectional	High	High^{+}	High
Legro et al., 1999 (US)	IV	Cross-sectional	High	High^{+}	High
Matz et al., 2006 (Austria)	IV	Cross-sectional	High	High^{+}	High
Meslier et al., 2003 (France)	IV	Cross-sectional	Medium	High^{+}	Medium
Mooy et al., 1995 (The Netherlands)	IV	Cross-sectional	High	High^{+}	High
Norhammar et al., 2002 (Sweden)	II	Prospective cohort	High	High^{+}	High
Persson et al., 2000 (Sweden)	IV	Cross-sectional	High	Medium^{+}	Medium
Punjabi et al., 2004 (US)	IV	Cross-sectional	Medium	High^{+}	Medium
Qiao et al., 2003 (Asia)	IV	Cross-sectional	High	High^{+}	High

Identifiable risk factors for undiagnosed type 2 diabetes (cont.)

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Ramaswamy et al., 2006 (International)	I	Systematic review	Medium	Medium[+]	High
Rathmann et al., 2002 (German)	IV	Cross-sectional	Medium	High[+]	High
Reichmuth et al., 2005 (US)	II	Prospective cohort	Medium	Medium[+]	Medium
Resnick et al., 1998 (US)	II	Prospective cohort	Medium	High[+]	High
Ruige et al., 1997 (The Netherlands)	III-2	Diagnostic accuracy	High	High[+]	High
Simmons et al., 2007 (Australia)	III-2	Retrospective cohort	High	High[+]	High
Soma and Rheeder, 2006	III-2	Diagnostic accuracy	High	High[+]	High
Sugimori et al., 1998 (Japan)	II	Prospective cohort	High	Medium[+]	Low
Sundborn et al., 2007 (New Zealand: Maori, Pacific and European descent)	IV	Cross-sectional	High	High[+]	Medium
Taubert et al., 2003 (German)	IV	Cross-sectional	High	High[+]	High
Vancheri et al., 2005 (Italy)	II	Prospective cohort	High	High[+]	High
Voruganti et al., 2007 (Canada)	IV	Cross-sectional	Medium	High[+]	High
Wallander et al., 2008 (Sweden)	II	Prospective cohort	Medium	High[+]	High
Wang and Hoy, 2004 (Australian Aboriginal)	IV	Cross-sectional	Medium	Medium[+]	High
Willi et al., 2007 (International)	I	Systematic review	High	Medium[+]	Medium

[+] The majority of people with undiagnosed type 2 diabetes have readily identifiable risk factors
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Single or multiple risk factors

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Colagiuri et al., 2004 (Australia)	III-2	Diagnostic accuracy	High	High[+]	High
Dallo and Weller, 2003 (US)	IV	Cross-sectional	High	Low[+]	High
Featherstone and Goyder, 2007 (UK)	III-2	Diagnostic accuracy	Medium	Medium[+]	High
Hariri et al., 2006a (US)	IV	Cross-sectional	High	High[+]	High
Hariri et al., 2006b (US)	IV	Cross-sectional	High	High[+]	High
Lawrence et al., 2001 (UK)	IV	Cross-sectional	Medium	Low[+]	Medium
Leiter et al., 2001 (Canada)	IV	Cross-sectional	Medium	High[+]	High
Rathmann et al., 2003 (Germany)	IV	Cross-sectional	High	High[+]	Medium

[+] Single or multiple risk factors can be used to screen for type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Risk scores

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Baan et al., 1999a (The Netherlands)	III-2	Diagnostic accuracy	Medium	Low[+]	High
Barriga et al., 1996 (US)	III-2	Diagnostic accuracy	Medium	Low[+]	Medium
Franciosi et al., 2005 (Italy)	III-2	Diagnostic accuracy	High	Medium[+]	High
Glumer et al., 2004a (Denmark)	III-2	Diagnostic accuracy	High	High[+]	High
Glumer et al., 2006 (DETECT-2)	III-2	Diagnostic accuracy	High	Low[+]	High
Griffin et al., 2000 (UK)	III-2	Diagnostic accuracy	High	High[+]	High
Heikes et al., 2008 (US)	III-2	Diagnostic accuracy	Medium	High[+]	High
Heldgaard and Griffin, 2006 (Denmark)	III-2	Diagnostic accuracy	High	High[+]	High
Herman et al., 1995 (US)	III-2	Diagnostic accuracy	Medium	Medium[+]	High
Ramachandran et al., 2005 (India, UK – South Asian)	III-2	Diagnostic accuracy	High	Low[+]	Medium
Rathmann et al., 2005 (Germany)	III-2	Diagnostic accuracy	High	Low[+]	High
Ruige et al., 1997 (The Netherlands)	III-2	Diagnostic accuracy	High	High[+]	High
Saaristo et al., 2005 (Finland)	III-2	Diagnostic accuracy	High	Medium[+]	High
Schulze et al., 2007 (Germany)	II	Prospective cohort	Medium	High[+]	Medium
Spijkerman et al., 2002b (The Netherlands)	III-2	Diagnostic accuracy	Medium	Low[+]	High
Tabaei and Herman, 2002 (Egypt, US)	III-2	Diagnostic accuracy	High	Low[+]	Medium

[+] Risk scores are commonly used to screen for type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Comparability of glucose measurement in blood

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Colagiuri et al., 2003b (Denmark)	IV	Cross-sectional	Medium	High[+]	High
Stahl et al., 2002 (Denmark)	IV	Cross-sectional	Medium	High[+]	High

[+] The comparability of glucose measurement in blood is affected by a number of factors
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Laboratory vs. Point of Care Testing

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Kruijshoop et al., 2004 (The Netherlands)	III-2	Diagnostic accuracy	High	High[+]	High
Puntmann et al., 2003 (Germany)	III-2	Diagnostic accuracy	High	High[+]	Medium

[+] Laboratory or point of care testing can be used to measure glucose in blood

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Fasting Glucose

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Appleton, 1999 (Australia)	III-2	Diagnostic accuracy	Medium	High^{-}	High
Blunt et al., 1991 (US)	III-2	Diagnostic accuracy	High	Medium^{+}	High
Bortheiry et al., 1994 (Brazil)	III-2	Diagnostic accuracy	Medium	High^{+}	Low
Cockram et al., 1992 (China)	III-2	Diagnostic accuracy	High	High^{+}	Medium
Colagiuri et al., 2004 (Australia)	III-2	Diagnostic accuracy	High	High^{+}	High
Costa et al., 1999 (Spain)	III-2	Diagnostic accuracy	Medium	High^{+}	High
Davies et al., 1993 (UK)	III-2	Diagnostic accuracy	Medium	Low^{+}	High
DECODE, 1999b (Europe)	III-2	Diagnostic accuracy	High	High^{+}	High
Diamond and Meerkin, 1999 (Australia)	III-2	Diagnostic accuracy	High	High^{-}	High
Larsson et al., 1995 (Sweden)	III-2	Diagnostic accuracy	High	High^{+}	High
Lawrence et al., 2001 (UK)	IV	Cross-sectional	Medium	Low^{-}	Medium
Levitan et al., 2004 (International)	I	Systematic review	Medium	High^{+}	High
Modan and Harris, 1994 (US, Israel)	III-2	Diagnostic accuracy	High	Low^{+}	High
Ramachandran et al., 1993 (India)	IV	Cross-sectional	High	High^{+}	Medium
Spijkerman et al., 2002a (The Netherlands)	IV	Cross-sectional	High	High^{+}	High
Wiener et al., 1995 (UK)	III-2	Diagnostic accuracy	High	Medium^{+}	High

$^{+}$ Fasting glucose measurement using a cut-point of 5.5mmol/L performs well as a screening test for undiagnosed type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Non-fasting Glucose

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Engelgau et al., 1995 (Egypt)	III-2	Diagnostic accuracy	High	High[+]	Low
Marley et al., 2007 (Australia)	III-2	Diagnostic accuracy	Medium	High[+]	High
Rolka et al., 2001 (US)	III-2	Diagnostic accuracy	High	Medium[+]	High
Welborn et al., 1997 (Australia)	III-2	Diagnostic accuracy	High	High[+]	High

[+] Non-fasting glucose measurement can be used to screen for undiagnosed type 2 diabetes
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Glycated Haemoglobin (HbA1c)

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Bennett et al., 2007	III-2	Systematic review	Medium	High[+]	High
Buell et al., 2007 (US)	III-2	Diagnostic accuracy	Medium	High[+]	High
Ellison et al., 2005 (New Zealand)	III-2	Diagnostic accuracy	Medium	High[+]	High
Martin et al., 2005 (Australia)	IV	Cross-sectional	Medium	High[+]	High
Nakagami et al., 2007 (Japan)	III-2	Diagnostic accuracy	High	High[+]	High
Shirasaya et al., 1999 (Japan)	III-2	Diagnostic accuracy	Medium	High[+]	High

[+] Measurement of glycated haemoglobin (HbA1c) is another option for screening for undiagnosed type 2 diabetes but the appropriate cut-point is uncertain

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Oral Glucose Tolerance Test

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Albareda et al., 2004	II	Prospective cohort	Medium	High[+]	Medium
Barrett-Connor and Ferrarra, 1998 (US)	II	Prospective cohort	High	High[+]	High
Burke et al., 1998 (US)	II	Prospective cohort	High	High[+]	High
Christensen et al., 2004 (Denmark)	III-2	Diagnostic accuracy	Medium	High[+]	Medium
Cummings and Fraser, 1988 (Scotland)	IV	Cross-sectional	Medium	Medium[+]	High
DECODE, 1998 (Europe)	III-2	Diagnostic accuracy	High	Medium[+]	High
DECODE, 1999b (Europe)	IV	Cross-sectional	High	Low[-]	High
Eriksson and Lingarde, 1990 (Sweden)	IV	Cross-sectional	High	High[+]	High
Ko et al., 1998 (Hong Kong)	IV	Cross-sectional	High	High[+]	Medium
Mooy et al., 1996 (The Netherlands)	IV	Cross-sectional	High	High[+]	High
Rasmussen et al., 2008 (Denmark)	IV	Cross-sectional	High	High[+]	High
Schousboe et al., 2002 (Denmark)	IV	Cross-sectional	Medium	High[+]	High
Selvin et al., 2007 (US)	IV	Cross-sectional	High	High[+]	High

[+] The 2006 WHO/IDF diagnostic criteria should be used to diagnose type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Stepwise Screening

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Chetty and Bruce Zellner, 2007 (US)	III-2	Diagnostic accuracy	Medium	High[+]	High
Christensen et al., 2004 (Denmark)	III-2	Diagnostic accuracy	Medium	Low[-]	Medium
Colagiuri et al., 2004 (Australia)	III-2	Diagnostic accuracy	High	High[+]	High
Franciosi et al., 2005 (Italy)	III-2	Diagnostic accuracy	High	Medium[+]	High
Glumer et al., 2005 (Denmark, Australia)	III-2	Diagnostic accuracy	High	High[+]	High
Krass et al., 2007 (Australia)	IV	Cross-sectional	Medium	High[+]	High
Lidfeldt et al., 2001 (Sweden)	III-2	Diagnostic accuracy	Medium	Low[+]	Medium
Smith et al., 2003 (Ireland)	IV	Cross-sectional	Medium	N/A	High

[+] A two-step screening procedure with risk assessment followed by glucose measurement in blood performs well in detecting undiagnosed type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Laboratory Blood Testing

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Engelgau et al., 1995 (Egypt)	III-2	Diagnostic accuracy	High	Medium[+]	Low
Franciosi et al., 2005 (Italy)	III-2	Diagnostic accuracy	High	Low[+]	High
Qiao et al., 1995 (Finland)	III-2	Diagnostic accuracy	High	Medium[+]	High
Simmons et al., 2005b (New Zealand)	III-2	Diagnostic accuracy	Medium	High[+]	High
Ziemer et al., 2008 (US)	III-2	Diagnostic accuracy	High	High[+]	High

[+] Blood testing without risk factor assessment performs well but requires blood testing in all

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Case Detection Setting

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Drivsholm and de Fine Olivarius, 2006 (Denmark)	IV	Cross-sectional	Medium	N/A	Low
Ealovega et al., 2004 (US)	III-2	Retrospective cohort	Medium	High[+]	Medium
Greaves et al., 2004 (UK)	IV	Cross-sectional	Medium	N/A	High
Hersberger et al., 2006 (Switzerland)	IV	Cross-sectional	Medium	Low[-]	Medium
John et al., 2006 (UK)	IV	Cross-sectional	Medium	High[+]	High
Krass et al., 2007 (Australia)	IV	Cross-sectional	Medium	Low[-]	High
Snella et al., 2006 (US)	II	Prospective cohort	Medium	Low[-]	High

[+] General practice is the usual setting for case detection for undiagnosed type 2 diabetes
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Aids to Implementation

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Boltri et al., 2007a (US)	II	RCT	High	High[+]	High
Boltri et al., 2007b (US)	II	RCT	High	Low[+]	High
Kenealy et al., 2005 (New Zealand)	II	RCT	High	High[+]	High
Klein Woolthuis et al., 2007b (Netherlands)	IV	Cross-sectional	High	N/A	Medium

[+] A number of aids facilitate screening for undiagnosed type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 3: How Often to Test

Question

How often should testing be performed?

Recommendation

Periodic re-testing for undiagnosed type 2 diabetes is recommended according to the following schedule (Grade C):

- Each year for people with impaired glucose tolerance or impaired fasting glucose
- Every 3 years for all other people

Practice Point

All people with identified risk factors for type 2 diabetes who have a negative screening test are at risk of cardiovascular disease and the future development of type 2 diabetes, and should be given appropriate advice on risk factor reduction

Evidence Statements

- Screening for undiagnosed type 2 diabetes every 3-5 years is supported by modelling and clinical studies
  Evidence Level II

- The annual rate of progression to type 2 diabetes from IGT and IFG is high and warrants annual testing for undiagnosed type 2 diabetes
  Evidence Level II

- There is a low risk of the development of retinopathy over a 4-5 year period following a negative screening test for type 2 diabetes
  Evidence Level II

Background – How Often to Test

Most people identified as being at risk through risk factor assessments remain at increased risk for the future development of type 2 diabetes. Many risk factors used to identify at risk people are not modifiable, although there are some exceptions such as obesity which can be modified by weight loss.

Blood glucose testing only excludes diabetes at a particular point in time. Therefore, those people who have risk factors but have a negative screening or diagnostic blood test require ongoing surveillance and testing for the future development of type 2 diabetes.

The purpose of this section is to determine a time period during which at risk people who were tested and in whom the result was negative, will have progressed to a point where they again have a significant chance of having undiagnosed type 2 diabetes. An additional consideration is the risk that an individual in whom diabetes has been excluded by testing, could have progressed to diabetes and developed diabetes related complications before the next testing time point.

Evidence – How Often to Test

- **Screening for undiagnosed type 2 diabetes every 3-5 years is supported by modelling and clinical studies *(Evidence Level II)***

A number of modelling studies have examined intervals for screening for undiagnosed diabetes.

A study was conducted to compare the yield and costs of simulated screening in the US population (45-74 years old; 72.6 million individuals) over 15 years with various screening intervals using RPG with cut-points of 5.5, 7.2 or 8.9 mmol/L or a multivariate logistic equation that incorporated RPG, postprandial time, age, sex, and BMI (Johnson et al, 2005). Using a screening interval of 3 years, the number of false negatives using an RPG of 5.5 mmol/L was 0.2 million, using an RPG of 7.2 mmol/L or the multivariate equation was 1.3 million, and using an RPG of 8.9 mmol/L was 2.8 million. The total cost associated with annual screening was more than double that of screening every 3 years at every RPG cut-point.

A cohort of 965 participants from the Ely Diabetes Project were used to examine the effect of varying the screening interval from 1 to 5 years on false positives and duration of undiagnosed type 2 diabetes (Park et al, 2000). Results indicate that the prevalence of diabetes in this population increases gradually with increasing screening interval, returning to the baseline level of 4.5% after approximately 5 years. Person years of exposure to undiagnosed diabetes increase approximately exponentially with screening interval, while the false positive percentage decreases approximately linearly. Comparing a 1 year to a 5 year screening interval, the duration of exposure to undiagnosed diabetes was 13 vs. 144 person years, respectively, while the false positive percentage was 48 vs. 28%, respectively. These results therefore illustrate a balance between the advantages and disadvantages of frequent screening. A more frequent screening interval is associated with reduced exposure to undiagnosed diabetes; however this is offset by an increased number of false positives.

Three publications from Taiwan have addressed this issue. In one study a Markov chain model was used to assess the efficacy of screening for type 2 diabetes in Taiwan (Kuo et al, 1999). There was no substantial difference in mortality rates from type 2 diabetes using annual, 2 yearly or 4 yearly screening intervals. A 4 yearly screening interval significantly reduced deaths from type 2 diabetes by 40% (95%CI 26-51%). The authors concluded that a 4 yearly screening interval would be most effective and feasible in Taiwan. Another study using a Markov model evaluated the effects of early detection of type 2 diabetes on the risk of death from the disease in a simulated population (Chang et al, 2000). Simulation of a 5 year screening interval versus no screening resulted in a 31% (95%CI 12-46%) reduction in the rate of deaths from type 2 diabetes, with a similar result for biennial screening (36%, [17-50%]). Furthermore, in accordance with a prevalence/incidence ratio of 10 years, it was suggested that a 5 year screening interval may be optimal for the early detection of type 2 diabetes in Taiwan. A third study performed a cost-effectiveness analysis of mass screening for type 2 diabetes using a computer simulation model in a hypothetical cohort of 30,000 adults aged over 30 years in Taiwan (Chen et al, 2001). Life years gained due to mass screening for type 2 diabetes was reported to be 0.08 for both 2 and 5 year screening intervals. Quality adjusted life years (QALYs) gained due to mass screening were 0.12 and 0.13 for 2 year and 5 year screening regimes, respectively. It was concluded based on these

results that mass screening for type 2 diabetes with a 5 year screening interval was cost-effective, particularly for younger subjects, in a country such as Taiwan where the prevalence of diabetes was 6-12%.

The performance of testing procedures is also affected by frequency of testing. This is supported by data from a cohort of 2,389 American Indians aged 45-74 years from the Strong Heart Study, of whom 1,644 were re-examined ~4 years later (Wang et al, 2002). An FPG cut-point of 7.0 mmol/L alone produced a low sensitivity for detecting newly diagnosed diabetes (63% at baseline and 45% at the second examination). The sensitivity of a 2h post-load glucose test in detecting diabetes was higher and more stable over time (75% at baseline and 81% at the second examination). It therefore appears that the efficacy of using FPG alone in screening for diabetes is affected by the time interval between successive screenings, and that a 4 year interval may be inappropriate in this population. Among those participants with 2h post-load glucose $\geq$ 11.1 mmol/L, 49% had FPG < 7.0 mmol/L, who would therefore not have been diagnosed by FPG alone.

Another study compared the cost and time to diagnosis of several simulated screening strategies for type 2 diabetes in women with a history of GDM (Kim et al, 2007). The methods used to screen for diabetes were FPG, OGTT, and HbA1c annually, every 2 years, and every 3 years over a period of 12 years. The OGTT resulted in the lowest costs per case detected, regardless of screening interval. Using a 3 yearly screening interval resulted in lower costs per case detected compared with more frequent testing, with minimal increments in the time spent with undiagnosed diabetes. It was concluded that a screening interval of 3 years using an OGTT yields the lowest cost per case of detected diabetes in women with a previous history of GDM.

- **The annual rate of progression to type 2 diabetes from IGT and IFG is high and warrants annual testing for undiagnosed type 2 diabetes *(Evidence Level II)***

The AusDiab study followed up 5,842 participants without diabetes aged 25 years and over for 5 years (Magliano et al, 2008). The age-standardised annual incidence of type 2 diabetes was 0.8% (95%CI 0.6-0.9) for men and 0.7% (0.5-0.8%) for women. In those subjects with IFG and IGT at baseline the annual incidence of type 2 diabetes was 2.6% (1.8-3.4%) and 3.5% (2.9-4.2%), respectively. In those with IFG the incidence of type 2 diabetes was significantly higher in women than men (4.0 vs. 2.0%, p = 0.03), while the opposite occurred in those with IGT (2.9 vs. 4.4%, p = 0.02). The incidence of type 2 diabetes was 10-20 times greater in those with IFG or IGT compared with those with normal glycaemia.

The US Diabetes Prevention Program involved 3,234 subjects without diabetes (mean age: 51 years; mean BMI: 34 kg/m^2) with elevated fasting and post-load plasma glucose who were randomly assigned to either a placebo, metformin or lifestyle intervention group, with an average follow-up of 2.8 years (Knowler et al, 2002). The incidence of type 2 diabetes was 11 cases per 100 person years in the placebo group. The estimated cumulative incidence of type 2 diabetes at 3 years was 29% in the placebo group.

A cohort of 522 overweight subjects (mean age: 55 years, mean BMI: 31 kg/m^2) who had IGT were randomly assigned to a lifestyle intervention or control group and followed-up for an average of 3.2 years in the Finish Diabetes Prevention Study (Tuomilehto et al, 2001). The cumulative incidence of type 2 diabetes in the control group was 14% (95%CI 10-19%) after 2 years and 23% (17-29%) after 4 years. The average proportion of subjects who progressed

from IGT to type 2 diabetes was 6% per year in the control group. The absolute incidence of type 2 diabetes was 78 per 1,000 person years in the control group.

Subjects from the ADDITION Study aged 40-69 years were screened for type 2 diabetes based on a high-risk stepwise screening strategy in general practice to determine the progression from IFG and IGT to type 2 diabetes (Rasmussen et al, 2007). Of the 1,160 subjects, 811 had normal glucose tolerance, 308 had IFG and 503 had IGT. The overall incidence of type 2 diabetes after one year was 19%. Confirmatory testing was completed in 88% of the incident type 2 diabetes cases, with type 2 diabetes confirmed in 62% of these cases. The incidence of type 2 diabetes was 17.6 and 18.8 per 100 person-years in those with IFG and IGT, respectively. The authors recommend that these high-risk individuals receive annual testing for type 2 diabetes.

The progression from newly acquired IFG to type 2 diabetes has been examined in a US population of 5,452 subjects with at least two elevated FPG tests (5.6-6.9 mmol/L) and with a previously normal FPG test (Nichols et al, 2007). In this study IFG was divided into two stages corresponding to the old and new ADA criteria: 5.6-6.0 mmol/L (added IFG subjects); 6.1-6.9 mmol/L (original IFG subjects). In total, 8% of added IFG subjects and 24% of original IFG subjects developed diabetes ($p < 0.0001$). Added IFG subjects progressed to diabetes at a rate of 1.34% per year after an average of 41 months. Original IFG subjects progressed to diabetes at a rate of 5.56% per year after an average of 29 months. Overall, 11% of the total subjects progressed to diabetes at a rate of 1.95% per year after an average of 36 months. From these results it is also evident that many newly identified IFG subjects progress to diabetes in ≤ 3 years.

The progression from normal glucose tolerance (NGT) and IFG/IGT to type 2 diabetes was assessed using biennial OGTTs in a cohort of 815 subjects aged 20-89 years at baseline from the Baltimore Longitudinal Study of Aging (Meigs et al, 2003). Of the 488 subjects with NGT at baseline, 12 (2.5%) progressed directly to diabetes (at the first biennial OGTT), while 267 (55%) progressed to either IFG and/or IGT, with 43 (9%) subsequently progressing further to diabetes. Of the 265 subjects with IFG and/or IGT at baseline, 104 (39%) progressed to diabetes at follow-up. Eight out of 20 (40%) subjects with IFG progressed to diabetes, 81 out of 218 (37%) subjects with IGT progressed to diabetes and 15 out of 27 (56%) subjects with IFG and IGT progressed to diabetes. In subjects with NGT at baseline the 5 year cumulative incidence rates of diabetic FPG (0.22%) and diabetic 2-h post-load glucose (2.1%) were lower than that for subjects with IFG and/or IGT at baseline (2.8 and 21%, respectively). The 5 year cumulative incidence of diabetes after development of IFG and/or IGT in subjects with NGT at baseline (diabetic FPG: 2.8%; diabetic 2-h post-load glucose: 5.7%) was also lower than that for those with IFG and/or IGT at baseline.

The relationship between IFG and IGT with incident type 2 diabetes was examined in a cohort of 1,342 subjects aged 50-75 years at baseline from the Hoorn Study (de Vegt et al, 2001). After a mean follow-up of 6.4 years the cumulative incidence was 9.9% according to WHO 1999 criteria. The cumulative incidence of type 2 diabetes was 65% for subjects with both IFG and IGT, 33% in those with IFG, 34% in those with IGT and 4.5% in those with NGT at baseline. However the mean follow-up duration was not equal in each of these categories, ranging from 5.75 to 6.47 years. The adjusted ORs for type 2 diabetes were 10.0 (95%CI 6.1-16.5), 10.9 (6.0-19.9), and 39.5 (17.0-92.1) for those with IFG, IGT, and both IFG and IGT, respectively.

From these data, it can be concluded that the rate of progression of IGT and IFG to diabetes warrants annual testing for undiagnosed diabetes.

- **There is a low risk of the development of retinopathy over a 4-5 year period following a negative screening test for type 2 diabetes *(Evidence Level II)***

The other consideration in determining an appropriate re-testing interval is the likelihood of development of diabetes complications between successive testing. Provided people present for testing, case detection programs will detect most of the people with severe degrees of hyperglycaemia who are at particular risk of the development of complications. In the US NHANES III study (Harris et al, 1998) 30% of all people with undiagnosed type 2 diabetes were in this category. The mean HbA1c of this group was 8.2%, levels which are associated with the development of microvascular complications.

Few prospective studies have addressed the development of diabetes complications in people as their glucose tolerance declines from normal (or slightly impaired) to overt diabetes. According to recent Ausdiab data, the 5-year incidence of retinopathy in a cohort of 277 adults aged ≥ 25 years with NGT at baseline was 1.8% (Tapp et al, 2008). In those subjects with IFG/IGT at baseline (n = 557, age ≥ 25 years) the 5-year incidence of retinopathy was 0.7%. In a small study of British men with IGT (Jarrett, 1986), retinopathy took a minimum of five years to develop after the onset of diabetes. Diabetes was determined by annual OGTT, and retinopathy was detected by clinical ophthalmoscopy. In a larger study of Pima Indians (Nagi et al, 1997), the prevalence of retinopathy in people who were newly diagnosed by screening and had had a non-diabetic OGTT (which could have been IGT) within the previous 4 years was 8.3%. Unpublished data from Mauritius (Zimmet, personal communication, 1999) show that of 79 people screened as having undiagnosed diabetes by OGTT who had a normal glucose tolerance test five years earlier, 8.9% had retinopathy at the time of diabetes diagnosis. In both of the last two studies, retinopathy was diagnosed by retinal photography and there were no instances of vision threatening retinopathy.

These limited data indicate that there is some risk of the development of non-vision threatening retinopathy in the interval between a negative test and a subsequent positive test for diabetes, and that this risk is of the order of 2-9% over a 4 to 5 year period.

Evidence Tables: Section 3

How Often to Test

Frequency of screening

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Chang et al., 2000 (Taiwan)	N/A	Modelling	Medium	High[+]	Medium
Chen et al., 2001 (Taiwan)	N/A	Modelling	Medium	N/A	Medium
Johnson et al., 2005 (US)	N/A	Modelling	Medium	N/A	Medium
Kim et al., 2007 (US)	N/A	Modelling	Medium	N/A	High
Kuo et al., 1999 (Taiwan)	N/A	Modelling	Medium	High[+]	High
Park et al., 2000 (UK)	II	Prospective cohort	Medium	Low[+]	High
Wang et al., 2002 (US – American Indians)	II	Prospective cohort	Medium	Medium[+]	Medium

[+] Screening for undiagnosed type 2 diabetes every 3-5 years is supported by modelling and clinical studies
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Progression to diabetes

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
de Vegt et al., 2001 (The Netherlands)	II	Prospective cohort	High	High[+]	High
Knowler et al., 2002 (US)	III-2	Cohort*	High	High[+]	High
Magliano et al., 2008 (Australia)	II	Prospective cohort	High	High[+]	High
Meigs et al., 2003 (US)	II	Prospective cohort	High	High[+]	High
Nichols et al., 2007 (US)	III-2	Retrospective cohort	High	Low[+]	High
Rasmussen et al., 2007 (Denmark)	II	Prospective cohort	High	High[+]	High
Tuomilehto et al., 2001 (Finland)	III-2	Cohort*	High	High[+]	High

[+] The annual rate of progression to type 2 diabetes from IGT and IFG is high and warrants annual testing for undiagnosed type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

* Cohort study within an RCT

Development of retinopathy

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Jarrett, 1986 (UK)	II	Prospective cohort	High	High[+]	High
Nagi et al., 1997 (US: Pima Indians)	II	Prospective cohort	High	High[+]	Low
Zimmet, 1999 (Mauritius)	IV	Cross-sectional	High	High[+]	Low

[+] There is a low risk of the development of retinopathy over a 4-5 year period following a negative screening test for type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Section 4: Socio-economic Implications

Question

What are the socio-economic implications for case detection and diagnosis of type 2 diabetes?

Recommendation

Screening for undiagnosed type 2 diabetes in high risk individuals should be an integral component of a diabetes prevention program (Grade C)

Practice Point

Socio-economic factors should be considered when developing programs for screening for undiagnosed type 2 diabetes

Evidence Statements

- Socio-economic status influences the prevalence of undiagnosed type 2 diabetes
  Evidence Level IV

- Screening for type 2 diabetes in high risk groups is cost-effective, especially when integrated with a diabetes prevention program
  Evidence Level III-2

Background – Socio-economic Implications

It is well recognised that many socio-economic issues impact on people with diabetes. These not only influence risk of developing and having undiagnosed diabetes, but also access to services and a range of equity issues. Despite the recognition of the relevance of socio-economic issues (Strong et al, 2005), there is very limited literature on the topic.

A French study of 9,294 people aged over 65 showed that people with diabetes were less likely to have a high income and more likely to have a lower educational level than people without diabetes (Bourdel-Marchasson et al, 2007).

The prevalence of type 2 diabetes is reportedly higher in those of lower socio-economic status (SES) (Wandell and Gafvels, 2004). In addition, higher education level was a protective factor against microvascular complications (OR 0.50).

The relationship between social factors and morbidity and mortality rates in people with diabetes was assessed in a cohort of 332 subjects in the UK (Weng et al, 2000). The people living in deprived areas (n = 181) were significantly older (61.3 vs. 58.6 years, $p = 0.01$), had a higher BMI (29.2 vs. 25.7 kg/m^2, $p = 0.003$) and had worse glycaemic control (HbA1c 10.5 vs. 9.1%, $p = 0.003$) than people living in prosperous areas (n = 59). People living in deprived areas were significantly more likely to be Caucasian (55 vs. 36%, $p < 0.005$), current smokers ($p = 0.02$), have microvascular diabetic complications (neuropathy: 52 vs. 20%; proteinuria: 57 vs. 22%; and lower extremity complications: 16 vs. 7%, $p < 0.001$) and were less-likely to be insulin treated (24 vs. 49%, $p = 0.004$) than people from prosperous areas. The age-and sex-adjusted mortality rate was significantly higher in people who lived in deprived areas than those who lived in prosperous areas (2.6 vs. 1.9 per 100 person-years). The authors concluded that increased morbidity and mortality rates in people with diabetes are associated with socio-economic and ethnic status.

The increased prevalence of diabetes and related complications in Indigenous communities in Australia can in part be explained by the low SES, low incomes and poor living conditions common among this population (O'Dea, 2005).

Both a deprived social environment and unhealthy behaviours have been suggested as potential factors responsible for higher rates of type 2 diabetes (Chaufan, 2004). It is possible that a person who is poor is more likely to eat cheaply (i.e. fast food) and have other unhealthy behaviours such as smoking or drinking provoked by debt or unemployment.

Cost-effectiveness ratios which are considered to represent value for money to a health system vary according to country resources and willingness to pay. In the US, consensus indicates that interventions having cost-effectiveness ratios less than US$20,000 per QALY should be readily adopted, those having ratios between US$20,000 and US$100,000 per QALY are usually provided, and those with ratios greater than US$100,000 per QALY have weak evidence for adoption (Laupacis et al, 1992).

Evidence – Socio-economic Implications

- **Socio-economic status influences the prevalence of undiagnosed type 2 diabetes *(Evidence Level IV)***

The DRUID study was conducted in a cohort of 777 Indigenous Australians aged 15-64 years and included an assessment of the relationship between SES and diabetes (Cunningham et al, 2008). After adjustment for age and sex, the prevalence of diabetes was significantly higher in those of lower SES, as determined by home ownership, household income or employment status. After adjusting for age and sex the OR for diabetes was 3.05 (95%CI 1.95-4.79) in unemployed participants, compared with those who were employed. After excluding subjects with previously diagnosed diabetes and adjusting for age and sex, in comparison to those living in a household that was owned/being purchased by its occupants, the OR for newly diagnosed diabetes for those who were living in rented/other accommodation was 3.68 (1.73-7.80). There was no significant association between education level and the prevalence of diabetes.

A cohort of 3,128 healthy Swedish men and 4,821 women aged 35-56 years were studied to investigate socio-economic differences in risk for type 2 diabetes (identified via OGTT) (Agardh et al, 2004). In middle and low socio-economic groups the relative risks for type 2 diabetes in men were 2.4 (95%CI 1.0-5.3) and 2.9 (1.5-5.7), respectively, and 3.2 (1.5-6.6) and 2.7 (1.3-5.9), respectively, in women. In men, the excess risk for type 2 diabetes in those of middle and lower socio-economic groups was only partly explained by established risk factors (obesity, physical inactivity, smoking, and heredity) (36-42%), while psychosocial factors (low decision latitude at work and low sense of coherence) had no effect. In women, adjustment for both established and psychosocial risk factors explained the majority of the socio-economic differences in type 2 diabetes (81-100%).

The relationship between SES (poverty income ratio, education, and occupational status) and type 2 diabetes in African-American and non-Hispanic white women and men was examined in a cohort of 4,978 subjects aged 40-74 years from NHANES III (Robbins et al, 2001). All 3 SES variables were significantly associated with type 2 diabetes in white women, while only poverty income ratio was associated with type 2 diabetes in African-American women. Only poverty income ratio was associated with type 2 diabetes in white men, and none of the SES variables were associated with type 2 diabetes in African-American men. Overall a consistent association between SES and type 2 diabetes was shown in women, but not men. The prevalence of type 2 diabetes was most strongly associated with poverty income ratio, largely independent of other risk factors (body size, physical activity, diet, and alcohol and tobacco use).

A recent review analysed data from various waves of NHANES (IV: 1999-2002; III: 1988-1994; and II: 1976-1980) including subjects aged 25-70 years to assess 25-year trends in the relationship between SES and diabetes prevalence in males over time (Smith, 2007). During this period the prevalence of diabetes in males has increased from 3.1% to 7.1%. The main contributors to this increased prevalence were excessive weight and obesity, and family history of diabetes. In the most recent NHANES IV data, approximately 1 in 5 males (22%) with diabetes were undiagnosed, while 25 years earlier it was closer to one in two males (48%) with diabetes who were undiagnosed. Despite the elimination of race and ethnic disparities in undiagnosed diabetes over the last 25 years, there was an increase in

discrepancy according to education level. Those in lowest education group (32%) are at almost double the risk of having undiagnosed diabetes than those in the highest education group (16%).

Using data from the 1999-2004 NHANES, in a cohort of adults aged 18-64 years the associations between access to health care and detection of diabetes was assessed (Zhang et al, 2008). One hundred and ten participants were identified as undiagnosed or "missed patients" (FPG ≥ 7.0 mmol/L but no diagnosis of diabetes), 704 participants with diagnosed diabetes and 4,782 people without diabetes. The undiagnosed group were significantly more likely to be uninsured ($p < 0.01$) and significantly more likely to be uninsured for more than 1 year compared to the other 2 groups ($p < 0.01$). Among those participants with diabetes, the proportion with undiagnosed diabetes was 42% for those uninsured, 26% for those insured, 49% for those uninsured for > 1 year, 39% for those uninsured for < 1 year and 25% for those continuously insured over the past year. Multivariate adjusted ORs for having undiagnosed diabetes were 1.7 (95%CI 1.0-2.9) in those who were uninsured and 2.6 (1.4-5.0) in those uninsured for > 1 year. The prevalence of undiagnosed diabetes was 73% among those who did not see a health professional in the last year, 47% among those receiving care just once in the last year, 33% among those receiving care 2 to 3 times in the last year, and 17% among those receiving care 4 or times in the last year. It is therefore evident that limited access to health care and being uninsured, particularly for an extended period, is significantly associated with undiagnosed diabetes.

The association between socio-economic position and type 2 diabetes was assessed at three points in life (childhood and adolescence [father's occupational position]; education; and adult occupational position) in a cross-sectional study using baseline data from 7,949 Swedish subjects aged 35-56 years from the Stockholm Diabetes Prevention Program (Agardh et al, 2007). Having a father with a middle compared to a high occupational position was associated with type 2 diabetes in women, as was low education (age-adjusted RR [95%CI] 2.3 [1.0-5.1] and 2.5 [1.2-4.9], respectively). In comparison to high occupational position during adulthood, both low (age-adjusted RR men: 2.9 [1.5-5.7]; women: 2.7 [1.3-5.9]) and middle occupational position (age-adjusted RR men: 2.4 [1.0-5.3]; women: 3.2 [1.5-6.6]) were associated with type 2 diabetes. The association between type 2 diabetes and early low socio-economic position (father's occupational position and participant's education) disappeared after adjusting for adult socio-economic position and adult risk factors related to type 2 diabetes.

Economic impact

The main questions relating to economic impact concern cost and cost-effectiveness of case detection protocols and recommendations.

Cost

In general, the cost of case detection for undiagnosed diabetes is low but is dependent on the screening protocol. Screening procedures which use routinely available information to identify people at high risk of diabetes (e.g. Cambridge risk score (Griffin et al, 2000)) or are linked to other screening programs (e.g. screening for glucose and lipids on the same fasting blood sample as part of a cardiovascular screening program) are usually low cost (WHO, 2003).

The Australian Diabetes Screening Study (Welborn et al, 1997) used a case detection and diagnosis strategy based on opportunistic testing of high risk people presenting to GPs for

routine visits. Testing procedures included a RPG and a diagnostic OGTT for individuals with a RPG result over 5.5 mmol/L. Using the data from this study, the cost of identifying each new case of type 2 diabetes or IGT was A$535 (Colagiuri et al, 1998).

These are similar to more recent estimates based on the application of the NHMRC Case Detection and Diagnosis Guideline (2002) to the AusDiab population. The Australian screening protocol for identifying undiagnosed type 2 diabetes was assessed in a population-based sample of 10,508 Australian adults (Colagiuri et al, 2004). The protocol involves an initial assessment of risk status, measurement of FPG in individuals at risk, and further testing with either FPG (if FPG ≥ 7.0 mmol/L) or OGTT (if FPG 5.5-6.9 mmol/L). The cost per case of newly diagnosed diabetes using the Australian protocol was A$746, and A$260 for each person with IFG or IGT. Using HbA1c measurement following risk assessment instead of FPG measurement increases costs to A$828. These costs were considered to be reasonable and generally affordable in the context of opportunistic screening programs.

A recent Australian study compared the use of two different screening methods for undiagnosed type 2 diabetes in Australian community pharmacies (Krass et al, 2007). A cohort of 1,286 people were allocated to either the tick test only (TTO) or the sequential screening (SS) method, using the TTO followed by CBG testing. The total cost of screening each individual in a pharmacy was A$7.76 for the TTO method and A$11.83 for the SS method. However, the average cost of GP-based screening to diagnose diabetes was higher using the TTO method (A$14.03) than the SS method (A$9.35), since a higher proportion of those in the TTO group were referred to a GP. The SS method was more cost-effective as it resulted in fewer referrals to the GP (24% vs. 77%, $p < 0.01$) and a higher uptake of referrals than the TTO method (42% vs. 21%, $p < 0.01$). The average cost per case detected was A$6,241 for the TTO method and A$788 using the SS method.

Zhang and colleagues (2005) conducted a modelling study to determine efficient cut-points for multiple screening tests for detecting undiagnosed diabetes alone, or both undiagnosed diabetes and pre-diabetes in a US population aged 45-74 years. The most efficient cut-points for cost per case detected for both undiagnosed diabetes and pre-diabetes (FPG ≥ 5.5 mmol/L, HbA1c ≥ 5.0%, rCBG ≥ 5.5 mmol/L) were lower than those for undiagnosed diabetes alone (FPG ≥ 6.1 mmol/L, HbA1c ≥ 5.7%, rCBG ≥ 6.7 mmol/L). From a single payer perspective, the costs per case identified by cut-point value were higher when screening for undiagnosed diabetes alone than for both undiagnosed diabetes and pre-diabetes for rCBG (US$392-671 vs. US$125-321), FPG (US$556-717 vs. US$114-476) and HbA1c (US$590-817 vs. US$153-536). From the societal perspective, the same trend was apparent for the rCBG (US$504-990 vs. US$175-389), FPG (US$816-1,177 vs. US$172-674) and HbA1c ($US 728-1,165 vs. $US 215-605). It was therefore concluded that a lower cut-point should be used when screening for both undiagnosed diabetes and prediabetes than when screening for undiagnosed diabetes alone.

Results from the Inter99 study indicate that when taking into consideration workload, burden on the population, and cost per identified case of undiagnosed diabetes, targeted screening in the form of a Danish risk score questionnaire followed by FPG is preferred to using either a questionnaire, FPG or HbA1c alone (Glumer et al, 2004b). Specifically, the cost per case of newly diagnosed diabetes using FPG in population based screening was €583 compared to €270 using a questionnaire followed by FPG, equating to a 54% reduction in cost. Sensitivity and specificity values using FPG were 79% and 88% respectively, and 62% and 89% respectively using the questionnaire and FPG. Furthermore, targeted screening using the questionnaire prior to FPG reduced the FPG measurements by 72%.

A recent study was conducted to compare the yield and costs of simulated screening in the US population (45-74 years old; 72.6 million individuals) over 15 years with various screening intervals using RPG with cut-points of 5.5, 7.2 or 8.9 mmol/L or a multivariate logistic equation that incorporated RPG, postprandial time, age, sex, and BMI (Johnson et al, 2005). The total cost over 15 years of the most sensitive screening strategy (RPG 5.5 mmol/L every year) was US$42.7 billion, and for the most specific screening strategy (RPG 8.9 mmol/L every 5 years) was US$6.9 billion. Over the 15 years, the most sensitive screening strategy produced 4.5 million more true positives and 476 million more false positives than the most specific screening strategy. Therefore screening with a high specificity strategy will produce a minimal reduction in the number of true positives but will substantially reduce the number of false positives. Using a screening interval of 3 years, the number of false negatives using an RPG of 5.5 mmol/L was 0.2 million, using an RPG of 7.2 mmol/L or the multivariate equation was 1.3 million, and using an RPG of 8.9 mmol/L was 2.8 million. The cost per true positive is US$916 for an RPG of 5.5 mmol/L, US$642 for an RPG of 7.2 mmol/L, US$626 for an RPG of 8.9 mmol/L, and US$563 using the multivariate equation. Overall costs are lower with opportunistic screening than for population screening. Using an RPG of 7.2 mmol/L every 3 years, the cost per true positive is US$275 for opportunistic screening and US$1,745 for population screening.

Lee and colleagues (2000) have estimated the costs and savings associated with a community screening program for diabetes in the Central Wisconsin population. Of the 826 subjects (aged 65 and older) without known diabetes screened, 4% were diagnosed with type 2 diabetes. The costs of screening this population were estimated at US$3,200, or US$100 per subject diagnosed with type 2 diabetes. Using the assumptions offered by the Centers for Disease Control and Prevention (CDC) study group, the lifetime costs for routine diabetes care were US$4,750 greater for those detected during screening compared with those not detected earlier with screening (US$11,716 vs. US$6,966). However, the costs associated with treating microvascular complications were reduced by US$278 as a result of screening and the additional routine care. By altering assumptions about CVD risk reduction (reduced by 30%) based on UKPDS findings (a 39% reduction in myocardial infarction with glycaemic control and tight BP control) (UKPDS, 1998a), costs were further reduced by US$1,224. Thus, total excess lifetime costs associated with screening range from US$3,246 to US$4,471 depending on the extent of CVD risk reduction. The authors also assumed that routine care costs would be reduced by one third (US$11,716 to US$7,850) in subjects with type 2 diabetes detected by screening for the first 5 years of care. Combining this with a 30% CVD risk reduction results in a saving of US$619 per subject with type 2 diabetes detected by screening.

Cost-effectiveness

- **Screening for type 2 diabetes is cost-effective, especially when integrated with a diabetes prevention program *(Evidence Level III-2)***

Since there are no definitive outcomes studies on the effectiveness of early intervention in people with screen-detected diabetes, there can be no definitive statement of its cost-effectiveness (WHO, 2003). However, a number of models have been developed to address this issue. It should be noted that the outcomes of these modelling exercises are dependent on the model structure and assumptions, particularly the estimated clinical benefits of the modelled scenario. For example, using a model based on population data from the Danish Inter99 study, the overall cost-effectiveness ratio for screening for type 2 diabetes was not

sensitive to decisions about which groups to screen or to the costs of screening or treatment (Glumer et al, 2006). However, it was strongly affected by assumptions about how treatments combine to reduce risk.

Using the US CDC model (CDC, 1998), the cost per QALY gained by a one time opportunistic population screening of all people over age 25 was calculated. Risks of complications were derived from a variety of epidemiological studies, and the impact of treatment on microvascular complications was calculated from DCCT data. Macrovascular complications were not considered. The cost/QALY (US$56,649 per QALY gained) was judged to be acceptable (i.e. comparable to that of screening for other diseases), and lowest in young people and among African Americans.

In another study (Goyder and Irwig, 2000), the health difference (measured in QALYs) between a screened and an unscreened population of people aged 45-60 years was calculated, and the negative impact of screening was included. DCCT data were used to calculate the reduction of microvascular complications, while it was assumed that treatment for diabetes would have a similar impact on macrovascular disease as does treatment for hypertension and hyperlipidaemia. Screening led to a net benefit of 10 QALYs for every 10,000 people screened, mainly from fewer cardiovascular events.

Engelgau et al. (2000) used the CDC model to review screening for type 2 diabetes compared with screening for other conditions and concluded that diabetes screening is less favorable than some and more favorable than others. Consensus indicates that interventions having cost-effectiveness ratios less than US$20,000 per QALY should be readily adopted, those having ratios between US$20,000 and US$100,000 per QALY are usually provided, and those with ratios greater than US$100,000 per QALY have weak evidence for adoption (Laupacis et al, 1992). The following are some examples provided in the review by Engelgau and colleagues of cost-effectiveness ratios:

- screening and treating with statins in people with no cardiac history ranged from US$54,000 per QALY to US$1,400,000 per QALY
- screening for breast cancer costs US$150,000 per QALY
- screening for colon cancer costs US$16,000 per QALY in persons 50-75 years of age
- screening for cervical cancer costs US$16,000 per QALY by pap smear every 4 years for women 20-75 years of age (for every year the figure is >US$1,600,000/QALY).

Compared with these the estimate for clinic-based opportunistic screening for undiagnosed diabetes was US$56,649 per QALY.

With regard to cost-effectiveness standards in Australia, a study by George and colleagues (2001) attempted to identify a threshold incremental cost-effectiveness ratio beyond which the Australian Pharmaceutical Benefits Advisory Committee (PBAC) is not prepared to recommend reimbursement of a drug. The study included all 355 submissions made to the PBAC between January 1991 and June 1996. Twenty-six submissions included cost per life-year gained data and nine submissions contained cost per QALY gained data. Results indicate a statistically significant difference ($p = 0.0008$) between the cost per life-year gained for drugs recommended for listing and those that were not, suggesting that economic efficiency is a key criterion for decision making by the PBAC. Although no explicit threshold was found, the PBAC appears unlikely to recommend a drug for listing if the additional cost per life-year exceeded A$76,000 (1998/1999 values) and was unlikely to reject a drug for which the additional cost per life-year gained was less than A$42,000. There were insufficient data to identify any possible threshold for cost per QALY gained.

Using a Markov model of type 2 diabetes disease progression to simulate lifetime diabetes-related health care costs and QALYs, screening for type 2 diabetes targeted to people with hypertension was found to be more cost-effective than universal screening (Hoerger et al, 2004). In addition, universal or targeted screening was more cost-effective for people at 55, 65 and 75 years of age than for those at 35 and 45 years of age. Although universal screening achieved greater overall benefit than targeted screening, the additional cost is high. A more efficient strategy would target individuals with hypertension aged 55 to 75 years, with intensive hypertension control for those diagnosed with diabetes.

In a literature review and economic modelling study it was concluded that screening for type 2 diabetes seems to be cost effective in the 40-70 year age group, more so for the older age bands (50-59 and 60-69 years) (Waugh et al, 2007). Findings from the modelling study indicate that the cost-effectiveness of this screening strategy results from cost reductions and QALY gains from a reduction in complications. Screening for type 2 diabetes appears to be even more cost effective in hypertensive and obese populations. The costs associated with screening are offset in many subgroups by reduced future treatment costs. Assumptions regarding the degree of blood glucose control and future treatment protocols influence the cost effectiveness of screening for type 2 diabetes as much as or more so than assumptions relating to the screening program itself.

A recent study has examined the cost-effectiveness of four potential screening and treatment strategies for type 2 diabetes in a hypothetical cohort of adults aged 45 years with above average risk of diabetes (Gillies et al, 2008). A hybrid decision tree/Markov model was developed to simulate the long term clinical and cost-effectiveness outcomes of each screening strategy. Compared with no screening, the estimated costs associated with each QALY gained were £14,150 for screening for type 2 diabetes, £6,242 for screening type 2 diabetes and IGT followed by lifestyle interventions, and £7,023 for screening for type 2 diabetes and IGT followed by pharmacological interventions. At a willingness-to-pay threshold of £20,000 per QALY the probability of each of these screening strategies being cost-effective was 49%, 93%, and 85%, respectively. Compared with no screening, QALYs gained were 0.03 for type 2 diabetes screening only, 0.09 for screening and lifestyle interventions, and 0.07 for screening and pharmacological interventions. It was concluded that in this 45 year old above average risk population, screening for type 2 diabetes and IGT followed by appropriate interventions in those with IGT appears to be cost-effective. However, the cost-effectiveness of screening for type 2 diabetes alone without offering any follow-up treatment for those with IGT remains uncertain.

Icks and colleagues (2004) examined the cost-effectiveness of various screening procedures for type 2 diabetes using a decision-analytic model with a time horizon of 1 year in 1,353 subjects aged 55-75 years from the KORA Survey 2000. The four screening strategies analysed were (1) FPG alone; (2) FPG + OGTT; (3) OGTT alone; and (4) HbA1c + OGTT. It was concluded that HbA1c combined with an OGTT was the most effective (54% detected cases) but also the most expensive screening strategy (€21.44 and €31.77 per study subject from the statutory health insurance perspective and the societal perspective, respectively). Costs per study subject were lowest for the FPG test combined with an OGTT (€10.85) from the societal perspective, and for an OGTT alone (€4.90) from the statutory health insurance perspective. However, these strategies detected only approximately one fourth and one third, respectively, of subjects with undiagnosed diabetes. Costs per study subject were highest in the HbA1c + OGTT strategy due to the large number of subjects using this strategy (100% participation in the HbA1c testing). In deciding on the most favourable strategy it is

necessary to assess whether the primary objective is identify a maximum number of cases or to incur lower costs whilst still being reasonably effective.

One study has compared the cost and time to diagnosis of several simulated screening strategies for type 2 diabetes in women with histories of GDM (Kim et al, 2007). The methods used to screen for diabetes were FPG, OGTT, and HbA1c annually, every 2 years, and every 3 years over a period of 12 years. The OGTT resulted in the lowest costs per case detected, regardless of screening interval. Using a 3 yearly screening interval resulted in lower costs per case detected compared with more frequent testing, with minimal increments in the time spent with undiagnosed diabetes. In sensitivity analyses these patterns persisted, except that FPG resulted in lower costs per case detected than OGTT, based on the assumption of an annual screening interval and inclusion of indirect costs or assuming annual screening without a confirmatory FPG. However, lack of confirmatory testing for FPG increased the number of false positives. It was concluded that a screening interval of 3 years using an OGTT yields the lowest cost per case of detected diabetes in women with a previous history of GDM.

The Australian Diabetes Cost-Benefit Model was developed to estimate the health benefits and costs associated with a national diabetes screening and prevention program among Australians aged 45-74 years (Colagiuri and Walker, 2008). Screening for undiagnosed diabetes and intermediate hyperglycaemia (IFG and IGT) was performed in Australians aged 55-74 years and in those aged 45-54 years who were obese (BMI $\geq$ 30 kg/m^2), had a family history of diabetes, or had hypertension. The simulated interventions include screening at a cost of A$112.50 per person and unspecified lifestyle intervention at A$500 per person per year for those with IFG or IGT. The model compares baseline and program outcomes from 2000 to 2010, with those newly diagnosed in 2000 provided with intensive care, while those at high risk of developing diabetes are offered lifestyle intervention. According to the model, of the 2.1 million people screened, a total of 115,000 people were newly diagnosed with diabetes in 2000 and 53,000 of those at high risk avoided developing diabetes by 2010. The average annual intervention and incremental treatment cost was A$179 million and the cost per disability-adjusted life-year (DALY) was A$50,000.

Evidence Tables: Section 4

Socio-economic Implications

Socio-economic status

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
Agardh et al., 2004 (Sweden)	IV	Cross-sectional	High	High[+]	Medium
Agardh et al., 2007 (Sweden)	IV	Cross-sectional	High	Medium[+]	High
Cunningham et al., 2008 (Australia)	IV	Cross-sectional	High	High[+]	High
Robbins et al., 2001 (US)	IV	Cross-sectional	High	Medium[+]	Medium
Smith, 2007 (US)	III-2	Retrospective cohort	High	High[+]	Medium
Zhang et al., 2008 (US)	IV	Cross-sectional	Medium	High[+]	Medium

[+] Socio-economic status influences the prevalence of undiagnosed type 2 diabetes

Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

Cost-effectiveness

Author, year (population)	Evidence				
	Level of Evidence		*Quality Rating*	*Magnitude of the effect Rating*	*Relevance Rating*
	Level	*Study Type*			
CDC, 1998 (US – African American)	III-2	Cohort	Medium	High[+]	Low
Colagiuri and Walker, 2008 (Australia)	N/A	Modelling	Medium	N/A	High
Colagiuri et al., 2004 (Australia)	III-2	Diagnostic accuracy	High	High[+]	High
Engelgau et al., 2000 (International)	N/A	Technical review	Medium	N/A	High
George et al., 2001 (Australia)	N/A	Technical review	Medium	N/A	Medium
Gillies et al., 2008 (UK)	N/A	Modelling	Medium	Medium[+]	High
Glumer et al., 2004b (Denmark)	III-2	Diagnostic accuracy	High	Medium[+]	High
Glumer et al., 2006 (Denmark)	N/A	Modelling	Medium	N/A	Medium
Goyder and Irwig, 2000 (Australia)	III-2	Cohort	Medium	High[+]	Medium
Hoerger et al., 2004 (UK, US)	N/A	Modelling	Medium	N/A	Medium
Icks et al., 2004 (Germany)	III-2	Diagnostic accuracy	Medium	N/A	Medium
Johnson et al., 2005 (US)	N/A	Modelling	Medium	N/A	Medium
Kim et al., 2007 (US)	N/A	Modelling	Medium	N/A	High
Krass et al., 2007 (Australia)	IV	Cross-sectional	Medium	High[+]	High
Laupacis et al., 1992 (International)	N/A	Technical review	Medium	N/A	Medium
Lee et al., 2000 (US)	N/A	Modelling	Medium	N/A	Medium
Waugh et al., 2007 (UK)	N/A	Modelling	Medium	N/A	High
Zhang et al., 2005 (US)	N/A	Modelling	Medium	N/A	High

[+] Screening for type 2 diabetes is cost-effective, especially when integrated with a diabetes prevention program
Magnitude of the effect rating: The direction of the effect is '+' for a positive effect and '-' for a negative effect

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APPENDICES

Appendix 1: Search Strategy and Yield Table

Electronic databases searched:

Medline
Embase.com
Cochrane Library
Cinahl
PsycINFO

Terms used to search the databases:

Detailed in search strategy tables

Other searching:

Reference lists of relevant articles were hand searched
Relevant articles were solicited from expert colleagues and organisations
Local and international practice guidelines were reviewed for relevant references

Search inclusion criteria:

Where possible searches were limited by the English language, human research and to the years of publication between 1999 and 2008. Literature searches were completed on the following dates:
Section 1: February 25, 2008
Section 2:
Part 1 (Risk factors): April 23, 2008
Part 2 (How should testing be performed?): March 20, 2008
Section 3: March 20, 2008
Section 4: February 25, 2008

No additional formal searching was performed after these dates. However, if important and relevant studies published after these dates were identified or brought to our attention before the completion of the guideline (October 31, 2008) they were included.

Abbreviations and explanation of table headings

Identified = number of articles which matched the mesh terms listed or contained the text terms in each particular database
Relevant = those articles considered relevant to the questions being asked after viewing titles or abstracts
Articles identified by other strategies = articles identified by hand searching, from searches for other questions, or from colleagues
Total for Review = those articles considered relevant to the question after viewing titles and abstracts, contained original data or were systematic reviews of original articles and met the inclusion/exclusion criteria
Total no. reviewed and graded = articles used in the evidence section of the guidelines which have been summarised and graded

Inclusion Criteria - General

- Present original data or reviews of original data
- Focus on type 2 diabetes
- Address one or more of the specified research questions
- Applicable to diabetes care in Australia
- Conducted in humans
- Published in the English language
- Published between 1999-2008
- Selection of subjects was unbiased and representative of the general population being studied
- Conducted in an appropriate population for the question being addressed
- Studies containing data on newly diagnosed diabetes separate from people with known diabetes
- Population based studies of at least 100 individuals with newly diagnosed diabetes
- Articles were obtained from journals able to be accessed within our library network, ordered through an interlibrary loan or obtained via other sources

1. Method for diagnosis of type 2 diabetes
The criteria for considering the diagnosis of diabetes were, in the following order of preference:

- Oral glucose tolerance test (OGTT) with collection of fasting and 2 hour post glucose load plasma glucose samples interpreted using WHO criteria (either 1999 or 2006)
- OGTT with collection of only the 2 hour post glucose load plasma glucose sample interpreted using WHO criteria (either 1999 or 2006)
- Fasting plasma glucose – using current WHO (either 1999 or 2006) or ADA criteria (1997)
- Medication treated diabetes
- Medical records with explicit criteria for confirming diagnosis
- Non-fasting plasma glucose
- Self reported diabetes (unconfirmed)

NB Studies using laboratory blood testing to measure plasma glucose concentration were considered ahead of studies using blood glucose meter testing

2. Studies dealing with risk factors for diabetes were considered if they:

- Included data predominantly relating to Caucasians, Aboriginal and Torres Strait Islanders, or other populations with high prevalence of type 2 diabetes represented in Australia
- Were prospective or cross sectional studies which considered newly diagnosed type 2 diabetes
- Reported age- and sex-standardised data
- Included multivariate analyses when more than one risk factor was reported

Exclusion Criteria

- Studies of inappropriate patient population
- Prospective or cross sectional studies on people with established type 2 diabetes
- Articles and reviews which present the author's opinion rather than evidence
- Small review articles where the material is covered more adequately by more recent or more comprehensive reviews
- In vitro and animal studies
- Genetic studies that are not clinically applicable

Questions		No. articles identified	No. relevant articles	Articles identified by other strategies	Total for review	Total no. reviewed and graded	Level I	Level II	Level III	Level IV	Highest level of evidence
1	**Is case detection and diagnosis of type 2 diabetes worthwhile?**	3165	559	89	205	48	3	18	2	23	I
2 – Risk factors	**How should case detection and diagnosis be performed?**	6749	603	85	233	62	6	16	7	33	I
2 – How should testing be performed	**How should case detection and diagnosis be performed?**	3751	1005	44	188	87	1	8	48	30	I
2 - Total	**How should case detection and diagnosis be performed?**	10500	1608	129	421	149	7	24	55	63	I
3	**How often should testing be performed?**	1918	309	22	37	17	0	8	3	1	II
4	**What are the socio-economic implications of case detection and diagnosis of type 2 diabetes?**	N/A*	N/A*	33	33	21	0	0	6	6	III-2

* Note: There was no search strategy for question 4 since the material for question 4 was originally intended to be included in question 1 and hence is covered in the search strategy for question 1. There were 2 studies in Q1, 5 studies in Q3 and 9 studies in Q4 that could not been assigned a level of evidence.

Appendix 2: Search Strategies and Terms

Question 1 – Is case detection and diagnosis of type 2 diabetes worthwhile?

#	Searches	Results
1	Diabetes Mellitus, Type 2/	50625
2	(type 2 diabetes or type II diabetes).tw.	30888
3	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	938
4	(diabetes type 2 or diabetes type II).tw.	487
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11607
6	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
7	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1204
8	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	469
9	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	350
10	(screen detected diabetes or diabetes screen detected or diabetes mellitus screen detected).tw.	8
11	(undiagnosed diabetes or diabetes undiagnosed or diabetes mellitus undiagnosed).tw.	385
12	or/1-11	63090
13	diagnosis/ or "diagnostic techniques and procedures"/ or early diagnosis/	20993
14	(diagnosis or diagnoses).tw.	768142
15	(diagnostic test or diagnostic tests or diagnostic testing or diagnostic technique$ or diagnostic procedure$).tw.	36908
16	case detection$.tw.	796
17	case finding$.tw.	2356
18	early detection$.tw.	23275
19	Mass Screening/	61491
20	(screening$ or screened).tw.	243248
21	or/13-20	1046000
22	"costs and cost analysis"/ or cost-benefit analysis/ or "cost of illness"/ or exp health care costs/ or health expenditures/	118668
23	(cost analysis or cost analyses).tw.	2799
24	cost effect$.tw.	43939
25	cost benefit$.tw.	5425

26	(cost of illness$ or illness cost$).tw.	587
27	(burden of disease or disease burden$).tw.	3327
28	(burden of illness or illness burden$).tw.	710
29	(cost$ of disease or disease cost$).tw.	272
30	(cost$ of sickness or sickness cost$).tw.	14
31	(health care cost$ or medical care cost$ or treatment cost$).tw.	8777
32	health expenditure$.tw.	1028
33	economic impact$.tw.	3006
34	economic consideration$.tw.	688
35	health impact$.tw.	2530
36	health problem$.tw.	27891
37	worthwhile.tw.	6199
38	benefi$.tw.	301549
39	harm$.tw.	50163
40	adverse effect$.tw.	62023
41	adverse event$.tw.	35268
42	outcome$.tw.	473991
43	consequence$.tw.	176968
44	Stress/ or Stress, Psychological/	95125
45	stress$.tw.	297298
46	(psychological or psychosocial or psycho-social).tw.	115895
47	exp Diabetes Complications/	80268
48	(diabetes complication$ or diabetes mellitus complication$ or diabetes related complication$ or complication$ of diabetes or diabetic complication$).tw.	7197
49	(risk benefit ratio$ or risk:benefit ratio$ or risk to benefit ratio$).tw.	1878
50	false negative reactions/ or false positive reactions/	28502
51	(false positive reaction$ or false negative reaction$).tw.	1247
52	(false positive result$ or false negative result$).tw.	9948
53	or/22-52	1606561
54	morbidity/ or incidence/ or prevalence/ or exp mortality/	427285

55	morbidit$.tw.	152432
56	incidence$.tw.	354879
57	prevalence$.tw.	224305
58	mortalit$.tw.	282510
59	(survival rate$ or survival time$).tw.	83044
60	health status indicators/ or "severity of illness index"/ or sickness impact profile/ or health status/	149725
61	(health status or health level$ or level$ of health).tw.	24493
62	health risk appraisal$.tw.	268
63	(severity of illness$ or illness index severit$ or illness severit$).tw.	5340
64	sickness impact profile$.tw.	883
65	or/54-64	1223106
66	exp Australia/	69420
67	australia$.tw.	47851
68	or/66-67	86367
69	meta-analysis.pt.	19122
70	(meta-anal$ or metaanal$).tw.	22390
71	(quantitativ$ review$ or quantitativ$ overview$).tw.	405
72	(systematic$ review$ or systematic$ overview$).tw.	15976
73	(methodologic$ review$ or methodologic$ overview$).tw.	195
74	review.pt. and medline.tw.	19425
75	or/69-74	53304
76	randomized controlled trial.pt.	262367
77	controlled clinical trial.pt.	79684
78	randomized controlled trials as topic/	56200
79	random allocation/	62329
80	double blind method/	99559
81	single blind method/	12383
82	or/76-81	442869
83	animals/ not (animals/ and humans/)	3241353
84	82 not 83	414709

85	clinical trial.pt.	456623
86	exp clinical trials as topic/	209671
87	(clinic$ adj25 trial$).tw.	149731
88	cross-over studies/	22648
89	(crossover or cross-over or cross over).tw.	41577
90	((singl$ or doubl$ or tebl$ or tripl$) adj25 (blind$ or mask$)).tw.	99073
91	placebos/	27892
92	placebo$.tw.	112671
93	(randomi?ation or random allocation or random selection or random assignment or randomly allocated or randomly selected or randomly assigned or randomly divided or randomly distributed).tw.	101960
94	research design/	53877
95	or/85-94	798689
96	95 not 83	761595
97	84 or 96	799312
98	and/12,21,53,75	45
99	and/12,21,53,97	396
100	(and/12,21,53) not 98 not 99	2391
101	and/12,65,68,75	4
102	and/12,65,68,97	26
103	(and/12,65,68) not 101 not 102	184
104	98	45
105	limit 104 to (english language and humans and yr="1999 - 2008")	38
106	99	396
107	limit 106 to (english language and humans and yr="1999 - 2008")	261
108	100	2391
109	limit 108 to (english language and humans and yr="1999 - 2008")	1425
110	101	4
111	limit 110 to (english language and humans and yr="1999 - 2008")	4
112	102	26
113	limit 112 to (english language and humans and yr="1999 - 2008")	25

114	103	184
115	limit 114 to (english language and humans and yr="1999 - 2008")	123

Question 2 – How should case detection and diagnostic testing for type 2 diabetes be performed?

Part 1 – Risk factor search strategy

#	Searches	Results
1	Diabetes Mellitus, Type 2/	50625
2	(type 2 diabetes or type II diabetes).tw.	30888
3	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	938
4	(diabetes type 2 or diabetes type II).tw.	487
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11607
6	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
7	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1204
8	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	469
9	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	350
10	(screen detected diabetes or diabetes screen detected or diabetes mellitus screen detected).tw.	8
11	(undiagnosed diabetes or diabetes undiagnosed or diabetes mellitus undiagnosed).tw.	385
12	or/1-11	63090
13	risk/ or risk factors/	438826
14	risk$.tw.	747337
15	(associated or association).tw.	1664736
16	or/13-15	2299753
17	hyperglycemia/ or glucose intolerance/	17043
18	glucose intolerance$.tw.	4749
19	(hyperglycemia$ or hyperglycaemia$).tw.	21667
20	glucose intolerance$.tw.	4749
21	impaired glucose tolerance.tw.	5429
22	impaired fasting glucose.tw.	963
23	Prediabetic State/	2390
24	(prediabetic$ or prediabetes).tw.	1816
25	pregnancy/ or pregnant women/ or pregnancy in diabetics/ or pregnancy, prolonged/ or diabetes, gestational/	595900

26	(pregnan$ or gestation$).tw.	326570
27	birth weight/ or fetal macrosomia/ or fetal weight/	28656
28	(birth weight$ or birth mass or fetal macrosomia$ or foetal macrosomia$ or fetal weight$ or foetal weight$ or fetal mass or foetal mass).tw.	31690
29	Obesity/ or Overweight/ or Body Weight/	206251
30	obes$.tw.	93518
31	overweight.tw.	16895
32	(body weight$ or body mass).tw.	162978
33	adiposity/ or exp adipose tissue/ or skinfold thickness/ or abdominal fat/ or intra-abdominal fat/ or subcutaneous fat/ or subcutaneous fat, abdominal/	57248
34	(adiposity or adipose tissue$ or fatty tissue$ or body fat or fat pad$ or skinfold thickness$ or abdominal fat$ or subcutaneous fat$ or brown fat$ or white fat$ or intra-abdominal fat$ or visceral fat$ or retroperitoneal fat$).tw.	55314
35	body fat distribution/ or waist-hip ratio/	1742
36	(waist-hip ratio$ or waist:hip ratio$ or waist to hip ratio$).tw.	4198
37	waist circumference$.tw.	4200
38	Lipids/	72911
39	lipid$.tw.	237719
40	Triglycerides/	49979
41	(triglyceride$ or triacylglycerol$).tw.	61081
42	fats/ or exp dietary fats/ or exp fats, unsaturated/	65297
43	diet/	81007
44	dietary intake$.tw.	11107
45	glycemic index/	727
46	(high GI or high glycemic index).tw.	236
47	(dietary fat$ or unsaturated fat$).tw.	14172
48	Cholesterol, HDL/ or Cholesterol/ or Cholesterol, LDL/ or Cholesterol, VLDL/ or Cholesterol, Dietary/	108496
49	cholesterol$.tw.	129994
50	exp Cardiovascular Diseases/	1489382
51	(vascular disease$ or heart disease$ or myocardial infarct$ or myocardial ischemia$ or myocardial ischaemia$ or angina$ or coronary disease$ or coronary artery disease$).tw.	272688
52	exp stroke/	48953

53	stroke$.tw.	89196
54	(microvascular or macrovascular).tw.	28396
55	"Age of Onset"/ or Age Factors/	321716
56	aged/	1766990
57	middle aged/	2546644
58	age$.tw.	1629079
59	Gender Identity/	12174
60	gender$.tw.	98951
61	family histor$.tw.	28656
62	parental diabetes.tw.	51
63	continental population groups/ or oceanic ancestry group/ or ethnic groups/	45912
64	(race or racial).tw.	48153
65	(continental population group$ or oceanic ancestry group$ or ethnic group$ or nationalit$ or aborigin$ or caucasian$).tw.	43726
66	minority groups/ or socioeconomic factors/ or poverty/ or social class/	114708
67	(minority group$ or social class$ or class population$ or socioeconomic or socio-economic or high income$ or low income$ or standard$ of living or living standard$ or poverty or wealth$).tw.	64980
68	exp Hypertension/	176989
69	(hypertension$ or hypertensive$ or high blood pressure$ or antihypertensive therap$ or antihypertensive medication$).tw.	240307
70	Smoking/	90870
71	(smoking or smoker$).tw.	109476
72	Polycystic Ovary Syndrome/	7130
73	(polycystic ovar$ syndrome or polycystic ovar$ disease or sclerocystic ovar$ or stein leventhal syndrome).tw.	6051
74	medication$.tw.	116159
75	drug therapy/ or drug therapy, combination/ or prescriptions, drug/ or drugs, non-prescription/	158085
76	Pharmaceutical Preparations/	35324
77	pharmaceutical preparations/ or drug therapy/ or drug therapy, combination/ or prescriptions, drug/ or drugs, non-prescription/	190443
78	(drug$ or pharmaceutical preparation$).tw.	756258
79	stress/ or stress, psychological/ or stress disorders, traumatic/ or stress disorders, traumatic, acute/ or stress	153299

	disorders, post-traumatic/ or anxiety/ or anxiety disorders/	
80	(stress$ or anxiet$ or anxious$).tw.	356377
81	exp Sleep Disorders/	40801
82	sleep disorder$.tw.	6365
83	Depression/	50863
84	(depression and depressive).tw.	22950
85	Motor Activity/ or exp Exercise/	112235
86	(exercis$ or motor activit$ or physical activit$ or physical inactivit$).tw.	169392
87	Physical Fitness/	16221
88	(fitness or physical condition$).tw.	23863
89	sedentar$.tw.	9958
90	Food Habits/ or Energy Intake/	35557
91	(energy intake$ or calor$ intake or eating habit$ or food habit$ or diet$ habit$ or diet$ intake$ or diet$ modification$ or unhealthy eating).tw.	30972
92	or/17-91	6923687
93	Meta Analysis/	19122
94	meta-analysis.pt.	19122
95	(meta-anal$ or metaanal$).tw.	22390
96	(quantitativ$ review$ or quantitativ$ overview$).tw.	405
97	(systematic$ review$ or systematic$ overview$).tw.	15976
98	(methodologic$ review$ or methodologic$ overview$).tw.	195
99	review.pt. and medline.tw.	19425
100	or/93-99	53304
101	epidemiologic studies/ or case-control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or cross-sectional studies/	594620
102	(cohort stud$ or case-control stud$ or cross-sectional stud$ or epidemiologic$ stud$ or retrosepctive stud$ or longitudinal stud$).tw.	161061
103	101 or 102	660355
104	and/12,16,92,100	571
105	and/12,16,92,103	5919
106	(and/12,16,92) not 104 not 105	21006

107	(and/12,16,100) not 104 not 105 not 106	51
108	(and/12,16,103) not 104 not 105 not 106	129
109	(and/12,16) not 104 not 105 not 106 not 107 not 108	1506
110	104	571
111	limit 110 to (english language and humans and yr="1999 - 2008")	506
112	105	5919
113	limit 112 to (english language and humans and yr="1999 - 2008")	4472
114	106	21006
115	limit 114 to (english language and humans and yr="1999 - 2008")	12715
116	107	51
117	limit 116 to (english language and humans and yr="1999 - 2008")	44
118	108	129
119	limit 118 to (english language and humans and yr="1999 - 2008")	97
120	109	1506
121	limit 120 to (english language and humans and yr="1999 - 2008")	839

Question 2 Part 2 – How should case detection and diagnostic testing be performed search strategy

and

Question 3 – How often should testing be performed?

#	Searches	Results
1	Diabetes Mellitus, Type 2/	50625
2	(type 2 diabetes or type II diabetes).tw.	30888
3	(diabetes mellitus type 2 or diabetes mellitus type II).tw.	938
4	(diabetes type 2 or diabetes type II).tw.	487
5	(non insulin dependent diabetes or noninsulin dependent diabetes or diabetes non insulin dependent or diabetes mellitus non insulin dependent or NIDDM).tw.	11607
6	(adult onset diabetes or diabetes adult onset or diabetes mellitus adult onset).tw.	338
7	(maturity onset diabetes or diabetes maturity onset or diabetes mellitus maturity onset).tw.	1204
8	(new onset diabetes or diabetes new onset or diabetes mellitus new onset).tw.	469
9	(newly diagnosed diabetes or diabetes newly diagnosed or diabetes mellitus newly diagnosed).tw.	350
10	(screen detected diabetes or diabetes screen detected or diabetes mellitus screen detected).tw.	8
11	(undiagnosed diabetes or diabetes undiagnosed or diabetes mellitus undiagnosed).tw.	385
12	or/1-11	63090
13	diagnosis/ or "diagnostic techniques and procedures"/ or early diagnosis/	20993
14	(diagnosis or diagnoses).tw.	768142
15	(diagnostic test or diagnostic tests or diagnostic testing or diagnostic technique$ or diagnostic procedure$).tw.	36908
16	case detection$.tw.	796
17	case finding$.tw.	2356
18	early detection$.tw.	23275
19	Mass Screening/	61491
20	(screening$ or screened).tw.	243248
21	or/13-20	1046000
22	risk score$.tw.	2588
23	risk factor score$.tw.	100
24	risk assessment/	93881
25	risk assessment$.tw.	17289

26	Questionnaires/	183061
27	questionnaire$.tw.	170207
28	Glucose Tolerance Test/ or Glucose Intolerance/	26137
29	(glucose tolerance$ or glucose intolerance$ or fasting glucose).tw.	26859
30	Blood Glucose/	100005
31	(blood glucose or plasma glucose or blood sugar or plasma sugar).tw.	49961
32	Hemoglobin A, Glycosylated/	13680
33	(hemoglobin a glycosylated or haemoglobin a glycosylated or glycosylated hemoglobin$ or glycosylated haemoglobin$ or glycated hemoglobin$ or glycated haemoglobin$ or glycohemoglobin a or glycohaemoglobin a or hba1c or hb a1c).tw.	12436
34	"laboratory techniques and procedures"/ or hematologic tests/ or urinalysis/	18912
35	(lab$ test$ or hematologic$ test$ or blood test$ or urinalys$ or urine test$).tw.	32577
36	Glycosuria/	4131
37	(glycosuria or urin$ glucose).tw.	2205
38	Fructosamine/	1173
39	fructosamine$.tw.	1445
40	Reagent Strips/	2399
41	(reagent strip$ or test strip$).tw.	1333
42	World Health Organization/	20622
43	world health organi?ation.tw.	15166
44	(world health organi?ation adj5 criteria).tw.	1625
45	((american diabetes association or ada) not american dental association).tw.	5962
46	australian diabetes society.tw.	17
47	"reproducibility of results"/ or exp "sensitivity and specificity"/	376568
48	(reproducibility of results or reproducibility of findings or reliabilit$ or validit$ or sensitivit$ or specificit$ or accurac$ or efficac$).tw.	989749
49	or/22-48	1715268
50	frequen$.tw.	776240
51	time interval$.tw.	24860
52	how often.tw.	2370
53	disease progression/	56365

54	(disease progress$ or progress$ of disease$).tw.	26654
55	(rate of progress$ or progress$ rate).tw.	3141
56	longitudinal studies/ or follow-up studies/ or prospective studies/	630671
57	(longitudinal stud$ or longitudinal survey$ or follow up stud$ or followup stud$ or prospective stud$).tw.	132568
58	periodic$ test$.tw.	134
59	re test$.tw.	815
60	or/50-59	1458710
61	meta-analysis.pt.	19122
62	(meta-anal$ or metaanal$).tw.	22390
63	(quantitativ$ review$ or quantitativ$ overview$).tw.	405
64	(systematic$ review$ or systematic$ overview$).tw.	15976
65	(methodologic$ review$ or methodologic$ overview$).tw.	195
66	review.pt. and medline.tw.	19425
67	or/61-66	53304
68	randomized controlled trial.pt.	262367
69	controlled clinical trial.pt.	79684
70	randomized controlled trials as topic/	56200
71	random allocation/	62329
72	double blind method/	99559
73	single blind method/	12383
74	or/68-73	442869
75	animals/ not (animals/ and humans/)	3241353
76	74 not 75	414709
77	clinical trial.pt.	456623
78	exp clinical trials as topic/	209671
79	(clinic$ adj25 trial$).tw.	149731
80	cross-over studies/	22648
81	(crossover or cross-over or cross over).tw.	41577
82	((singl$ or doubl$ or tebl$ or tripl$) adj25 (blind$ or mask$)).tw.	99073
83	placebos/	27892

84	placebo$.tw.	112671
85	(randomi?ation or random allocation or random selection or random assignment or randomly allocated or randomly selected or randomly assigned or randomly divided or randomly distributed).tw.	101960
86	research design/	53877
87	or/77-86	798689
88	87 not 75	761595
89	76 or 88	799312
90	and/12,21,49,67	45
91	and/12,21,49,89	518
92	(and/12,21,49) not 90 not 91	2971
93	and/12,21,60,67	26
94	and/12,21,60,89	250
95	(and/12,21,60) not 93 not 94	1633
96	90	45
97	limit 96 to (english language and humans and yr="1999 - 2008")	42
98	91	518
99	limit 98 to (english language and humans and yr="1999 - 2008")	352
100	92	2971
101	limit 100 to (english language and humans and yr="1999 - 2008")	1760
102	93	26
103	limit 102 to (english language and humans and yr="1999 - 2008")	22
104	94	250
105	limit 104 to (english language and humans and yr="1999 - 2008")	156
106	95	1633
107	limit 106 to (english language and humans and yr="1999 - 2008")	983

Appendix 3: NHMRC Evidence Statement Grading Form

(If rating is not completely clear, use the space next to each criteria to note how the group came to a judgment.)

Key question(s): 1. Is case detection and diagnosis of type 2 diabetes worthwhile?		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One RCT is currently addressing this issue – result not available until 2010. Studies cited in this section are Level III and Level IV	~~A~~	Several Level I or II studies with low risk of bias
	~~B~~	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of
	D	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Studies consistently reported potential benefit of case detection	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	~~A~~	Very large
	B	Moderate
	~~C~~	Slight
	~~D~~	Restricted
4. Generalisability		

	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be
	D	Evidence not directly generalisable to target population and hard to judge
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C/D	
2. Consistency	B	
3. Clinical impact	B	
4. Generalisability	A	
5. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	Grade C	

Identify and treat type 2 diabetes at a stage before clinical presentation in order to reduce morbidity from long term complications

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	~~YES~~
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation? Awareness of guideline recommendation by primary care physicians	YES
	~~NO~~

NHMRC Evidence Statement
(If rating is not completely clear, use the space next to each criteria to note how the group came to a judgment.)

Key question(s): 2. How should case detection and diagnostic testing for type 2 diabetes be performed?		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Several studies providing the evidence base for this question	~~A~~	Several Level I or II studies with low risk of bias
	B	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Most studies agree on the preferred protocol for case detection	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	~~A~~	Very large
	B	Moderate
	~~C~~	Slight
	~~D~~	Restricted

4. Generalisability		
	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be
	~~D~~	Evidence not directly generalisable to target population and hard to judge
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	
2. Consistency	B	
3. Clinical impact	B	
4. Generalisability	A	
5. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	Grade B	

A three-step case detection and diagnosis procedure is recommended for detecting people with undiagnosed type 2 diabetes:

1. Initial risk assessment determined using a risk assessment tool or risk factors commonly associated with undiagnosed type 2 diabetes

2. Measurement of fasting plasma glucose

3. An oral glucose tolerance test performed in all people with an equivocal result – FPG of 5.5-6.9 mmol/L, or random plasma glucose of 5.5-11.0 mmol/L

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	~~YES~~
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

NHMRC Evidence Statement
(If rating is not completely clear, use the space next to each criteria to note how the group came to a judgment.)

Key question(s): 3. How often should testing be performed?		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Few studies have specifically addressed this issue	~~A~~	Several Level I or II studies with low risk of bias
	~~B~~	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The few studies report consistent findings	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	~~A~~	Very large
	B	Moderate
	C	Slight
	~~D~~	Restricted

4. Generalisability		
	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be
	~~D~~	Evidence not directly generalisable to target population and hard to judge
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	
2. Consistency	B	
3. Clinical impact	B/C	
4. Generalisability	A	
5. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	Grade C	

Periodic re-testing for undiagnosed type 2 diabetes is recommended according to the following schedule:
- Each year for people with impaired glucose tolerance or impaired fasting glucose
- Every 3 years for all other people

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	~~YES~~
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

NHMRC Evidence Statement
(If rating is not completely clear, use the space next to each criteria to note how the group came to a judgment.)

Key question(s): 4. What are the socio-economic implications for case detection and diagnosis of type 2 diabetes?		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Evidence based on modelling for which there is no level of evidence	~~A~~	Several Level I or II studies with low risk of bias
	~~B~~	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
	N/A	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Modelling studies provide consistent results	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	~~A~~	Very large
	B	Moderate
	C	Slight
	~~D~~	Restricted

4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be
	D	Evidence not directly generalisable to target population and hard to judge
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	N/A	
2. Consistency	B	
3. Clinical impact	B	
4. Generalisability	A	
5. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	Grade C	

Screening for undiagnosed type 2 diabetes in high risk individuals should be an integral component of a diabetes prevention program

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	~~YES~~
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

Appendix 4: Overview of Guideline Development Process and Methods

National Evidence Based Guidelines for the Prevention and Management of Type 2 Diabetes

Overview of Guideline Development Process and Methods

Prepared by
The Diabetes Unit
Menzies Centre for Health Policy
The University of Sydney

for the
Diabetes Australia Guideline Development Consortium

Last updated 5 May 2009

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Purpose and Structure of the Document

Purpose

This 2008-9 series of guidelines for type 2 diabetes updates and builds on the original suite of evidence based diabetes guidelines which were initiated in 1999 under funding from the Department of Health and Ageing (DoHA) to the Diabetes Australia (DA) Guideline Development Consortium. Under the initial diabetes guideline project, six evidence based guidelines for type 2 diabetes were endorsed by the NHMRC. The purpose of the initial guidelines and the current guidelines is to provide systematically derived, objective guidance to:

1. Improve quality and consistency of care and reduce inappropriate variations in practice by assisting clinicians' and consumers' understanding of and decisions about treatment and management options
2. Inform fund holders and health service planners about the effectiveness and feasibility of the various options
3. Assist researchers and research authorities to highlight i) areas of diabetes prevention and care for which there is inconclusive evidence and ii) areas of deficiency in the evidence which require further or definitive research.

The specific purpose of this current project which commenced in early 2008 was to update two of the previous guidelines - Primary Prevention, and Case Detection and Diagnosis – and to develop three new guidelines, one for Blood Glucose Control, one for Chronic Kidney Disease and one for Patient Education.

Structure

This *Overview of the Guideline Development Process and Methods* outlines the rationale for the guidelines and the organisational structure, methods and processes adopted for the Type 2 Diabetes Guideline project, including the Blood Glucose Control Guideline. The guidelines are structured to present the recommendations, practice points, evidence statements, documentation of search strategies and search yield and a textual account of the evidence underpinning each recommendation.

Final format and implementation

The contract between the DoHA and the DA Guideline Development Consortium makes provision for locating and synthesising the available evidence on the five index areas into guideline recommendations and describing the objective justification for the recommendations. Thus, the contract covers the development of the guidelines up to and including endorsement by the NHMRC but does not include implementation of the guidelines.

However, following endorsement by the NHMRC there will need to be an independent process of consultation with potential guideline users to determine the final format of the guidelines for wide dissemination to clinicians and consumers. Once this format has been agreed, an implementation strategy to encourage and facilitate the widespread uptake of the guidelines in everyday practice will need to be developed and actioned at national and state

and territory level. It is our understanding that the DoHA has developed an implementation plan and strategies and is currently obtaining internal sign-off on these before enacting them.

1.0 Introduction and Overview

1.1 Diabetes as a health burden

Results of the national diabetes prevalence survey, AusDiab (Dunstan et al, 2002), which was conducted on representative sample of some 11,000 people across Australia, found a prevalence of diabetes of 7.4% in people aged 25 years or older. Another 16.4% of the study population had either impaired glucose tolerance or impaired fasting glucose. AusDiab also confirmed that there is one person with undiagnosed diabetes for every person with diagnosed diabetes. Findings from the second phase of AusDiab, a 5-year follow-up survey of people who participated in the baseline study, have indicated that every year eight out of every 1,000 people in Australia developed diabetes (Barry et al, 2006). This, together with the increasing number of new cases of pre-diabetes, obesity, the metabolic syndrome, and kidney disease, has demonstrated that abnormal glucose metabolism is exerting a major impact on the health of Australians (Magliano et al, 2008).

Diabetes has a demonstrably high health and cost burden (Colagiuri et al, 2003; AIHW, 2008) resulting from its long term complications which include:

- heart disease and stroke
- foot ulceration, gangrene and lower limb amputation
- kidney failure
- visual impairment up to and including blindness
- erectile dysfunction

The health burden of diabetes is described in more detail throughout the guideline series but to put these complications in perspective, it is worth noting here that, in Australia, diabetes is the most common cause of:

- blindness in people under the age of 60 years
- end stage kidney disease
- non-traumatic amputation

Diabetes is heavily implicated in deaths from cardiovascular disease (CVD) but, due to death certificate documentation deficiencies; this link is believed to be substantially under reported. At a global level, diabetes is predicted to increase dramatically in the next decade or two (IDF, 2006). With an ageing and increasingly overweight and physically inactive population, and a cultural mix comprising numerous groups known to be at high risk of type 2 diabetes, Australia is a prime candidate for realising the projected increases.

Due to sheer numbers, the major proportion of the total diabetes burden is attributable to type 2 diabetes which is the most common form of diabetes and accounts for approximately 85% of all diabetes in Australia. Type 2 diabetes occurs predominantly in mature adults with the prevalence increasing in older age groups. However, in high risk populations such as Aboriginal and Torres Strait Islander people it may become manifest much earlier.

These guidelines focus exclusively on type 2 diabetes in non-pregnant adults. Like type 1 diabetes, type 2 diabetes is characterised by high blood glucose levels. However, unlike type 1 diabetes, the key feature of type 2 diabetes is insulin resistance rather than insulin deficiency. Consequently, its treatment does not necessarily require insulin and in many people, particularly in the initial years following diagnosis, type 2 diabetes can be successfully

managed with dietary and general lifestyle modification alone or in combination with oral anti-diabetic medications. Insulin therapy may be required if and when oral medication becomes ineffective in lowering and maintaining the blood glucose within an acceptable range. Assiduous attention to the management of elevated blood pressure, lipid problems and overweight is also required as these common features of type 2 diabetes markedly increase the risk of long term complications.

1.2 Key components and principles of diabetes care

Key components of care
In 1995, the NSW Health Department identified three key components of diabetes care, stating that …. 'there is consensus supported by published literature that diabetes care and outcomes can be improved by providing access for all people with diabetes to:

- information about their condition and self care education
- ongoing clinical care to provide optimal metabolic control
- screening for and appropriate treatment of complications' (Colagiuri R et al, 1995).

These and the principles of care below were included in the initial suite of guidelines for type 2 diabetes and remain as valid now as they were then.

Principles of care
The particular expression of the universally accepted diabetes care principles set out below was abbreviated from those developed by the UK Clinical Advisory Group (CSAG, 1994) and later summarised by the NSW Health Expert Panel on Diabetes (New South Wales (NSW) Department of Health, 1996) and was further adapted for this project:

- People with diabetes should have access to timely and ongoing care from a diabetes team. This should ideally include a doctor, nurse and dietitian with specific training and experience in the management of diabetes. Additional expertise, for example in podiatry, social work, behavioural psychology and counselling, should be available as required as should referral access to specialist services for the management of identified complications

- People with diabetes are entitled to access to opportunities for information, education and skills acquisition to enable them to participate optimally in their diabetes management

- People with diabetes are entitled to access high quality health services regardless of their financial status, cultural background, or place of residence

- For people with diabetes from community groups who may have special needs eg people from Aboriginal, Torres Strait Islander or culturally and linguistically diverse backgrounds and the elderly, diabetes care should be specifically tailored to overcoming access barriers and providing opportunities for optimising diabetes care and outcomes

- Diabetes teams should routinely evaluate the effectiveness of the care they provide

1.3 Rationale for the Guidelines

The magnitude of the impact of diabetes on individuals and society in Australia is manifest in its status as a National Health Priority Area since 1996 and the current attention directed to it by the Council of Australian Governments' National Reform Agenda which seeks to address and avert a greater impact on productivity than already exists as a result of diabetes.

For tangible and lasting benefits, evidence based information is required which synthesises new and existing evidence to guide primary prevention efforts and assist clinicians to identify and treat modifiable primary risk factors, accurately diagnose type 2 diabetes, assess metabolic control, provide effective routine care, and make appropriate and timely referrals.

Since the initial suite of NHMRC diabetes guidelines was released there has been a vast improvement in both the volume and quality of the evidence about preventing type 2 diabetes which is detailed in the Primary Prevention Guideline. Nonetheless, there remain grave concerns that the rapidly increasing prevalence of obesity combined with decreasing levels of physical activity will continue to impact negatively on the incidence and prevalence of diabetes unless addressed as a mater of urgency. Consequently, the Primary Prevention Guideline also cites some of the emerging evidence about environmental influences on food consumption and physical activity.

Type 2 diabetes represents a complex interaction of patho-physiological factors and its prevention and successful management requires clinicians and public health practitioners to maintain a thorough understanding of these interactions especially since there is now irrefutable evidence that both the onset of diabetes and the onset of its complications can be prevented or significantly delayed. Given the typically long pre-clinical phase of type 2 diabetes and that half of all people with diabetes are undiagnosed, the Case Detection and Diagnosis Guideline is an important component of this suite of guidelines.

Integral to the successful management of diabetes is self care knowledge and skills, and the capacity of the person with diabetes to adapt their lifestyle to optimise their physical and psychological well being. The Patient Education Guideline presents evidence addressing these issues.

The care of type 2 diabetes is predominantly carried out by general practitioners, often under 'shared care' arrangements with local Diabetes Centres and/or private endocrinologists. In remote Australia, and even in more densely settled rural regions, the population base is insufficient to support specialist diabetes teams and the general practitioner may not have local access to specialist referral and support. Regardless of geographical factors, standards of diabetes clinical care in Australia are known to be variable. The Chronic Kidney Disease Guideline sets out diagnostic criteria and therapies for achieving the treatment targets to guide the identification, prevention and management of kidney disease in people with diabetes.

Microvascular complications (retinopathy, nephropathy and neuropathy) and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease) are associated with reduced life expectancy and significant morbidity in type 2 diabetes. Using therapeutic interventions to lower blood glucose and achieve optimal HbA1c levels is critical in preventing diabetes complications and improving the quality of life. The Blood Glucose Control Guideline examines the evidence and the relationships among these issues.

1.4 Funding source

The Type 2 Diabetes Guidelines project is funded by the DoHA under a head contract with DA as convenor of the Guideline Development Consortium. The development of the guidelines is managed in partnership with DA by The Diabetes Unit at the University Sydney under the direction of A/Professor Ruth Colagiuri.

1.5 The Guideline Development Consortium

The Guideline Development Consortium led by DA comprises organisations representing consumers, specialist diabetes practitioners and primary care physicians and includes:

- The Australian Diabetes Society (ADS)
- The Australian Diabetes Educators Association (ADEA)
- The Royal Australian College of General Practitioners (RACGP)
- The Diabetes Unit – Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), the University of Sydney.

Additionally there are a number of collaborators:

- The NSW Centre for Evidence Based Health Care (University of Western Sydney)
- The Cochrane Renal Review Group (Westmead Children's Hospital)
- The Cochrane Consumer Network
- The Caring for Australians with Renal Impairment Guidelines Group (CARI),
- Kidney Health Australia.

1.6 The scope of the Guidelines

The brief for the Guideline Development Project was to prepare a set of evidence based guidelines for type 2 diabetes to NHMRC standard.

The Type 2 Diabetes Guidelines target public heath practitioners, clinicians (medical, nursing and allied health), diabetes educators and consumers and were designed to be appropriate for use in a wide variety of practice settings. The guidelines focus on care processes and interventions that are primarily undertaken in the non-acute setting ie they do not deal with highly technical procedural interventions such as renal dialysis.

1.7 Use of the Guidelines

Guidelines are systematically generated statements which are designed to assist health care clinicians and consumers to make informed decisions about appropriate treatment in specific circumstances (Field MJ & Lohr, 1990).

Guidelines are not applicable to all people in all circumstances at all times. The recommendations contained in these guidelines are a general guide to appropriate practice and are based on the best information available at the time of their development. The clinical guidelines should be interpreted and applied on an individual basis in the light of the health care practitioner's clinical experience, common sense, and the personal judgments of consumers about what is appropriate for, and acceptable to them.

1.8 Review date

New information on type 2 diabetes is continually and rapidly becoming available. The Project Management Team and Steering Committee recommend that these guidelines are reviewed and revised at least every three years after publication. We anticipate this will be June 2012.

1.9 Economic analysis

Assessment of economic impact i.e., analysing the cost implications of recommendations has become a mandatory component of guideline development.

1.10 Socio-economic impact

The Expert Advisory Groups for each guideline were encouraged to adopt a framework that is recommended by the NHMRC to identify, appraise and collate evidence of the impact of socioeconomic position and other markers of interest eg income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

2.0 Organisational structure and staffing

The organisational structure of the Guideline Development Project (Figure 1) comprises:

- A Steering Committee
- Project Management Team
- Expert Advisory Groups
- Guidelines Assessment Register Consultant
- Research Officers
- Research team

The Steering Committee consists of a representation from each of the Consortium members, the Guideline Project Medical Advisor, and the DoHA. Refer to Appendix i for Terms of Reference. The Project Steering Committee provides guidance and directions to the project and to the DoHA via DA. The main role was to oversee the project progress and timeline.

Expert Advisory Groups (EAGs) were established for each of the five guideline areas. They have a core composition of a consumer, a general practitioner, content experts nominated by the Australian Diabetes Society and the Australian Diabetes Educators Association, and other representation as appropriate. Consumers on the expert advisory groups were provided by Diabetes Australia as being representative of people with type 2 diabetes who are experienced in acting as consumer representatives and who had a detailed understanding of issues affecting people with diabetes. Terms of Reference of the EAGs is provided in Appendix ii. Lists of the individual members of each of the EAGs are provided in each guideline.

The Project Management Team. The Diabetes Unit, at Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), University of Sydney was subcontracted by DA to manage the project on behalf of the Consortium. The Diabetes Unit provides guidance on methods, technical support, data management, co-ordinates the input of the EAGs and supervises the project staff on a daily basis. The Project Management Team consists of the Director of the Diabetes Unit, the CEO of Diabetes Australia and the project's Medical Advisor.

Guidelines Assessment Register (GAR) consultans. The NHMRC nominated a GAR consultant for each guideline (except the Blood Glucose Control guideline) to provide guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. Specifically, the GAR consultants provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Research Officers were recruited or seconded from a variety of research and health care disciplines and given additional training to conduct the literature searches, and review, grade and synthesise the evidence under the supervision of the Senior Research and Project Manager, Dr Seham Girgis, the Chairs of the EAGs and the Project Management Team.

Research Team refers to the Project Director, Senior Project Manager, Research Officers, and the project's Medical Advisor.

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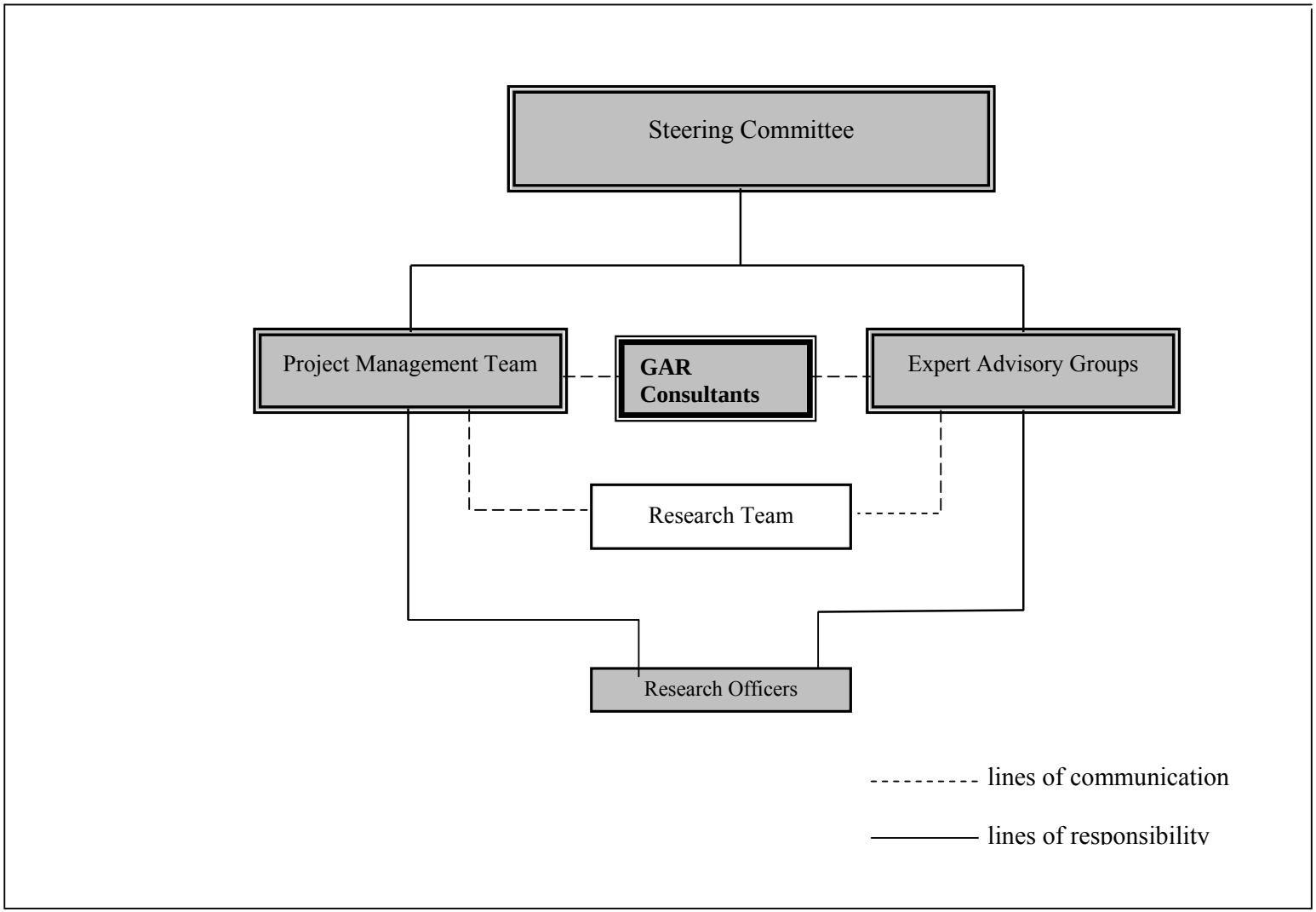
Figure 1: Organisational Structure



3.0 Methods

3.1 Development of Protocols

At the beginning of the project, a Methods Manual was developed for the EAGs and project staff. The Manual was based on the NHMRC *Standards and procedures for externally developed guidelines* (NHMRC, 2007) and the series of handbooks on the development, implementation and evaluation of clinical practice guidelines published by the NHMRC from 2000–03. The NHMRC Standards and procedures document (NHMRC, 2007) introduced an extended set of levels of evidence and an approach to assessing a body of evidence and grading of recommendations. These standards and handbooks have superseded *A guide to the development, implementation and evaluation of clinical practice guidelines* (NHMRC, 1999), which formed the basis of the initial suite of NHMRC guidelines for type 2 diabetes.

The NHMRC has introduced a requirement for guidelines to consider issues related to cost-effectiveness and socioeconomic impact. Two publications in the NHMRC toolkit for developing clinical practice guidelines have been used to address these issues - how to compare the costs and benefits: evaluation of the economic evidence (NHMRC, 2001) and using socioeconomic evidence in clinical practice guidelines (NHMRC, 2003).

The Methods Manual developed for the project contains definitions, procedures and protocols, descriptions of study type classifications, checklists and examples of steps and methods for critical appraisal of the literature. It also includes the revised level of evidence and the minimum requirements for formulating NHMRC evidence based guidelines.

3.2 Guideline Development Process

From the literature and expert opinion the following steps were identified as central to the process of identifying sources of rigorously objective, peer reviewed information and reviewing, grading, and synthesising the literature to generate guideline recommendations:

1. Define specific issues and generate clinically relevant questions to guide the literature searches for each guideline topic.
2. Search the literature systematically using a range of databases and search strategies.
3. Sort the search yield on the basis of relevance to the topic area and scientific rigour.
4. Document the search strategy and the search yield.
5. Critically review, grade and summarise the evidence.
6. Assess the body of evidence according to the published NHMRC standard and formulate guideline statements and recommendation/s in accordance with the evidence.
7. Formulate the evidence statements and recommendations.
8. Conduct quality assurance throughout all these steps.

Step 1: Defining issues and questions to direct the literature searches

Each EAG was asked to define key issues for the guideline and to generate a set of questions focusing on clinically relevant issues to guide the literature searches. These critical clinical issues also formed the focus of the guideline recommendations and accompanying evidence statements. A generic framework was developed and centred on issues such as:

- What are the key treatment/management issues for this area?
- What anthropometric, clinical or behavioural parameters need to be assessed?
- Should everyone be assessed or are there particular risk factors which warrant selective testing or preventative treatment?
- What assessment techniques should be used?
- How often should the assessment be done?
- How should the results be interpreted?
- What action should follow from the results (if abnormal) e.g., management, further investigation, referral?
- What are the overall costs of using the intervention? (particularly in relation to changes in costs if changes to management are recommended)
- What is the impact of socioeconomic position and other markers of interest e.g., income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

EAGs were also advised to frame each question using the **'PICO'** elements as follows: **P**opulation **or P**roblem; **I**ntervention (for a treatment intervention question), **or I**ndicator or exposure (for a prognosis or aetiology or question), **or I**ndex test (for a diagnostic accuracy question); **C**omparator; and **O**utcome.

The resulting questions developed by each EAG are presented at the beginning of each guideline and again in the Search Strategy and Yield Table.

Step 2: Searching the literature

NHMRC clinical practice guidelines are required to be based on systematic identification and synthesis of the best available scientific evidence (NHMRC, 2007). A number of systematic strategies were used in this project to identify and assess scientific information from the published literature. The search strategies were designed to reduce bias and ensure that most of the relevant data available on type 2 diabetes were included in the present review and were similar to those detailed in the Cochrane Collaboration Reviewers Handbook (Higgins JPT et al). Several strategies were used to identify potentially relevant studies and reviews from the literature such as:

Electronic Databases
Searches were carried out using the following databases:

- Medline
- Cochrane Library: Databases of Systematic Reviews, DARE, Controlled Trials Register, Central, HTA.
- Additional databases searched where indicated included:
  Embase
  Cinahl
  Psycho Info
  Eric
  Other (where appropriate) such as Internet, Expert sources, Hand searching of reference lists at the end of relevant articles.

Key words
The key words (MeSH terms and some free text terms) used when searching these electronic databases are presented in detail in the Search Strategy and Yield Table at the end of each guideline topic. The EAGs limited their searches through a number of methods including:
- specification of temporal constraints (e.g. 1999-2008 for the updated guideline)
- language constraints (English only)
- where there were overwhelming amounts of literature or if there was a large volume of poor quality research, some groups imposed limits by experimental design to exclude the less rigorous forms of research.

Details of specific inclusion criteria for the EAG are also presented, together with the key words, at the end of each individual guideline.

Consultation with colleagues
The EAGs were encouraged to gather relevant information/articles from other experts and colleagues. The Project Management Team collated the questions developed by each EAG to direct the literature searches and highlight overlapping questions and requested EAGs and Research Officers to send any articles identified as applicable to other guideline topics to the EAG.

Step 3: Sorting the search yield

Two or more members of each EAG were responsible for sorting through the search results by scanning the lists of titles and abstracts generated by the electronic database searches, highlighting potentially relevant articles and requesting printed full articles. Full articles were retrieved and those which were relevant were assessed for quality. Articles were considered relevant if they provided direct or indirect information addressing one or more of the specified 'clinical issues' questions and were applicable to diabetes care or prevention in Australia.

Sorting according to study design

Articles with original data were sorted according to study design. Articles with the most rigorous experimental designs were reviewed in the first instance. Articles conducted to other study designs were included if they added new information not found in the papers of highest levels of evidence. Relevant papers were sorted as follows:

- Meta-analysis, systematic review of randomised controlled trials (interventions)
- Randomised controlled trials (RCT)
- Cohort studies
- Case control studies
- Case series, pre-post or post studies

Exclusion criteria

Articles were not included for review if it was apparent that their relevance to formulating a guideline recommendation was non-existent or negligible. Examples of reasons for non review included criteria such as:

- Studies of inappropriate patient population(s) for the question being addressed (epidemiology, specific diet)
- Hypothesis/mechanism/in vitro study/animal studies
- Genetic studies that are clinically inapplicable
- Non-systematic reviews which presented the author's opinion rather than evidence

Step 4: Documenting the search strategy and its yield

The search strategy (terms and limits) and yield were documented and are available for viewing in a table at the end of each guideline. In brief, the Search Strategy and Yield Table recorded details about the:

1. Questions being investigated
2. Electronic databases searched
3. MeSH terms and key words used to search the database
4. Methods for limiting the searches
5. Number of articles identified by each search
6. Number of articles relevant from that search
7. Number of relevant articles identified through other search processes
8. Number of articles obtained for review
9. Number of relevant articles which were systematic reviews, RCTs or well designed population based studies, quasi-experimental and other (these were documented in the tables according to the updated NHMRC Evidence Levels I –IV).
10. Number of articles reviewed
11. Highest level of evidence found for each question

Step 5. Critically reviewing, grading and summarising the evidence

All relevant articles were reviewed and critically assessed using checklists recommended by the NHMRC (2000) (NHMRC, 2000a; NHMRC, 2000b).The NHMRC checklist sets out an explicit standardised approach to reviewing and incorporating scientific evidence into clinical practice guidelines.

In addition, Research Officers were asked to construct tables to summarise extraction of data and to provide a brief summary of the key results for each article.

Overall assessment of individual studies
At the conclusion of reviewing each article, the reviewers rated the evidence in a summary form as shown in (Table 1) using the following criteria:

- *Levels of evidence*
  The 'interim' NHMRC levels of evidence (NHMRC, 2007) was used in this project to assess levels of evidence for a range of study designs (Appendix iv).
- *Quality rating*
- *Magnitude of effect*
- *Relevance rating*

Criteria for quality of evidence, magnitude of effect, and relevance of evidence were based on those provided by the NHMRC (2000a &b). These criteria are presented in Appendix iv.

Table 1: Example of an Overall Assessment Report

Assessment Category	**Rating**			
	Value	Low	Medium	High
Level of evidence				
Quality rating				
Magnitude of effect				
Relevance rating				

These assessments were then used in the evidence tables which summarises basic information about **Each Study** reviewed, including an overall assessment of the evidence (Table 2).

Table 2: Example of an evidence table with overall study assessment

Author, Year	**Evidence**				
	Level of Evidence		***Quality Rating***	***Magnitude of Effect Rating***	***Relevance Rating***
	Level	***Study Type***			
Author X (1999)	III-2	Cohort	High	Low	High

Step 6. Assessing the body of evidence and formulating guideline evidence statements and recommendations

In addition to considerations of the rigour of the research providing the evidence (Tables 1 and 2), principles for formulating guideline evidence statements and recommendations were derived consistent with the NHMRC recommended standard '*The NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

For each identified clinical question, evidence statements are based on an assessment of all included studies for that question (**the Body of Evidence**). The NHMRC considers the following five components in judging the overall body of evidence (NHMRC, 2007) as specified in the '*NHMRC Body of Evidence Matrix'* (Table 3):

- The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
- The consistency of the study results.
- The potential clinical impact of the proposed recommendation.
- The generalisability of the body of evidence to the target population for the guideline.
- The applicability of the body of evidence to the Australian healthcare context.

Based on the body of evidence, recommendation/s was formulated to address each of the identified clinical questions for the area. Recommendation/s was written as an action statement.

Principles for formulating the guideline recommendation/s

In the course of the face-to-face meetings of the EAGs, and from published sources, principles were identified re-affirming the need for guideline recommendations to:

- Be developed systematically and objectively by synthesising the best available evidence.
- Have potential to improve health and related outcomes whilst minimising possible harms.
- Be clinically relevant and feasible.
- Take account of ethical considerations, and acceptability to patients.
- Centre on interventions which are accessible to those who need them.
- Propose activities within the scope of the role of those expected to use the guidelines e.g., interventions which could be expected to be conducted in routine general practice.

Grading of recommendation/s

The grading of each recommendation reflects the strength of the recommendation (Table 4) and is based on 'The *NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

In face-to-face meetings, the EAG, initially graded each of the five components of the NHMRC Body of Evidence Matrix (Table 3) for each recommendation and then determined the overall grade for the body of evidence by summing the individual component grades (Appendix v).

Cost effectiveness analyses that were based on modelling, could not be evaluated using the NHMRC 'Body of Evidence Matrix'. Hence, cost-effectiveness recommendations were not graded.

Table 3: NHMRC Body of Evidence Matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Table 4: Definition of NHMRC grades of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Step 7. Articulate the guidelines

For each guideline, clinical questions identified by EAGs are addressed in separate sections in a format presenting:

- *Recommendation(s*) - including grading.
- *Practice Point (s)* – including expert consensus in absence of gradable evidence.
- *Evidence Statements* - supporting the recommendations.
- *Background* - to issues for the guideline.
- *Evidence* - detailing and interpreting the key findings.
- *Evidence tables* - summarising the evidence ratings for the articles reviewed.
  At the end of the guideline, references and Search Strategy and Yield Tables documenting the identification of the evidence sources were provided.

To ensure consistency between the guidelines, a template was designed for writers to use when drafting the guidelines.

Step 8. Methods for Quality Assurance across the project

To ensure optimal accuracy and consistency within and between guideline areas, the Project Management Team conducted a range of quality assurance activities throughout the project:

Quality Assurance, Procedures and Protocols

- The provision of a Methods Manual which provides written instructions to the Chairs of the EAGs and research staff identifying the steps and processes to be followed.

- The provision to the EAGs of a selection of key published resource material relevant to the development of the guidelines (NHMRC tool kit 2000-2003; NHMRC, 2007).

- Specification and training of research staff on the search process.

Quality Assurance, Methods

- The appointment of a Senior Research Officer to the Project Management Team to advise on research methods, and provide a resource and support service to the research staff.

- The establishment of a Methods Advisory Group.

- The development of questions based on key clinical issues for each guideline topic to focus and guide the literature searches and the formulation of the guideline recommendations. As previously indicated, these are listed at the beginning of each guideline and the Search Strategy and Yield Table at the end of the guideline.

- The Project Management Team collated and reviewed the questions and undertook a Delphi - like process with the Chairs of EAGs to refine these questions. In addition, all EAGs and the Project Management Team reviewed the combined questions during one of the three face-to-face meetings.

- The design and provision to Chairs of EAGs and Research Officers of standardised forms documenting aspects of the search strategy used, the search yield, and the inclusion and exclusion of articles for review. A completed Search Strategy and Yield Table follows each guideline topic.

- The Senior Research Officer reviewed:
  - all search terms used to ensure that the searches were comprehensive and that the approach was similar across groups.

  - the documentation of the search process.

- The GAR Consultants worked closely with the Senior Research Officer and EAGs. The GAR Consultants provided advice on evaluating and documenting the scientific evidence, developing evidence-based recommendations based on the scientific literature, and NHMRC procedures.

- Double culling of the search yield for each guideline topic by project staff and members of the EAG.

- Double reviewing of a sample of completed reviews for each guideline topic by the Senior Research Officer or an experienced Research Officer, or by a member of the relevant EAG.

- Review of the completed recommendations and written description of the literature review for each guideline area was undertaken to check for:
  - appropriate use of references
  - accurate application of evidence ratings
  - congruence between the recommendations and evidence statements
  - consistency between recommendations
  - clarity of the literature review findings

4.0 Consultation Process

The organisational structure for the Type 2 Diabetes Guidelines Development Project was designed to involve and ensure consultation between the Guideline Development Consortium (DA, ADS, ADEA, RACGP) and the Diabetes Unit. A number of other strategies were employed to ensure wide consultation with a range of stakeholders and interested groups and individuals.

Initial Consultation
Prior to commencement of the project, initial consultation included contacting relevant professional organisations to discuss the guideline development and to seek nomination of content experts.

Internal Consultation
The internal communication and interaction between the Project Management Team and the research officers included fortnightly meetings, email communications, and regular telephone contact. In addition, for each guideline, there was individual informal meetings between the research officers and their project managers.

The Project Steering Committee
The Project Steering Committee comprised representatives from various organisations (who should be consulting with their colleagues in that organisation) include:

- Diabetes Australia (Mr Matt O'Brien)
- Medical Advisor (Professor Stephen Colagiuri)
- Australian Diabetes Society (Dr Maarten Kamp)
- Australian Diabetes Educators Association (Ms Jane Giles)
- Royal Australian Collage of General Practice (Professor Mark Harris)
- Department of Health and Ageing (Ms Suzanne Prosser)
- The Diabetes Unit, Menzies Centre for Health Policy (Associate Professor Ruth Colagiuri)

During the course of the project, DA convened two face-to-face meetings and three teleconferences of the Project Steering Committee members to provide guidance and direction to the project.

Expert Advisory Groups
The EAGs consulted formally through the inclusion of specific interest groups on the individual EAG. Examples include dietitians, clinicians, educators, researches, and consumers.

Communication strategies with EAG members included:

- Face-to-face meetings
  - an initial meeting to scope the coverage of the guideline and view the processes required to develop it, identify and agree on the roles of the EAG.
  - a final meeting to review and grade the recommendations and body of evidence form.

- Email communication seeking advice on research questions and search terms and requesting review of material developed.

- Chairs and individual members of EAGs, consulted with additional content experts regarding approaches and clinical/content issues as required.

Consultation with Guidelines Assessment Register (GAR) Consultants.
The GAR consultant for each guideline provided guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. GAR consultants attended face-to-face meetings with EAGs. They provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Consultation with Consumers
Consumer representatives were selected and appointed by Diabetes Australia for each EAG to ensure the consideration of people with type 2 diabetes with respect to their acceptability of the proposed guideline recommendations.

Public Consultation
All guidelines went through a formal public consultation process. This process was as follows:

- The guidelines were released for public consultation by Diabetes Australia through the NHMRC designated public consultation process between August and October 2008.

- The call for submissions was advertised in the national public press and a front page website advertisement was placed on the Diabetes Australia website, which linked to a full website advertisement.

- The NHMRC also advertised the draft guidelines in their 'bulletin'.

- Key stakeholder organisations (Appendix vi) were notified directly by email of the availability of the guidelines for public review and requested to comment. The emailed notice provided a link to the advertisement on the Diabetes Australia website.

- As a result of public consultation, submissions were received and referred to the Project Management Team:
  - six submissions relating to the Primary Prevention Guideline
  - four submissions relating to Case Detection and Diagnosis Guideline
  - two submissions relating to Patient Education
  - two submissions relating to Chronic Kidney Disease
  - five submissions relating to Blood Glucose Control
  - one submission did not relate to any of the guidelines but made comments on the overall process of the guideline development which was subsequently referred to the Diabetes Australia Guideline Consortium Steering Committee.

- The issues raised in these submissions were considered and consulted about internally and externally by the guideline developers and were reviewed by the Project Management and Research Teams, the Medical Advisor, the relevant EAG, and the GAR Consultant.

- Key issues from the submissions for each guideline were summarised into table form and corresponding responses addressing each issue were presented in separate documents entitled *"Response to Public Consultation on … "* and accompanied the guideline drafts presented to independent review by the NHMRC.

- Changes to the guidelines as a result of public consultation and as a result of independent review by the NHMRC were incorporated into the revised final guidelines.

Informal Consultation

Further consultation occurred throughout the project with a wide variety of groups and individuals in response to particular issues and needs. For example, the Chronic Kidney Disease Guideline has been reviewed by the CARI peer reviewers and presented at the Dialysis, Nephrology Transplant 2009 Workshop, Lorne Victoria. Comments from the peer reviewers and from the workshop have been incorporated into the subsequent revision of the draft guideline.

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APPENDICES

Appendix i: Terms of Reference of Steering Committee

Type 2 Diabetes Guidelines Project

1. Scope

The Steering Committee is a composite body which provides guidance and direction to the project and advice in relation to the project to the Department of Health and Ageing via Diabetes Australia.

2. Function

The role of the Steering Committee is to oversight and monitors the project progress and timelines.

3. Membership

The Steering Committee will comprise representatives from the following organisations:

- Diabetes Australia
- The Diabetes Unit, Australian Health Policy Institute
- Australian Diabetes Society
- Australian Diabetes Educators Association
- Royal Australian College of General Practitioners
- Medical Advisor
- Consumer – person with type 2 diabetes nominated by Diabetes Australia.

The Department of Health and Ageing (the Department) will be represented in an advisory role.

The final composition of the Steering Committee, the operating procedures and the Chair of the Committee will be agreed by the Department.

If a representative is unable to attend a meeting/teleconference they may nominate a proxy representative from their own organisation.

4. Quorum and Voting

The quorum for Steering Committee meetings is to be 50% of membership plus one additional member.

The Steering Committee shall always attempt to achieve consensus. In the event of decisions requiring a vote, each member of the Committee shall exercise a single vote. Decisions will be by a majority and the Chair shall have a casting vote.

5. Communication

The Steering Committee will communicate directly with Diabetes Australia who in turn will liaise with the Department. Communication between the Steering Group and other teams and groups is essential and will be facilitated by the Chair of the Committee.

Frequency of Meetings

The Steering Committee will meet on at least five occasions throughout the contract period. These meetings will comprise two face-to-face meetings and three teleconferences, throughout the contract period.

6. Executive and Operational Support

The Steering Group Secretariat will be provided by Diabetes Australia. The Secretariat will provide support in writing minutes and co-ordinating meetings

7. Funding

The costs of travel, accommodation, meeting location (or teleconference) expenses and other activities proposed by the Steering Committee will be agreed and borne by Diabetes Australia.

Appendix ii: Terms of Reference for Expert Advisory Groups

Type 2 Diabetes Guidelines Project

Purpose

The Expert Advisory Groups (EAGs) for the National Evidence Based Guidelines for Type 2 Diabetes are convened by The Diabetes Unit, Menzies Centre for Health Policy (formerly Australian Health Policy Institute), The University of Sydney under the head agreement between Diabetes Australia and the Department of Health and Ageing to support the development of the guidelines by providing:

1. Overall technical and content advice and critical comment

2. Input into the development or revision of research questions to guide the literature reviews

3. Guidance on search terms and for the literature review

4. Review of drafts of the guidelines and recommendations at critical points along the continuum of their development

5. Perspectives on the feasibility and applicability of the guidelines from the perspective of their own disciplines and their peers and colleagues

Duration

The EAGs are convened for the duration of the project. It is anticipated this will cover approximately 18 months up to end 2008.

Frequency of Meetings

It is anticipated that there will be three meetings of the EAGs mainly by teleconference with one face-to-face meeting at commencement.

The EAG members may also be asked to comment on emailed information from time to time.

Expenses

Reasonable expenses for travel to meeting will be reimbursed on presentation of original receipts

Conflict of Interests

EAG members are asked to declare any/all perceived conflict/s of interest

Appendix iii: NHMRC Evidence Hierarchy, designations of 'levels of evidence' according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II Studies	A systematic review of level II studies	A systematic review of level II studies	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, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised 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, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

(Source: NHMRC 2007)

Appendix iv: Study Assessment Criteria

I. Study quality criteria

Systematic reviews

1. Were the questions and methods clearly stated?
2. Is the search procedure sufficiently rigorous to identify all relevant studies?
3. Does the review include all the potential benefits and harms of the intervention?
4. Does the review only include randomised controlled trials?
5. Was the methodological quality of primary studies assessed?
6. Are the data summarised to give a point estimate of effect and confidence intervals?
7. Were differences in individual study results adequately explained?
8. Is there an examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention?
9. Were the reviewers' conclusions supported by data cited?
10. Were sources of heterogeneity explored?

Randomised controlled trials

1. Were the setting and study subjects clearly described?
2. Is the method of allocation to intervention and control groups/sites independent of the decision to enter the individual or group in the study ?
3. Was allocation to study groups adequately concealed from subjects, investigators and recruiters including blind assessment of outcome?
4. Are outcomes measured in a standard, valid and reliable way?
5. Are outcomes measured in the same way for both intervention and control groups?
6. Were all clinically relevant outcomes reported?
7. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?
8. Were >80% of subjects who entered the study accounted for at its conclusion?%
9. Is the analysis by intention to intervene (treat)?
10. Were both statistical and clinical significance considered?
11. Are results homogeneous between sites? (Multi-centre/multi-site studies only).

Cohort studies

1. Are study participants well-defined in terms of time, place and person?
2. What percentage (%) of individuals or clusters refused to participate?
3. Are outcomes measured in a standard, valid and reliable way?
4. Are outcomes measured in the same way for both intervention and control groups?
5. Was outcome assessment blind to exposure status?
6. Are confounding factors, comparable between the groups and if not comparable, are they adjusted for in the analysis?
7. Were >80% of subjects entered accounted for in results and clinical status described?
8. Was follow-up long enough for the outcome to occur
9. Was follow-up complete and were there exclusions from the analysis?
10. Are results homogeneous between sites? (Multicentre/multisite studies only).

Case-control studies

1. Was the definition of cases adequate?

2. Were the controls randomly selected from the source of population of the cases?
3. Were the non-response rates and reasons for non-response the same in both groups?
4. Is possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
5. Was ascertainment of exposure to the factor of interest blinded to case/control status?
6. Is exposure to the factor of interest measured in the same way for both case and control groups in a standard, valid and reliable way (avoidance of recall bias)?
7. Are outcomes measured in a standard, valid and reliable way for both case and control groups?
8. Are the two groups comparable on demographic characteristics and important potential confounders? and if not comparable, are they adjusted for in the analysis?
9. Were all selected subjects included in the analysis?
10. Was the appropriate statistical analysis used (matched or unmatched)?
11. Are results homogeneous between sites? (Multicentre/multisite studies only).

Diagnostic accuracy studies

1. Has selection bias been minimised
2. Were patients selected consecutively?
3. Was follow-up for final outcomes adequate?
4. Is the decision to perform the reference standard independent of the test results (ie avoidance of verification bias)?
5. If not, what per cent were not verified?
6. Has measurement bias been minimised?
7. Was there a valid reference standard?
8. Are the test and reference standards measured independently (ie blind to each other)
9. Are tests measured independently of other clinical and test information?
10. If tests are being compared, have they been assessed independently (blind to each other) in the same patients or done in randomly allocated patients?
11. Has confounding been avoided?
12. If the reference standard is a later event that the test aims to predict, is any intervention decision blind to the test result?

(Sources: adapted from NHMRC1999, NHMRC 2000a, NHMRC 2000b, Liddle et al 96; Khan et 2001)

Study quality – Rating

The following was used to rate the quality of each study against the study type criteria listed above.

High: all or all but one of the criteria were met

Medium: 2 or 3 of the criteria were not met

Low: 4 or more of the criteria were not met

II. Classifying magnitude of the effect

Ranking	Statistical significance		Clinical importance of benefit
High	Difference is statistically significant	AND	There is a clinically important benefit for the full range of estimates defined by the confidence interval.
Medium	Difference is statistically significant	AND	The point estimate of effect is clinically important BUT the confidence interval includes some clinically unimportant effects
Low	Difference is statistically significant OR Difference is not statistically significant (no effect) or shows a harmful effect	AND AND	The confidence interval does not include any clinically important effects The range of estimates defined by the confidence interval includes clinically important effects.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

III. Classifying the relevance of the evidence

Ranking	Relevance of the evidence
High	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival *Or* Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention
Medium	Evidence of an effect on proven surrogate outcomes but for a different intervention *Or* Evidence of an effect on proven surrogate outcomes but for a different intervention and population
Low	Evidence confined to unproven surrogate outcomes.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

Appendix v: NHMRC Evidence Statement Form

Key question(s):			Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	A	Several Level I or II studies with low risk of bias	
	B	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias	
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias	
	D	Level IV studies or Level I to III studies with high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
	A	Very large	
	B	Moderate	
	C	Slight	
	D	Restricted	
4. Generalisability			
	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability			
	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO

Appendix vi: Key stakeholder organisations notified of public consultation

- Diabetes Australia State and Territory member organisations including:
    - Australian Diabetes Society
    - Australian Diabetes Educators Association

- University Schools of Nursing, Medicine, Podiatry, Nutriton/ Dietetics
- Australian Podiatry Association
- Australian Podiatry Council
- Eyes on Diabetes
- Cooperative Centre for Aboriginal Health
- Australian Centre for Diabetes Strategies
- Public and private Diabetes Centres throughout Australia (for which we were able to obtain email addresses)
- State and Federal health departments