SCREENING FOR UNDIAGNOSED DIABETES AND PREDIABETES: COMPARING CANADIAN RECOMMENDATIONS AND WEIGHING THE EVIDENCE

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Guidelines Reviewed:

1. Canadian Diabetes Association 2003
2. American Diabetes Association 2004
3. Canadian Task Force on Preventive Health Care 2005 (and 1994)
4. USPSTF 2003
5. Diabetes UK 2002
6. New Zealand Guidelines Group 2003
7. New Zealand Health Strategy (New Zealand Ministry of Health) / Australian Diabetes Society / New Zealand Society for the Study of Diabetes / Royal College of Pathologists of Australasia / Australasian Society of Clinical Biochemists 2002
8. National Health and Medical Research Council (Australia) 2001
9. Finland Diabetes Association 2003
10. United States Department of Veterans Affairs 2003
11. Flemish Association of General Practitioners / Flemish Diabetes Association 2005
12. Dutch College of General Practitioners 1999
13. World Health Organization (& International Diabetes Federation) 2003 + World Health Organization 1999
14. International Diabetes Federation 2005
15. Primary Care Diabetes (PCD) Europe 2006

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SUMMARY

Introduction: Undiagnosed diabetes is common, but evidence is lacking as to how it should be sought for or whether diagnosing it makes a difference in outcomes. New evidence – in particular, results from the Finnish Diabetes Prevention Study, the Diabetes Prevention Study (DPP), and the Study To Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM), showing intensive lifestyle changes or pharmacotherapy can prevent or delay the onset of diabetes – suggest the need for new rationale for identifying pre-diabetes. In response, a number of organizations have updated their guidelines to recommend screening asymptomatic persons.

Method: This paper examines the updated screening guidelines and recommendations of the Canadian Diabetes Association (CDA – 2003) and the Canadian Task Force on Preventive Health Care (CTFPHC -2003/05), comparing each organization's rationale, evidence and evidence criteria, and discussing the strengths and weaknesses of each organization's position. We provide an outline of "How to Read the Evidence", summarized from Gerstein and Haynes (2001), and we present the evidence criteria adopted by the Cochrane Collaboration (UK) for its meta-analysis of randomized controlled trials which has been underway since 2005 and is anticipated to be published in 2006.

Finally, we provide a brief overview of international guidelines, including those from Australia, New Zealand, the United States (i.e. the USPSTF*, upon which the CTFPHC recommendations are based) and Europe.

Results: In its 1994 recommendations (adapted from the USPSTF recommendation, 1989), the Canadian Task Force on Preventive Health Care (CTFPHC) recommended against screening in the general asymptomatic population, given that there was "little direct evidence that asymptomatic persons benefit from the detection and treatment of IGT *(impaired glucose tolerance)*". Subsequently the CTFPHC's updated policy (2003/05) recommends diabetes screening only in individuals with hypertension and hyperlipidemia, with the objective of reducing cardiovascular events and/or cardiovascular mortality. The task force continues to recommend against screening in the general asymptomatic population, regardless of other criteria (including obesity and history of IGT/IFG) widely accepted as risk factors for diabetes.

Based on the same evidence, the Canadian Diabetes Association (CDA) concludes screening should be undertaken in high-risk individuals (ex. ≥ 40 years old, parent or sibling with diabetes, history of impaired glucose tolerance) and populations (ex. Aboriginals). The CDA recommendations do not focus as exclusively on prevention of cardiovascular outcomes, rather on "preventable diabetes complications", including the macrovascular complications associated with IGT.

Our comparison of international guidelines reveals the majority favoring targeted diabetes screening in asymptomatic individuals possessing one or two or more of a diversity of risk factors (including overweight/obesity, age, family history, IGT/IFG and ethnicity). Of the 12 sets of guidelines we reviewed, only the CTFPHC and USPSTF recommended against regular screening of the general asymptomatic population despite criteria widely accepted as risk factors for diabetes.

Conclusion: The CDA and the CTFPHC present similar interpretations of existing evidence regarding diabetes and pre-diabetes screening and prevention. The organizations differ, however, in their mechanism for translating evidence into evidence-based recommendations: while the CTFPHC makes recommendations based only on existing evidence ("**evidence takes precedence over consensus**"), the CDA ultimately depends on "**expert consensus**" on this particular topic.

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* *United States Preventive Services Task Force*

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1. SCREENING ASYMPTOMATIC PERSONS

When discussing "screening" or "early detection", a fundamental consideration is that we are talking about the health care system inducing (or imposing on) asymptomatic and possibly healthy individuals to undergo testing, with the potential consequence of determining they are not in fact healthy or that in addition to known conditions that are/were causing symptoms there is an additional condition that was not causing symptoms but which may now give rise to concerns.(1) This poses a number of potential harms: distress, anxiety, impact on family and employment (including insurability), stigma and disease labeling, exposure to treatments that may have negative side effects, as well as the potential for false positives. As such, before initiating screening activities – whether mass, selective, opportunistic or case-finding (defined in Table 1) – the health system has a heightened duty to ensure potential benefits outweigh potential harms in order to justify telling asymptomatic persons they may be at risk for a disease.(1)

It is also important to understand that screening does not constitute diagnostic testing. A screening test reveals a person's risk for having or developing a disease or condition, but normally a second, confirmatory test carried out on a different day and in a laboratory / gold standard setting, is required for diagnosis. Additionally, screening tests / diagnostic tests that yield an 'intermediary diagnosis', such as pre-diabetes (IFG/IGT) cannot predict with certainty a person's risk for developing the 'real' disease or condition (diabetes).(1) These considerations speak to the potential harms of false positives, and in particular the anxiety experienced between screening and confirmatory testing, and between the 'pre' condition and the 'real' condition, both of which, in the case of pre-diabetes and diabetes, may be entirely asymptomatic. Finally even for true positives with respect to diabetes, intensive treatment for glycemic control introduces the risk of hypoglycemia and weight gain; and can lead to "labeling" as well as employment and insurance consequences.

Importantly, mass screening for other conditions, notably hypertension,(2-5) has been associated with declines in health related quality of life (HRQOL). However Edelman et al. (2002) showed no differences in HRQOL in a population of US veterans when tested one year after undergoing diabetes screening.(6) Patients diagnosed clinically appear to benefit from intensive glycemic control with improved HRQOL.(7)

Table 1 – TYPES OF EARLY DETECTION TESTS (1)[1]

Test	Definition	Example
Screening	Use of early detection test prompted by the health care system or its representative in persons who otherwise have not entered the health care system.	Public advertisements recommending that women undergo mammography for possible breast cancer.
Mass	Early detection test used in an entire population.	Testing all newborns for congenital hypothyroidism by serum thyrotropin-stimulating hormone levels.
Selective	Early detection test used in a subset of a population.	Treating women ≥ 50 years old for possible breast cancer by mammography.
Case Finding / Opportunistic Screening	Use of early detection test prompted by the health care system or its representative in persons who enter the health care system for another reason.	Testing for Type 2 diabetes by fasting plasma glucose levels in all patients with acute myocardial infarctions.

[1] Reference #1;,p. 185.

As Gerstein and Haynes note, screening is an intervention, with the main purpose of improving health outcomes at affordable economic costs for those screened.(1) Screening should therefore be efficacious, i.e. cause clinically important health gains in those being tested. Evidence for effective treatment to prevent or delay onset or progression of diabetes or diabetes complications is therefore a necessary to justify initiating screening.(1)

1.1 Principles/Conditions of Screening

Table 2 outlines eight conditions endorsed by the World Health Organization (WHO) for determining whether screening in asymptomatic populations is appropriate:

Table 2 – GENERAL PRINCIPLES (CONDITIONS) OF SCREENING(8,9)

1. Is the disease a public health problem?
2. Is there an acceptable treatment for the recognized disease?
3. Is there a recognizable latent or early symptomatic stage?
4. Is the natural history of the disease understood?
5. ***Is there a consensus on whom to treat?***
6. ***Are facilities for diagnosis and treatment available and accessible?***
7. ***Is there an economic balance between case finding and subsequent medical care?***
8. ***Is the program sustainable?***

Type 2 diabetes clearly satisfies conditions 1-4. A recent statement published by the American Diabetes Association (ADA) recommends an additional condition for assessing the appropriateness of screening: "Treatment after early detection yields benefits superior to those obtained when treatment is delayed".(10) There is debate whether diabetes satisfies this condition, plus conditions 5-8 listed in Table 2.

2. JUSTIFYING TYPE 2 DIABETES SCREENING

Hyperglycemia (the marker for diabetes and the primary cause of diabetes complications) develops gradually over many years. On average, people have type 2 diabetes for ten to 12 years before diagnosis. Lengthy stages of IFG/IGT precede onset of diabetes, and individuals may have already developed complications by the time they receive a diabetes diagnosis.(11,12) For example, retinopathy may begin developing seven years before clinical diagnosis.(12)

Given this, it is not surprising that when systematic screening is undertaken in populations, a substantial amount of undiagnosed diabetes is discovered. Rates in the general population may be as high as 50% of all those with diabetes,(13) and even higher amongst certain populations,(14) depending on age parameters and the diagnostic cut-offs in use at the time of reporting. The latest US population-based study showed rates of 2.4% undiagnosed diabetes in adults (between ages 20-74), compared to ~6% known diabetes cases.(15) The DIASCAN study surveyed 400 family physician offices across Canada. A total of 9042 patients ≥40 years of age were enrolled. Of these, 16.4% had previously known diabetes; an additional 2.2% of patients were identified[2] as having diabetes, and an additional 3.5% were identified as having glucose intolerance.(16) With respect to Aboriginal communities in Canada, OGTT studies conducted in the James Bay Cree (Quebec) and Sandy Lake Oji-Cree (Ontario) communities revealed undiagnosed diabetes prevalence rates of 2.5% and 10.7%, respectively, representing 10.5% and 41% of the total cases of diabetes, respectively.(15,17,18) Pre-diabetes is also commonly found when screening for diabetes, with rates often similar or greater than the total rates of diabetes, specially in "developing" countries (14) or populations (e.g. including aboriginal communities in Canada).(18,19)

Therefore, because of its long pre-clinical stage, early detection is possible and may be an appropriate intervention. Simple, reliable and non-invasive tests are available for detecting diabetes and pre-diabetes, however there is very little consensus or clarity as to which should be used in which clinical or population based settings. The CDA, the CTFPHC and other organizations (see Appendix A) advocate venous fasting plasma glucose (FPG) as the preferred method that practically and reliably detects diabetes in the pre-clinical, asymptomatic stage. The "gold standard" remains the oral glucose tolerance test and it should be performed if there is still clinical doubt, or to further characterize pre-diabetes into IFG and/or IGT. Capillary blood glucose (finger pokes with glucometers) are

[2] Capillary blood glucose > 5.5 mmol/L followed by standard lab FPG; OGTT performed if FPG was 6.1-6.9 mmol/L

not generally recommended, although one US study showed they have very reasonable sensitivities and specificities, both fasting and "casual".(20) A recent paper from the US Center for Disease Control has suggested different cut off points for cost effective screening for undiagnosed diabetes alone, or for both pre-diabetes and undiagnosed diabetes, for three different tests: the fasting plasma glucose, the Hemoglobin A1c (A1c), and a random capillary blood glucose.(21)

Finally, a number of well-designed randomized trials have shown possibilities for preventive treatment of pre-diabetes,(22-25) discussed below, which financial modeling has shown may be cost-effective.(1,26) Since treatment of clinically diagnosed diabetes is only partially successful at best, and fails to avoid the greatest morbidity of diabetes, namely its cardiovascular and renal complications, and their significant expense, the appeal is great to prevent the disease by early identification and treatment. The rationale for screening is therefore quite strong, as outlined in Table 3.

Table 3 – CHARACTERISTICS OF TYPE 2 DIABETES THAT AFFECT EARLY DETECTION AND PREVENTION(1)

Characteristics that Justify Early Detection and Prevention:

- Chronic disease processes
- Prolonged clinically silent phases: non-diabetes -> prodromal diabetes -> sub-clinical diabetes
- Clinically silent phase can be identified through relatively non-invasive testing procedures
- Potential to modify disease course by therapies given before onset of clinically overt diabetes
- Current therapies, given after onset of clinically overt diabetes, do not always prevent complications

3. RATIONALE FOR SCREENING: THE CDA AND THE CTFPHC

The Canadian Diabetes Association's (CDA's) 2003 *Clinical Practice Guidelines*, and the Canadian Task Force on Preventive Health Care's (CTFPHC's) 2005 *Screening for Type 2 Diabetes to Prevent Vascular Complications* both recommend opportunistic diabetes screening in individuals with hypertension and hyperlipidemia/dyslipidemia/vascular disease. The CDA, however, extends its recommendation to include opportunistic screening in individuals with an array of other risk and prognostic factors, including age, ethnicity, obesity or overweight, history of IGT/IFG and gestational diabetes.(27) The CTFPHC, however, excludes these as factors to justify screening, limiting its recommendation to screening to only those with hypertension or hyperlipidemia. Table 4 summarizes the CDA and CTFPHC screening recommendations. Both incorporate new evidence from the same high-quality, well-designed randomized trials, but come to different conclusions.(28,29) In this section of this paper, we included a detailed review of the evidence upon which the CDA and CTFPHC base their recommendations. [Please see Appendix B for a general discussion on Evidence Criteria.]

Table 4 – SUMMARY OF SCREENING RECOMMENDATIONS (WITH GRADE)

Adapted from Canadian Diabetes Association (2003) (27)	• All individuals *regardless of age*[3] should be evaluated *(meaning the physician or primary care provider should intellectually assess for risk factors e.g. age, obesity, known other risk factors, to decide whether to screen)*[8] for risk every 2 years; and, (Recommendation 1; *"Screening and Prevention"*, CDA CPGs 2003: p. S12) • All individuals ≥ 40 years of age should be screened at 3-year intervals in a primary care setting. In adults with risk factors (see Appendix A), screening should begin earlier and be done more frequently. (Recommendation 2; *"Screening and Prevention"*, CDA CPGs 2003: p. S12) • FPG, confirmed by 2hPG 75g OGTT. FPG is recommended for its utility in screening, and is the most reproducible test available. (Recommendation 2; *"Screening and Prevention"*, CDA CPGs 2003: p. S10)

[3] Our emphasis.

- Obese children ≥10 years of age at 2-year intervals, if they have two or more of the following risk factors: member of a high risk ethnic group; family history of type 2 diabetes (especially if the child was exposed in utero); acanthosis nigricans; polycystic ovarian syndrome; hypertension; dyslipidemia. (Recommendation 1; *"Type 2 Diabetes in Children and Adolescents"*, CDA CPGs 2003: p. S91)
- "Community based" screening programs should be established in Aboriginal communities. (Recommendation 4; *"Type 2 Diabetes in Aboriginal Peoples"*, CDA CPGs 2003: p. S110)

[All recommendations are Grade D, Evidence Level 4: Expert Consensus]

Adapted from Canadian Task Force on Preventive Health Care

(2005) (28,29)

- Screen adults with hypertension for type 2 diabetes to reduce the incidence of cardiovascular events and cardiovascular mortality (Grade B Recommendation, Evidence Level I: Fair).
- Screen adults with hyperlipidemia for type 2 diabetes to reduce the incidence of cardiovascular events (Grade B Recommendation, Evidence Level I: Fair).
- Evidence is inadequate to recommend screening for IGT or IFG. (Grade I Recommendation: Insufficient Evidence).

3.1 CDA (2003):

3.1.1 Evidence Criteria

The recommendations for diabetes screening (who to screen, how often and with what screening tests) outlined in the CDA's 2003 CPGs are categorized as Grade D – expert consensus. This corresponds to the CDA's lowest evidence level category. We can, however, infer that consensus is at least partly based indirectly on evidence showing IGT progressing to diabetes, and on evidence suggesting available treatments may be able to prevent or delay the onset of diabetes in people with IGT and the onset of complications in people with diabetes. Therefore, screening to identify people with IGT or undiagnosed diabetes may be beneficial if it leads to treatment. The CDA's recommendations for treating IGT are based on evidence that meets the highest criteria: Grade A, Evidence Level 1A. Additionally, some treatments to prevent complications are categorized as Grade 1, Evidence Level 1A. (See Appendix C for details on recommendation grade and evidence level criteria.)

The CDA recommendations cite three well-designed indirect randomized trials on prevention (also see Appendix D for a description of the trials):

- **Finnish Diabetes Prevention Study** evaluated the efficacy of lifestyle changes to prevent or delay the onset of diabetes in individuals with IGT. Individuals were randomized to one of four groups: no intervention, intervention with diet only, intervention with exercise only, and intervention with diet and exercise. At six years, cumulative incidence of diabetes was 68% in the control group, 44% in the diet intervention group, 41% in the exercise group, and 46% in the diet and exercise group. In a proportional analysis adjusted for differences in baseline BMI and fasting glucose, the diet, exercise and diet and exercise interventions were associated with 31%, 46% and 42% reductions in risk of developing diabetes, respectively.(22)

- **The Diabetes Prevention Study (DPP)** assessed the efficacy of lifestyle changes or treatment with Metformin. Dietary modification and moderate physical activity (≥ 150 minutes per week) reduced diabetes risk by 58% at 4 years. Treatment with Metformin for an average of 2.8 years decreased progression to diabetes by 31% in individuals with IGT. (However, 26% of subjects converted to diabetes within 1-2 weeks after stopping treatment, with a confirmatory OGTT performed within six weeks of initial diagnosis. Therefore overall incidence of diabetes was reduced by 25%, rather than the 31% before the washout study.)(24,25)

- **Study To Prevent Non-Insulin Dependent Diabetes Mellitus (STOPP-NIDDM)** tested the efficacy of acarbose in preventing progression to diabetes in people with IGT. Over the five-year study (mean follow-up 3.3 years), there was a 30% reduction in risk of progression to diabetes.(23)

3.1.2 CDA Rationale for Screening (2003)

"Preventing type 2 diabetes would result in significant public health benefits, including lower rates of cardiovascular disease, renal failure, blindness and premature mortality".(27) The potential for screening to identify individuals in whom preventive efforts could be instituted would be an important reason for opportunistic screening of individuals with certain risk and prognostic factors. (See Appendix A for detailed lists of risk and prognostic factors.)

The CDA presents evidence showing that opportunistic screening beginning at age 40 as part of a routine clinical exam is effective for early detection in asymptomatic persons.(16) They postulate that greater benefit than harm may follow screening, if subsequent follow-up treatment to prevent onset or progression of diabetes can lead to improved outcomes including quality of life (QOL), and can be cost-effective in terms of avoiding costs for treating complications.(30) The fasting plasma glucose (FPG) test for opportunistic screening is relatively inexpensive, widely available and non-invasive, and is reliable because it is highly reproducible.(31,32) However an OGTT is often required to distinguish diabetes from IFG / IGT.

Cardiovascular mortality is the most common cause of death in diabetes patients. Strong evidence exists showing intervention for hypertension and lipid lowering can be successful at reducing cardiovascular mortality.(33-36) Therefore, early screening that leads to preventive treatment can be successful in addressing CVD. People with IGT are at increased risk for cardiovascular disease as well as for developing diabetes, and so identifying people with IGT or IFG helps target those who would benefit from cardiovascular risk factor reduction (as opposed to the other way around: diabetes screening of only those persons with hypertension or hyperlipidemia).(27,37,38)

Finally, the risk and prognostic factors the CDA recommends for identifying individuals who should be screened have been determined through cohort studies.(27,39-60**)** As part of a routine clinical exam, patients can be initially assessed for these factors (including hyperlipidemia) as a means to identifying and targeting patients who would most benefit from screening.

The 2003 CDA Clinical Practice Guidelines (CPGs) are targeted towards both a primary care audience (family practitioners, other clinicians) and a secondary audience of allied health care providers and health care planners.

3.1.3 Strengths of the CDA position:

- Assigns a high level of evidence to well-designed **indirect** trials.
- The recommendations on who to screen (i.e. the classification of 'high-risk') is based on "prospective cohort studies that have identified historical, physical and biochemical variables that are associated with subsequent development of diabetes".(27)
- The recommendation supporting screening high risk individuals is in part based on cost-modeling that shows screening may lead to cost-savings. (Mass screening is precluded on the basis of cost-effectiveness.)(30)
- The recommendation for diabetes screening is premised on identifying IGT and undiagnosed diabetes, with the presumption that early detection of either will lead to treatment.
- Treatment recommendations for IGT rely on evidence from the large, well-designed prevention studies described above, showing beneficial outcomes of lifestyle or pharmacological interventions in adults with IGT (see Appendix D for study entry criteria).
- Addresses higher prevalence and risk of diabetes in Aboriginal populations by recommending community-based screening programs be established in Aboriginal communities.
- Relies on experts for ultimate interpretation of evidence and formulation of recommendations.

3.1.4 Weaknesses of the CDA position:

- The recommendations on who to screen and how often to screen are based on consensus, and there is not a good distinction or discussion regarding screening t*o detect diabetes (Or pre-diabetes)* and screening *to address some important clinical outcome.*

- The recommendations supporting screening are not based on evidence from **direct** trials, as no studies have compared screening for IGT or diabetes with an unscreened population.

- The recommendation on testing with FPG (with a confirmatory OGTT) is based on consensus.

- Treatment recommendations for IGT state that Metformin or acarbose "should be considered" rather than "should be implemented", despite evidence of treatment efficacy categorized at Grade A, Evidence Level 1A.

3.2 CTFPHC (2005):

3.2.1 Evidence Criteria

The CTFPHC methodology for translating the evidence into evidence-based recommendations, relies steadfastly on the principle of "**evidence takes precedence over consensus"**.(61) In assessing evidence quality, study designs and analyses that eliminate or minimize biased results are prioritized, and in this respect the CTFPHC's methodology approximates the CDA's.

The CTFPHC recommends against screening in the general asymptomatic population, regardless of other criteria (including obesity and history of IGT/IFG), widely accepted by consensus to be risk/prognostic factors for diabetes. The CTFPHC states that there have been no studies to-date that have compared screening for diabetes with an unscreened population or examined health outcomes.[4]

Recommendations for diabetes screening by the CTFPHC are premised on prevention of vascular complications, and the CTFPHC concludes there is fair evidence (Grade B) to screen for diabetes in those individuals with hypertension or hyperlipidemia. Given that there is good evidence that suggests "individuals with diabetes, hypertension (35,36,63,64) and/or hyperlipidemia (34,65-74) treated with intensive blood pressure control, lipid lowering agents and aspirin have a reduction in cardiovascular events and mortality",(28) it is likely (although in fact there is no evidence in particular for this point) that screened patients diagnosed with diabetes 5-6 years earlier would also benefit if treated aggressively with respect to cardiovascular risk reduction.

With respect to screening for IFG / IGT the CTFPHC indicates there is inadequate evidence for screening for these conditions. It concludes that evidence from prevention trials suggesting treatment is effective (22-25) may only delay onset of diabetes, which would have a nominal impact on preventing microvascular complications since their incidence is low within the 15 years after diagnosis of diabetes.(28) With respect to macrovascular complications, although a trial involving treatment with acarbose has shown some possible cardiovascular benefits in hypertensive persons with IGT,(75,76) the CTFPHC concluded the evaluation of this study was inadequate, and therefore the data would not support a recommendation.(28) As noted above, the STOP-NIDDM and DPP studies suggested treatment with acarbose and metformin (respectively) may also be effective in reducing conversion to diabetes in persons with IGT, though the CTFPHC concludes the length of these prevention trials (3-6 years) were insufficient.(23,24,75,76) Results from the DPP study also suggested lifestyle modification may be beneficial in treating IGT,(24) but the CTFPHC notes the impact of lifestyle modification on cardiovascular disease in persons with IGT has not been demonstrated.(28)

The CTFPHC highlights the following:(28,29)

- Evidence two RCTs of fair quality – the HOT Study and UKPDS – revealed significant benefits to tight blood pressure control in patients with hypertension. The HOT Study randomized hypertensive patients to

[4]Young KT et al (2001) retrospectively assessed the prevalence and clinical outcomes of undiagnosed and diagnosed diabetes in a cohort of subjects in Manitoba recruited in 1990. They found that undiagnosed diabetes cases accounted for one-third of all diabetes cases. Importantly, they found that compared with diagnosed cases, undiagnosed cases either did not have a significantly better, and in fact had a worse metabolic profile (in terms of lipids, obesity, blood pressure. As well, compared to normoglycemic individuals, persons with undiagnosed diabetes had 1.35 more physician visits and were 1.23 times more likely to be hospitalized, comparable to persons with diagnosed diabetes who, compared to normoglycemic individuals, had 1.49 more physician visits and were 1.35 times more likely to be hospitalized.(62)

three diastolic blood pressure goals (<=90, 85 or 80 mm Hg), and treatment with ASA or placebo. At five years, no significant benefits were shown across all groups, but patients with diabetes in the <=90 group had significantly more cardiovascular events and higher cardiovascular mortaility compared with the <=80 mm Hg group.(35) In the UKPDS, patients with hypertension receiving tight blood pressure therapy for 10 years showed significant reductions in diabetes-related death (myocardial infarction, sudden death, stroke, PVD, renal failure), significant reductions in risk of stroke, any diabetes-related end-point, microvascular disease (aggregate clinical endpoint), and retinal photocoagulation.(36)

- Evidence from two smaller RCTs in diabetic patients given intensive blood pressure therapy showed significant reductions in all-cause mortality (63) and a reduction in stroke.(64)

- Several randomized trials of primary and secondary cardiac prevention have shown significant reductions in cardiovascular events in patients with diabetes and hyperlipidemia treated over 5 years.(34,65-74) (Absolute risk reduction would be larger in persons with diabetes given that their baseline risk of cardiovascular disease is 2-4 times higher than a non-diabetic person.).(28)

- Persons with IGT and IFG have higher risk of cardiovascular events and mortality than those with normal glucose tolerance.(68-72) been shown to increase one's risk of cardiovascular disease and mortality.(77-87)

Although the CTFPHC acknowledges that treating IGT to decrease progression to diabetes and possibly CVD may be beneficial, it concludes the evidence is still inadequate to recommend screening for IFG or IGT. However, the CTFPHC makes these recommends on treating IGT:(28,29)

- There is **good**[5] evidence to recommend lifestyle interventions for overweight individuals (BMI > 25 kg/m^2, or > 22 kg.m^2 if of Asian descent) with IGT to reduce the incidence of progression to diabetes (Evidence Level I, Grade B - good)[5].

- There is fair evidence to recommend acarbose treatment for overweight individuals with IGT to prevent cardiovascular events and hypertension (Evidence Level 1, Grade B - good).

- There is insufficient evidence in quantity and/or quality to make a recommendation as to whether or not to treat individuals with IGT with Metformin or acarbose to prevent progression to diabetes (Evidence Level I, Grade I - fair).[6]

The recommendations for treating IGT seem to imply that screening for IGT may be justified via the physician's clinical judgment if treatment with lifestyle intervention of acarbose or metformin follows. The CTFPHC points to a number of studies that have assessed the efficacy of lifestyle or pharmacological intervention on preventing or delaying progression to diabetes in overweight individuals with IGT:

- Finnish Diabetes Prevention Study
- DPP
- STOP-NIDDM
  (see "CDA – Evidence Criteria" section above and Appendix D for descriptions of these studies)

- The Da Qing Study in China assessed whether diet and/or exercise interventions in individuals with IGT may delay the onset of diabetes. Cumulative incidence of diabetes at six years was 68% in the control group, 44% in the diet intervention group, 41% in the exercise group, and 46% in the diet and exercise intervention group. In a proportional analysis adjusted for differences in baseline BMI and fasting glucose, the diet, exercise and diet and exercise interventions were associated with 31%, 46% and 42% reductions in risk of developing diabetes, respectively.(88)

[5] **"Good"** evidence corresponds to Grade A, however this recommendation is assigned Grade B which should correspond to **"fair"** evidence.
[6] Grade I means there is insufficient evidence in quality and/or quantity to make a recommendation for or against.

- Troglitazone in high-risk (i.e. previous gestational diabetes) Hispanic women. This study assessed whether chronic amelioration of insulin resistance would preserve pancreatic β-cell function and delay the onset of diabetes. During blinded treatment, the average annual diabetes incidence rates were 12% and 5% in the placebo and troglitazone groups, respectively. At 31-month follow-up, diabetes rates were 12% and 6% in the placebo and troglitazone groups, respectively.(89)

However, the CTFPHC concludes the above studies provide good evidence only for the short-term reduction in progression from IGT to diabetes, noting for example that "… because the primary diabetes outcomes in the acarbose and metformin studies were evaluated while the subjects were taking the drugs (acarbose), or taken off for a very brief period (metformin), the ability of these agents to prevent versus simply mask new diabetes is unclear."(27:p.14) [Interestingly, the DPP investigators believe the washout study demonstrated that Metformin did not have a "masking" effect.(25)]

The CTFPHC position paper and recommendations were adapted from the United States Preventive Services Task Force (USPSTF) recommendations (2003), which concluded that the knowledge of diabetes status in patients with hyperlipidemia and hypertension would lead to changes in treatment recommendations for blood pressure and lipid control, which in turn would reduce adverse cardiac outcomes over a ten-year horizon. This conclusion was dependent in part on baseline level of cardiac risk, and in certain circumstances, it was the diagnosis of diabetes that increased the CV risk to a level worthy of intervention.(90)

3.2.2 CTFPHC Rationale for Screening

The CTFPHC was originally established as the Canadian Task Force on the Periodic Health Examination in 1976 by the Conference of Deputy Ministers of Health. The Task Force is hosted by the University of Western Ontario. The 2003/05 CTFPHC recommendations are targeted towards primary care practitioners (clinical preventive practice).(61)

During its first two years, the Task Force developed a methodology for weighing scientific evidence to make recommendations for or against including preventive maneuvers in the **periodic health examination (PHE)** of asymptomatic people. This methodology employs an approach to decision-making on prevention issues whereby **evidence takes precedence over consensus**. In its first report (1979), the Task Force reviewed the scientific evidence for the preventability of 78 conditions, which led to the following recommendation: "… the undefined 'annual check-up' should be abandoned and replaced with a series of age-specific 'health protection packages' implemented during the course of medical visits for other purposes." CTFPHC methodology has been adopted by the USPTF, and is currently used by the U.S. Department of Health and Human Services.(61)

In its 1994 recommendations (91) the CTFPHC recommended against screening in the general asymptomatic population, given that there was "little direct evidence that asymptomatic persons benefit from the detection and treatment of IGT *(impaired glucose tolerance)*". In response to recently published results from the DPP, The Finnish Diabetes Prevention Study, STOP-NIDDM, Da Qing and a trial of troglitazone in high-risk Hispanic women,(22,24,25,75,88,89) and subsequent to the USPSTF's revisions to its recommendations, the CTFPHC updated its policy in 2003/05 to recommend diabetes screening in individuals with hypertension and hyperlipidemia, with the objective of reducing cardiovascular events and/or cardiovascular mortality (i.e. screening for diabetes would lead to changes in treatment recommendations for blood pressure and lipid control, which would reduce adverse cardiac outcomes over a 10-year period). They conclude: "There is good evidence that suggests that individuals with diabetes, hypertension and/or hyperlipidemia treated for five years with intensive blood pressure control, lipid lowering agents and aspirin have a reduction in cardiovascular events and mortality",(28,29) and therefore may benefit from screening if knowledge of their diabetes status leads to treatment.

3.2.3 Strengths of the CTFPHC position:

- The recommendations regarding screening rely on evidence, not expert consensus.
- The recommendations against diabetes screening are in part based on the lack of direct evidence, as no prospective studies have compared screening for IGT or diabetes with an unscreened population.
- The recommendation to screen individuals with hypertension and hyperlipidemia are based on fair evidence from well-designed trials, and on evidence that cardiovascular events comprise the highest largest morbidity and mortality impact associated with diabetes, i.e. are important clinical outcomes.

- The recommendation against screening is in part based on evidence that diabetes risk can be identified during screening for cardiovascular conditions.

- The recommendation for physicians to use clinical judgment in identifying who to screen in the absence of hypertension and hyperlipidemia acknowledges that prospective observational cohort studies have identified other risk/prognostic factors.

- The recommendation for screening via FPG is based on evidence that the FPG with a cut-point of 7.0 mmol/L has moderate sensitivity but good specificity in asymptomatic individuals; and is based on evidence that the FPG is more reliable and reproducible than the OGTT.(27, 81,92-96)

3.2.4 Weakness of the CTFPHC position:

- The recommendations are adopted from USFSTP recommendations. (However, the USFSTP adopted CTFPHC methodology for assessing evidence.)

- The recommendations on who to screen do not include those individuals who might be considered 'high-risk' based on the risk/prognostic factors identified in prospective observational cohort studies.

- The recommendations exclude evidence form large, well-designed indirect prevention studies. While it is acknowledged that IGT is a predictor of diabetes, and that treatment with lifestyle interventions (and possibly with metformin and acarbose) may reduce incidence of conversion to diabetes, the CTFPHC does not recommend screening for IGT. [However, the CTFPHC does acknowledge that evidence exists showing treatment with acarbose in persons with IGT and hypertension may be beneficial for preventing cardiovascular outcomes.]

- While higher prevalence and risk of IGT and diabetes in special populations (including Aboriginals) is acknowledged, no recommendations are provided to address this.

- The CTFPHC 2005 recommendations provide no comment on the overall cost-effectiveness of screening, noting only the economic burden of diabetes in Canada in 1993. The CTFPHC acknowledges that "while cost of care is an inescapable and serious consideration, economic analysis of clinical preventive actions is complex and not yet fully developed. It is not yet a major focus of Task Force evaluations."(61)

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4. THE COCHRANE COLLABORATION (97)

The Cochrane Collaboration is currently undertaking a powerful meta-anaylsis of multiple RCTs, They acknowledge that no diabetes screening trials are known, but point to the USPSTF's recent systematic review in developing its recommendations (upon which, as noted above, the CTFPHC recommendations are based). While the USPSTF did consider questions on the efficacy of type 2 diabetes screening, their main purpose was assessing the effectiveness of screening and earlier treatment in reducing morbidity and mortality associated with diabetes. The Cochrane Collaboration, on the other hand, are additionally investigating outcome measures such as adverse events (ex. Physical, psychological and social harm), QOL, and costs, and will base their conclusions on broader considerations and analyses of efficacies, as the CDA recommendations have.

Appendix C provides an outline of the trial selection and evidence quality criteria the Cochrane Collaboration is utilizing in its meta-analysis. Work has been underway since 2005 and is anticipated to be published in 2006.(98)

5. CURRENT/UPCOMING RECOMMENDATION/GUIDELINE UPDATES

CDA (personal communication, May 16, 2006)

A revision, consisting of a chapter addressing cardiovascular disease based on recent studies on prevention and treatment, is scheduled for release in September 2006. A full, revised set of Clinical Practice Guidelines are scheduled for release in 2008.

CTFPHC (personal communication May 9, 2006)
No further updates or revision are currently in development.

ADA
The ADA's guidelines undergo constant assessment and revisions. Its most recent revisions were the Clinical Practice Guidelines released in January 2006 (accessible at: http://care.diabetesjournals.org/content/vol29/suppl_1/

USPSTF (http://www.ahrq.gov/clinic/uspstfix.htm)
After releasing its 2003 recommendations on screening for diabetes, the USPSTF is currently focusing on topics other than diabetes.

WHO (http://www.who.int/diabetes/publications/en/)
A new scientifically-based review on the "Prevention of diabetes and its complications" will be available in 2006. Its contents will include:

- The impact of diabetes on individuals and populations
- Pathophysiology and risk factors for type 1 and type 2 diabetes
- Evidence for the prevention of type 2 diabetes
- Prospects for the prevention of type 1 diabetes
- Evidence for the prevention of diabetes-related complications
- Guidance on implementing the evidence, including population-based and high-risk approaches to the prevention of type 2 diabetes, and approaches to delivering effective health care.

A new technical report on **"Definition, diagnosis and classification of diabetes mellitus and its complications"** will be available in 2006.

SCREENING FOR UNDIAGNOSED DIABETES AND PREDIABETES: COMPARING CANADIAN RECOMMENDATIONS AND WEIGHING THE EVIDENCE

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GLOSSARY OF TERMS:

Evidence[7]: Results from applied clinical studies of prognosis, diagnosis, prevention, and therapy.

Evidence criteria[7]: The criteria utilized for quality assessment of evidence.

Levels of Evidence[7]: A rating system used to categorize evidence for clinical recommendations.

Best evidence[7]: Systematic reviews or meta-analyses of multiple randomized controlled trials, and large randomized controlled trials (RCTs) with adequate power to answer the question.

Recommendation Grades: A rating system used to identify the evidence level of the best available evidence upon which a given recommendation is based.

Direct trials[7]: Subjects are randomized to receive the test or not. Those testing positive are treated, whereas negative persons are not, and all three groups (i.e. positive, negative and untested) are followed for the outcome of interest.

Indirect trials[7]: Screens a population and then randomizes those who test positive to be treated or not.

Screening[7]: Use of early detection test prompted by the health care system or its representative in persons who otherwise have not entered the health care system.

Mass screening[7]: Screening used in an entire population.

Universal screening[7]: Mass screening

Selective screening[7]: Screening used in a subset of a population.

Case-finding / Opportunistic screening[7]: Use of early detection test prompted by the health care system or its representative in persons who enter the health care system for other reasons (e.g. during routine annual clinical activity, or during pre-operative assessment, or due to multi channel laboratory instruments that provide results of tests that were not specifically requested (termed "metabolic panels)..

Targeted screening: Mass/selective screening within high-risk (ex. ethnic) sub-populations. Case-finding in individuals with risk/prognostic factors.

Community-based screening: Systematic targeted screening carried out within a community setting, May be carried out as an initiative of the community being screened, or as an initiative from outside the community.

Screening test: Initial test to determine whether a person is at risk for having or developing a disease. Screening does not constitute a diagnosis, although on occasion screening can be diagnostic (when the abnormality is severe or obvious). A second, confirmatory test is usually required for diagnosis.

Diagnostic / confirmatory test: A second test performed on a different day in a laboratory setting to determine whether a person has a disease.

Prognostic factors: Demographic, disease-specific, or co-morbid factors that are associated with the outcome of interest. May or may not be causal.

Risk factors[7]: Aspects of personal behaviour or lifestyle, environmental exposure, or an inborn or inherited characteristic which is known to be associated with health-related conditions. May be continuous or discrete. May cluster together in an individual with a synergistic effect on the outcome of interest. May be modifiable or fixed.

[7] Adapted from Gerstein and Haynes, 2001.

Fasting plasma glucose (FPG): Glucose measurement on blood drawn subsequent to at least 8 hours of fasting.

Casual plasma glucose / random: Glucose measurement on blood drawn from a patient who has not fasted (i.e. regardless of the interval since the latest meal)

2 hour post glucose (2hPG) / Oral Glucose Tolerance Test (OGTT): Glucose measurement on blood (plasma) drawn two hours subsequent to the intake of a 75 gram glucose load.

Blood / whole blood: blood before it has been spun to obtain plasma, sometimes used to denote capillary blood used for "finger poke" for glucose meters. Glucose concentration in whole blood is somewhat higher than in plasma, however glucose meters are often calibrated against "plasma". Portable laboratory instruments such as DCA 2000 and Cholestec LDX also use whole (capillary) blood, also standardised against plasma.

Plasma: blood from which the cellular elements have been separated, the usual "blood" used by standard laboratrories.

A1c: Measurement of glycosylated haemoglobin on blood drawn casually/randomly. Fasting is not required because A1c measures the average of blood glucose levels over the preceding 180 days, and is not subject to fluctuations in blood glucose levels between fasting and non-fasting states.

Diabetes: FPG ≥7.0 mmol/L OR 2hPG ≥ 11.1 mmol/L on an OGTT OR casual plasma glucose $\geq$ 11.1 with classic symptoms of diabetes. Classic symptoms include polyuria, polydipsia, and unexplained weight loss.

IFG: Impaired fasting glucose. A condition on the continuum between normal blood glucose and diabetes. Criteria: FPG 6.1-6.9

IGT: Impaired glucose tolerance. A condition on the continuum between normal blood glucose and diabetes. Criteria: 2hPG 7.8-11.1 mmol/L on an OGTT.

Pre-diabetes: IFG and /or IGT

Primary prevention: Aims to prevent the occurrence of disease through immunization, by reducing exposure to risk factors or by modifying behaviours.[8] Interventions directed toward preventing the onset of a disease in the first place. Obesity prevention or intervention represent primary prevention efforts directed at diabetes, including subclinical, asymptomatic or undiagnosed diabetes, and IGT and IFG.[8]

Secondary prevention[8]: Focuses on sub-clinical type 2 diabetes. Aims to identify asymptomatic individuals with early stage disease when such early identification promises significantly better response to treatment than in those who first present with symptoms.

Tertiary prevention[7]: Focuses on limiting onset and progression of complications in persons with type 2 diabetes.

Periodic Health Examination (PHE)[8]: A group of activities, encompassing both primary and secondary prevention, designed either to determine a person's risk of developing disease or to identify early, asymptomatic disease.

[8] CTFPHC, 1997. *CTFPHC History/Methodology – Key Definitions.* www.ctfphc.org

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APPENDIX A – Comparison of diabetes screening guidelines

Organization	*Who to screen*	*Where to screen / who should screen*	*With what to screen*	*Screening Intervals*	*Recommendation grade*	*Special populations*	*Diagnostic Criteria**	*References*
Canadian Diabetes Association 2003	All individuals ≥ 40 years of age. Adults with risk factors: • First-degree relative with diabetes • Member of high-risk population (Aboriginal, Hispanic, Asian, South Asian or African decent) • History of IGT of IFG • Presence of complications associated with diabetes • Vascular disease • History of GDM • Hypertension • Dyslipidimia • Overweight (BMI > 25 kg/m2) • Abdominal obesity • PCOS • Acanthosis nigricans • Schizophrenia	Family physician offices	FPG 2hPG 75-g OGTT may be indicated when FPG is 5.7 to 6.9 mmol.L and suspician of diabetes or IGT is high.	3 years in adults ≥ 40 years of age. Before age 40 and/ or more frequently with FPG or 2hPG if additional risk factors present. *2 years in obese children with 2 or more risk factors.* All individuals should be "evaluated" annually for type 2 diabetes risk on the basis of demographic and clinical criteria.	D (best evidence is level 4 or consensus)	ABORIGINAL POPULATIONS: Establish screening programs within Aboriginal communities, using collaborative strategies incorporating local knowledge, traditions, culture and language. [Grade D] CHILDREN Obese children ≥ 10 years of age should be screened every 2 years using FPG if 2 or more risk factors are present: • Member of a high-risk ethnic group • Family history of type 2 diabetes, especially if the child was exposed to diabetes in utero • Acanthosis nigricans • PCOS • Hypertension • Dyslipidemia [Grade D]	*Diabetes:* FPG ≥ 7.0 mmol/L or Casual PG ≥ 11.1 mmol/L with symptoms of diabetes or 2hPG 75g OGTT ≥ 11.1 mmol/L *IFG:* FPG 6.1-6.9 mmol/L *IGT:* 2-h PG 75g OGTT > 7.8 and < 11.1 mg/dl Classic symptoms of diabetes are polyuria, polydipsia, and unexplained weight loss.	Can J Diabetes, 2003;27(Suppl 2).
American Diabetes Association 2006	• Asymptomatic non-pregnant adults age ≥ 45 years, "particularly if overweight" • Overweight (BMI ≥ 25 kg/m2) • Family history of diabetes (ie. parents, siblings) • Habitual physical inactivity • Race/ethnicity • Previously identified IFG or IGT • History of GDM or delivery of a baby weighing >9 lbs • Hypertension (≥ 140/90 mmHg in adults) • HDL cholesterol ≤ 35 mg/dl (0.90 mmol/L) and /or a TG level > 250 mg/dl (2.82 mmol/L) • Polycystic ovary syndrome • History of vascular disease	Health care settings / health professionals	FPG / OGTT [Grade C]	3 years Before age 45 and/ or more often if risk factors present	E (expert consensus or clinical experience)	Screening in community settings, even in high risk populations, is not recommended (lack of follow-up / potential for worry, labelling, lack of compliance with recommended treatment) [Grade E]	*Diabetes:* Symptoms of diabetes plus casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L) or FPG ≥126 mg/dL (7.0 mmol/L). or 2-h PG 75g OGTT ≥ 200 mg/dL (11.1 mmol/L) *IFG:* FPG > 100 and < 126 mg/dl *IGT:* FPG ≥100 and < 126 mg/dl 2-h PG 75g OGTT > 140 and < 200 mg/dl	Diabetes Care, 2006; 29(Suppl 1):S1-S74. Accessible at: http://care.diabetesjournals.org/content/vol29/suppl_1/ Diabetes Care, 2004; 27(10):S5-S10. Diabetes Care, 2004; 27(10):547-554.
CTFPHC 1994 *"Screening for Diabetes Mellitus in the Non-Pregnant Adult"*	Exclude screening of the general, non-pregnant population in the periodic health examination. Periodic testing of individuals with risk factors (obesity, older age, family history of diabetes, belonging to a high risk ethnic group) may be reasonable; however, no evidence that early detection improves outcomes in high-risk groups.	Periodic health examination; Case-finding in clinical practice	No screening test available that combines accuracy with practicality. Fasting blood glucose has low sensitivity in asymptomatic low risk populations. • *Croxson SC et al. Ann Clin Biochem 1991; 28: 279-282* • *Guillausseau PJ et al. Diabetes Care 1990; 13: 898-900* • *Little RR et al. Diabetes 1988; 37: 60-64*	N/A	D (**Fair** evidence **against** the recommendation)	Selective case-finding in high-risk groups (Native Canadians, Hispanic or Black Americans, the elderly, individuals who are obese, have a family history or gestational diabetes) may be prudent.	*Diabetes:* In symptomatic patients: Random venous plasma glucose > 11.1 mmol/L (200 mg/dL) or at at least two fasting venous plasma glucose levels >7.8 mmol/L (140 mg/dL). In asymptomatic patients: 2hPG 75g OGTT venous plasma glucose level >11.1 mmol/L (200 mg/dl) and one glucose value before two hours of >11.1 mmol/L (200 mg/dL). *IGT:* 2hPG 75g OGTT glucose value between 7.8 mmol/L (140 mg/dl) and 11.1 mmpl/L (200 mg/dl), and one intervening value >11.1 mmol/L (200 mg/dL).	Beaulieu M. *Screening for Diabetes Mellitus in the Non-Pregnant Adult.* Canadian Task Force on Preventive Health Care, 1994. Accessible at: http://www.ctfphc.org/
CTFPHC 2003/05 *"Screening for type 2 diabetes to prevent vascular complications"*	There is fair evidence to recommend screening adults with hypertension for type 2 diabetes to reduce the incidence of CV events and CV mortality. There is fair evidence to recommend screening adults with hyperlipidemia for type 2 diabetes to reduce the incidence of CV events. If patients do not meet the above criteria, the decision to screen for diabetes or IGT should be based on an estimate of the patient's overall cardiovascular risk. Patients whose overall risk would be raised by the diagnosis of diabetes to the extent that treatment would be changed, may merit screening. Patients with other cardic risk factors (such as smoking) that put them at increased risk for cardiovascular disease, may benefit from screening for diabetes. Evidence is inadequate to recommend screening for IFG or IGT.	Case finding (primary care)	FPG	No evidence for optimal screening interval.	B (**Fair** evidence **for** the recommendation)	N/A	*Diabetes:* FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT ≥ 11.1 mmol/L *IGT:* 2hPG 75g OGTT: 7.8-11.0 mmo/L *IFG:* FPG: 6.1-6.9 mmol/L	Feig DS et al. *Screening for type 2 diabetes to prevent vascular complications: updated recommendations from the Canadian Task Force on Preventive Health Care.* Canadian Task Force on Preventive Health Care, 2005. Accessible at: http://www.ctfphc.org/

USPSTF 2005	Adults with hypertension or hyperlipidemia should be screened [Grade B] as an approach to preventing CVD. Adults with symptoms suggestive of diabetes (ie. polidipsia, polyuria) Clinicians may decide to screen selected persons at high risk, based on clinical judgment. Insufficient evidence to recommend for or against routine screening in asymptomatic adults for diabetes, IGT or IFG. [Grade I]	Routine clinic visits	Good evidence that available screening tests (FPG, 2hPG, A1c, CBG) can accurately detect type 2 diabetes in preclinical, asymptomatic stage.	Optimal screening interval is unknown *ADA recommends 3 year intervals, more frequently for high risk individuals.*	B (at least fair improves important health outcomes and concludes that benefits outweigh harms)	Mexican, African and Native Americans experience higher rates of retinopathy and renal complications. While the benefits of screening are uncertain, screening may translate into greater benefits for these ethnic groups than for Whites if screening protects against onset or progression of complications.	ADA criteria *Diabetes:* 1. Symptoms of diabetes plus casual plasma or 2. FPG ≥126 mg/dL (7.0 mmol/L). or 2-h PG 75g OGTT ≥ 200 mg/dL *IFG:* FPG > 100 and < 126 mg/dl *IGT:* FPG ≥100 and < 126 mg/dl 2-h PG 75g OGTT > 140 and < 200 mg/dl	RTI International. *Screening for type 2 diabetes mellitus.* U.S. Department of Health and Human Services, Agency for Health Care Research and Quality, 2003; Systematic Evidence Review Number 19. Harris R, et al. *Screening adults for type 2 diabetes: a* . review of the evidence for the U.S. Preventive Task Force. Ann Int Med. 2003;138:215-229 U.S. Preventive Task Force. *Screening for type 2 diabetes mellitus in adults: recommendations and rationale.* Agency for Health Care Research and Quality, 2003; Pub No. 03-517A:1-11.
Diabetes UK 2002	There should be a National active programme. A person with 2 or more risk factors should be screened: White people > 40 years of age and Black, Asian and minority ethnic groups > 25 years, with one or more of the following: • first degree family history of diabetes • BMI of 25-30 kg/m2 and above and sedentary lifestyle • ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or hypertension • women who had gestational diabetes and tested normal following delivery (screen at 1 year post-partum and then every 3 years) • women with PCOS who are obese • those known to have IGT or IFG.	Targeted case-finding in high-risk groups during regular health care examinations. *Existing programmes of active case finding through opportunistic screening do not appear to be identifying people with Type 2 diabetes soon enough to prevent microvascular complications.* [Other venues such as pharmacies may be appropriate provided staff are trained.]	2hPG 75-g OGTT or FPG Postprandial urinalysis (recommended when other tests are not pracitcal)	3 years if risk factors present. 5 years > age 40.	N/A	In certain circumstances, such as screening within ethnic communities who may not routinely access primary care services, other screening programmes may be acceptable.	*Diabetes:* 2hPG 75g OGTT: > 11.1 mmol/L FPG: Venous plasma ≥ 7.0 mmol/L; Whole blood (venous or capillary) ≥ 6.1 mmol/L *IFG/IGT:* 2hPG 75g OGTT: 7.8-11.1 mmol/L Venous plasma 6.1-6.9 mmol/L; Whole blood (venous or capillary) 5.6-6.0 mmol/L	Diabetes U.K. *Position Statement: Early identification of people with type 2 diabetes.* 2002:1-8.
New Zealand Guidelines Group 2003	Comprehensive cardiovascular risk assessment including blood glucose measurements: begin at ≥ 45 in men, ≥ 55 in women Maori, Pacific peoples and peoples from Indian sub-continent: ≥ 35 for men, ≥45 for women Begin at ≥ 35 for men, ≥ 45 for women for all individuals with one or more cardiovascular or diabetes risk factors: • family history of CVD in parent or sibling (male relative under 55, female relative under 65) • family history of diabetes in parent or sibling • history of gestational diabetes • current or recent smoking • PCOS • known IGT or IFG • obesity (³ 30 BMI) or truncal obesity (waist circumference ≥ 100 cm for men, ≥ 90 for women. • prior BP > 160/95 mm Hg • prior TC:HDL ratio > 7	As part of a comprehensive cardiovascular risk assessment in primary care	FPG 2hPG OGGT can be used alone for epidemiological or population screening purposes.	People with 5-year CVD risk < 5% = 10 years People with 5-year CVD risk 5-15% = 5 years	C (a body of evidence (including well-conducted case-control or cohort studies) with a low risk of confounding or bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated from studies including high quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.)	Maori, Pacific peoples and peoples from the Indian sub-continent are at higher risk; should begin screening earlier.	*Diabetes:* FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT: ≥ 11.1 mmol/L *IGT:* FPG: < 7.0 2hPG 75g OGTT: ≥ 7.8 and < 11.1 mmol/L *IFG:* FPG: ≥ 6.21 and < 7.0 mmol/L 2hPG 75g OGTT: < 7.8 mmol/L	New Zealand Guidelines Group (NZGG). *Management of* type 2 diabetes. 2003. Accessible at: www.nzgg.org.ca New Zealand Guidelines Group (NZGG). *The Assessment and management of cardiovascular risk. 2003.* Accessible at: www.nzgg.org.ca
New Zealand Health Strategy (NZ Ministry of Health) 2003 *Australian Diabetes Society, New Zealand Society for the Study of Diabetes, Royal College of Pathologists of Australasia and Australasian Association of Clinical Biochemists* *-2002*	Non-Europeans > age 30, and Europeans > age 40 if other risk factors present (3-year intervals): • Obesity • High blood pressure • Low HDL • Raised triglyecerides • Parent or sibling with diabetes • Cardiovascular disease • Peripheral vascular disease • Cerebrovascular disease • PCOS Non-Europeans > age 40, and Europeans > age 50 in the absence of other risk factors (3-year intervals) All people (regardless of age) with a past history of impaired glucose tolerance or impaired fasting glucose (1-year intervals) All individuals presenting with hypertension, lipid abnormalities, or possible diabetes symptoms.	Opportunistic screening in primary health care.	FPG (preferred) or Random	3 years 1 year for individuals with histroy of IFG or IGT.	N/A	Screening amongst Maori, Pacific peoples and Asian peoples should begin at age 40, or at age 30 is risk factors are present.	*Diabetes:* FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT and / or random: ≥ 11.1 mmol/L *IGT:* 2hPG 75g OGTT: 7.8 - 11.0 mmol/L FPG: < 7.0 mmol/L (if measured) *IFG:* FPG: 6.1 - 6.9 mmol/L 2hPG 75g OGTT: <7.8 mmol/L (if measured)	Kenealy T, Scragg R, Baadvedt G. Screening for type 2 diabetes in non-pregnant adults in New Zealand: practice recommendations. NZ Med J, 2002;115(1152):194-6. Kenealy TW. *Systematic opportunistic screening for type 2 diabetes in general practice.* University of Auckland, 2003. [PhD thesis] New Zealand Health Strategy. *DHB Toolkit: Diabetes - To reduce the incidence and impact of diabetes (2nd edition).* Ministry of Health, New Zealand, 2003. Accessible at: http://www.newhealth.govt.nz/toolkits/diabetes.htm

Australian Diabetes Society, New Zealand Society for the Study of Diabetes, Royal College of Pathologists of Australasia and Australasian Association of Clinical Biochemists -1999 [led to new screening criteria -- see above]	*[see above]*	In clinical practice: • symptoms present: a single FPG, 2hPG or casual postprandial will suffice. • no symptoms present: a 2nd confirmatory test is required. In epidemiological settings for high-prevalence populations or selective screening of high risk individuals, a single 2hPG 75g OGTT of ≥ 11.1 mmol/L will suffice to describe prevalence of IGT.	FPG 2hPG or casual postprandial	*[see above]*	N/A	High-prevalence populations in an epidemiological setting.	*Diabetes:* FPG: ≥ 7.0 mmol/L Whole blood: ≥ 6.1 mmol/L 2hPG 75g OGTT or casual postprandial: ≥ 11.1 mmom/L *IGT:* 2hPG 75g OGTT: 7.8-11.0 mmol/L *IFG:* FPG: 6.1-6.0 mmom/L	Colman PG et al. *New classification and criteria for diagnosis of diabetes mellitus: Position Statement from the Australian Diabetes Society, New Zealand Society for the Study of Diabetes, Royal College of Pathologists of Australasia and Australasian Association of Clinical Biochemists.* MJA, 1999;170:375-8. Accessible at: http://www.mja.com.au/public/issues/apr19/colman/colman.html
National Health and Medical Research Council (Australia) 2001	• Age ≥ 55 years • Age ≥ 45 years with one or more of the following: - Obesity (BMI ≥ 30) - First degree relative with type 2 diabetes - Hypertension (taking medication or BP ≥ 140/90 mmHg) • Aboriginal or Torres Stat Islanders age ≥ 35 years • People from high-risk non-English-speaking background groups age ≥ 35 years • People with IGT of IFG • All people with clinical CVD • Gestational diabetes • PCOS • Women who are obese *[Evidence Level III-2]*	Primary care - Laboratory testing *[Evidence Level III]*	FPG *[Evidence Level III]* Random may be used if FPG is impractical in certain circumstances	3 years 1 year for people with IGT/IFG. 1 year if confimatory testing is not undertaken after initial screening suggested diabetes, IGT or IFG.	III (evidence obtained from less well-designed, non-representative cohort studies or well-designed case-control studies), and III-2 (evidence obtained from comparative studies with concurrent controls and allocation, non-randomized (cohort studies), case-control studies, or interupted time series with control group.)	Aboriginal, Torres Stait Islanders, and non-English speaking background people from the Pacific Islands, sub-Indian continent and of Chinese origin should be considered for screening every 3 years beginning at age 35 (or earlier or more frequently if other risk factors present).	1999 WHO criteria *[Evidence Level III]* *Diabetes:* Symptoms of diabetes and casual plasma glucose ≥11.1 mmol/L FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT: ≥ 11.1 mmol/L *IGT:* FPG: < 7.0 mmol/L AND 2hPG 75g OGTT: ≥ 7.8 and < 11.1 mmol/L *IFG:* FPG: ≥ 6.1 and < 7.0 mmol/L 2hPG 75g OGTT: < 7.8 mmol/L	Australian Centre for Diabetes Strategies. *National Evidence Based Guildelines for the Management of Type 2 Diabetes Mellitus: Primary Prevention - Case Detection and Diagnosis.* The Diabetes Australia Guidelines Development Consotium and the National Health and Medical Research Council. Sydney, 2001.
Finland Diabetes Association 2003 *Programme for the Prevention of Type 2 Diabetes in Finland - Implementation [pilot] Project 2003-2007*	Individuals at risk: • close relative with type 2 diabetes • history of gestational diabetes • hypertension • elevated blood glucose (IFG or IGT) • disturbance of fat metabolism or metabolic syndrome • overweight or central obesity	Targeted risk testing: • Primary health care exams / occupational health care units • Periodic age-related health examinations • call-up examinations for conscripts • pre-employment examinations and periodic re-examinations Follow-up investigation by a public health nurse or occupational health nurse: Fasting glucose concentration in plasma. • Laboratory tests of lipid metabolism, liver function, thyroid function, renal function, blood count and electrocardiography. • Weight, height, BMI, waist circumferance, and blood pressure. General risk testing: • internet • pharmacies • NGOs • media • health campaign events	Type 2 Diabetes Risk Assessment Form Available at:www.diabetes.fi *- used for targeted screening in conjunction with health exams in primary care or occupational health units.* Follow-up investigation by a public health nurse or occupational health nurse: • FPG (followed by 2hPG 75-g OGTT if FPG ≥ 7.0 mmol/L)	If initial test shows elevated glucose: • re-test in 6 months; • annually thereafter Initial test is normal: • re-test at 1-3 year intervlas, depending on risk factors	N/A	Public authorities, daycare centres, schools, NGOs and the health-care system will cooperate in healthy lifestyle education programmes for families, children and youth. (Enhanced training for health-care and catering staff, and nursery and school teachers.) *[Primary objective: prevention of childhood obesity]* Systematic prevention, management and monitoring of childhood obesity should be incorporated as part of regular health examination.	*Diabetes:* FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT: ≥ 11.1 mmol/L *Elevated glucose:* FPG: 6.1-6.9 mmol/L 2hPG 75g OGTT: 7.8-11.0 mmol/L	Etu-Seppälä L, et al. (eds.) *Programme for the Prevention of Type 2 Diabetes in Finland.* Finnish Diabetes Association, 2003. Accessible at: http://www.diabetes.fi/english/prevention/programme/index.html
US Department of Veterans Affairs / Department of Defense 2003	All adults ≥ 45 years of age In younger adults who have hypertension or dyslipidemia or multiple other risk factors such as: • History of IGT • BMI > 25 kg/m² • Sedentary lifestyle • Family history of DM (parent or sibling) • History of GD • Delivered >9 lb. baby • HDL-C < 35 mg/dL (0.90 mmol/L) • Fasting/serum triglycerides >250 mg/dL (2.82 mmol/L) • History of PCOS • Member of a high risk ethnic population • IFG on previous testing • Other clinical conditions associated with IR	Primary care setting	FPG (preferred) or casual plasma glucose [Grade B, fair evidence that method may be effective]. OGTT not recommended for clinical practice because it is an imprecise test with poor reproducability	1-3 years	C (good evidence that screening should be considered)	Vetereans at risk for diabetes mellitus and its complications (target population)	*Diabetes:* FPG: ≥ 126 mg/dL (≥ 7.0 mmol/L) Casual: ≥ 200 mg/dL (≥ 11.1 mmol/L) plus symptoms of diabetes *IGT:* FPG: ≥110 < 126 mg/dL	Veterans Health Administration, Department of Defense. *VA/DoD clinical practice guideline for the management of diabetes mellitus.* Washington (DC): Veterans Health Administration, Department of Defense; 2003. Accessible at: http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=5185

Flemish Association of General Practitioners and Flemish Diabetes Association 2005	Targeted opportunistic screening of persons with increased risk: • History of blood glucose disorders (gestational diabetes, stress hyperglycaemia due to surgical interventions) • People treated with certain medications (ex. corticoids, atypical neuroleptics, protease inhibitors, • People suffering from certain conditions that may cause diabetes (ex. pancreatitis, alcoholism) • Age ≥ 45 with first-degree relative with diabetes • Age ≥ 45 with signs of metabolic sydnrome • Age ≥ 65 All individuals presenting with symptoms suggesting type 2 diabetes (thirst, recurring urogential infections, signs of diabetes complications, etc.). Such cases more appropriately fall within the "diagnostic" rather than the "screening" category.	Primary care / GP	FPG, ideally laboratory assays of venous blood should be used.	3 years 1 year in individuals with IGT/IFG or history of gestational diabetes or stress hyperglycaemia	N/A	N/A	*Diabetes:* Fasting: ≥ 126 mg/dL (7.0 mmol/L) Random: ≥ 200 mg/dL (11.1 mmol/L) 2hPG 75g OGTT: ≥ 200 mg/dL (11.1 mmol/L) *IFG:* FPG: ≥ 100 mg/dL and < 126 mg/dL (5.5 - 7.0 mmol/L) *IGT:* 2hPG 75g OGTT: ≥ 140 mg/dL and < 200 mg/dL (7.0 - 11.1 mmol/L)	Wens J, et al. *Guideline for Good Medical Practice: Type 2 Diabetes Mellitus.* Flemmish Association of General Practitioners and Flemmish Diabetes Association. Belgium, 2005. English translation accessile at: http://pcdeurope.org/documents/guidelines/type_2_guideline%20051117.pdf
Dutch College of General Practitioners 1999	People over age 45 with: • Parents or siblings with Type 2 diabetes mellitus • An ethnic predisposition • Dyslipidaemia] • Obesity (BMI >27) • Hypertension • Manifest heart- and vascular disease • A history of gestational diabetes or women who have given birth to babies weighing more than 4 kg (8.98lbs) at birth. Any patient presenting with symptoms that may be the result of diabetes: • Thirst • Polyuria • Weight loss • Pruritus vulvae in the elderly • Mono-neuropathy • Neurogenic pain • Sensory disorders	Primary care / GP	FPG preferred	3 years	N/A	Recommend testing in high-risk ethnic population (Surinamers of Hindustani or Creole origin) beginning at age 45.	*Diabetes:* FPG: Full capillary blood ≥ 5.6 mmol/L; Venous plasma: ≥ 6.1 and ≤ 6.9 mmol/L Random: Full capillary blood >11.0 mmol/L; Venous plasma > 11.0 mmol/L *IFG:* FPG: full capillary blood ≥ 5.6 mmol/L Venous plasma: ≥ 6.1 and ≤ 6.9 mmol/L	Ruten GEHM et al. *The Dutch College of General Practitioners (NHG) Standard for Type 2 Diabetes Mellitus - Guidelines for Types 2 Diabetes Care.* Huisarts en wetenschap 1999;42(2): 67-84. Accessible at: www.diabetesinprimarycare.com/
International Guidelines:								
World Health Organization (and the International Diabetes Federation) 2003	There is direct evidence that the incidence of diabetes can be reduced in people at high risk of future development of type 2 diabetes who may be identified as a result of activities directed towards diabetes detection. There is currently no direct evidence (from RCTs specifically designed to answer questions related to early detection through screening) as to whether individuals will *or will not benefit from the early detection of type 2* diabetes through screening.	Opportunistic screening may be justified provided: 1) the reasons for testing are adequately explained to the individual, 2) the health system has the capacity for the clinical management of those who screen positive, 3) methods with adequate sensitivity and specificity are available, 4) the psychosocial needs of those who screen positive and those who screen negative can be met, and 5) the health system can implement effective preventive strategies for those confirmed to be at high risk for the development of diabetes.	The most appropriate protocol for screening 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. The choice of the method or methods for screening will depend on the resources available, the acceptability of the methods in the population being screened, and the levels of sensitivity, specificity etc., that are required. Methods of screening which might be regarded as unacceptable in high resource settings (i.e. testing urinary glucose) may be suitable in low resource settings.	There are no compelling data on which to decide how often to screen. One source of information are studies on diabetes incidience or progression to diabetes from a normal state, IGT or IFG.	N/A	Ethnicity may be a risk factor.	WHO 1999: *Diabetes:* FPG: ≥ 7.0 mmol/L 2hPG 75g OGTT and / or random: ≥ 11.1 mmol/L *IGT:* 2hPG 75g OGTT: 7.8 - 11.0 mmol/L FPG: < 7.0 mmol/L (if measured) *IFG:* FPG: 6.1 - 6.9 mmol/L 2hPG 75g OGTT: <7.8 mmol/L (if measured)	World Health Organization. *Screening for type 2 diabetes: report of the World Health Organization and International Diabetes Federation meeting.* WHO - Department of Noncommunicable Diaseease Management; Geneva, 2003. Accessible at: http://www.who.int/diabetes/publications/en/screening_mnc03.pdf World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation (Part 1: diagnosis and classification of diabetes mellitus). WHO - Department of Noncommunicable Diaseease; Geneva, 1999. Accessible at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf
International Diabetes Federation 2005	Detection programs should target high-risk individuals identified by assessment of risk factors.	Opportunistic screening depending on local resources	FPG preferred.	3-5 years	N/A	Ethnicity may be a risk factor.	(see WHO 1999 diagnostic criteria)	International Diabetes Federation Clinical Guidelines Task Force. *Chapter 1: Screening and diagnosis* in Global guideline for type 2 diabetes. IDF; Belgium, 2005. Accessible at: http://www.idf.org/webdata/docs/GGT2D%2001%20Screening%20and%20diagnosis.pdf
Primary Care Diabetes (PCD) Europe 2006	*[see Dutch College of General Practitioners, above] www.pcdeurope.org/*							

* It is important that acknowledge that a screening test for type 2 diabetes is not a diagnostic test. No final diagnosis of diabetes (or absence of diabetes) is possible and the person must be referred for appropriate confirmatory testing as necessary.
Fasting defined as no caloric intake for at least 8 h. Casual defined as any time of the day, without regard to the interval since the last meal.

APPENDIX B – EVIDENCE CRITERIA

For assessing evidence for use in developing clinical recommendations, the CDA and CTFPHC along with other organizations categorize evidence using Levels of Evidence and Recommendation Grades which identify the quality of evidence and the quality of the "best evidence" available, respectively, to support a recommendation. The higher the level assigned to evidence, the more likely the evidence is to be unbiased and have a valid conclusion.(1)

Appendix C outlines the levels of evidence and recommendation grades (and the criteria for each) employed by the CDA, CTFPHC, ADA, USPSTF and the Cochrane Collaboration (UK, 2005).

"Best evidence" would include systematic reviews or meta-analyses of multiple randomized controlled trials, and large randomized controlled trials (RCTs) with adequate power to answer the question. This would include a negative RCT if it were large enough to exclude a clinically relevant effect of treatment, determined by the confidence interval (CI) around the relative risk reduction. "Best evidence" may also include non-randomized clinical trials of cohort studies with indisputable results.

Because is has been assumed that "best evidence" can only be derived from direct trials, evaluating the efficacy of early detection for diabetes has led to conservative recommendations (i.e. Grade D – expert consensus) for screening and case-finding, justified by the absence of direct trials.(1) In the book "Evidence-Based Diabetes Care", Gerstein and Haynes (2001) state the following:

"Diabetes prediction studies report long durations of follow-up in large numbers of at-risk people; as such, they identify more subjects developing diabetes and therefore provide more precise estimates of risk. Based on studies of this nature, it has been possible to identify independent predictors with enough certainty to undertake large randomized prevention trials of type 2 diabetes…

… For type 2 diabetes, associations have been found between future disease + one or more of obesity, older age, family history, ethnicity, IGT and IFG, high serum insulin levels and gestational diabetes. IGT has emerged as the strongest independent predictor of future type 2 diabetes, (5% risk per year). This risk is refinable according to presence or absence of other factors (approaching 8% per year in people who have IFG). The predictive value of IGT has made it the primary entry criterion for large trials testing preventions for type 2 diabetes."(1) - [Evidence Level 1]

Appendix D summarizes the designs of important diabetes-related trials, some of which comprise part of the evidence cited by the CDA and CTFPHC recommendations. All are indirect trials. Figure 1 provides a diagram of direct and indirect trial study designs.

In addition, two studies on diabetes treatment and prevention of secondary complications have shown indisputable benefit on preventing or decreasing microvascular complications of diabetes in newly or recently diagnosed individuals, the DCCT in the case of Type 1 diabetes, and the UKPDS regarding Type 2 diabetes.(99-102) However the relevance of this evidence to the question of screening remains speculative, since the extra years of intervention (screening, diagnosis and treatment) may or may not yield extra clinical and economic benefits.

APPENDIX C - Criteria for Levels/Grades of Evidence and Quality Assessment of Evidence

CDA/Gerstein

Studies of Diagnosis:

1 i. Independent interpretation of test results (without knowledge of the results of the diagnostic or gold standard).
ii. Independent interpretation of the diagnostic standard (without knowledge of the test result).
III. Selection of people suspected (but not known) to have a disorder.
iv. Reproducible description of both the test and diagnostic driteria.
v. At least 50 patients with and 50 patients without the disorder.

2 Meets 4 of Level 1 Criteria

3 Meets 3 of Level 1 Criteria

4 Meets 1 or 2 of Level 1 Criteria

Studies of Treatment and Prevention:

1A Systematic overview or meta-analysis of high-quality RTC.
Appropriately designed RTC with adequate power to answer the question posed by the investigators.

1B Nonrandomized clinical trial or cohort study with indisputable results.

2 RCT or systematic overview that does not meet Level 1 criteria.

3 Nonrandomized clinical trial or cohort study.

4 Other

Studies of Prognosis:

1 a. Inception cohort of patients with the condition of interest, but free of the outcome of interest.
b. Reproducible inclusion/exclusion criteria.
c. Follow-up of at least 80% of subjects.
d. Statistical adjustment for extraneous prognostic factors (confounders).
e. Reproducible description of outcome measures.

2 Meets criterion a. above, plus 3 of the other 4.

3 Meets criterion a. above, plus 2 of the others.

4 Meets criterion a. above, plus 1 of the others.

Grades of Recommendations for Clinical Practice:

A The best evidence was at Level 1.

B The best evidence was at Level 2.

C The best evidence was at Level 3.

D The best evidence was at Level 4 or consensus.

CTFPHC

A. Research design rating:

I Evidence from RCTs

II-1 Evidence from non-randomized controlled trials

II-2 Evidence from cohort or case-control analytical studies, preferably from more than one centre or research group.

II-3 Evidence from comparisons between times or places with or without the intervention: dramatic results from uncontrolled studies could be included here.

III Opinions of respected authorities, based on clinical experiences; descriptive studies or reports of expert committees.

B. Quality (internal validity) rating (see Harris et al. 2001)*

Good A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.

Fair A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".

Poor A study (including meta-analyses or systematic reviews) that has at least one design-specific* fatal flaw, or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

Recommendation Grades for Specific Clinical Preventive Actions

A There is **good** evidence to recommend the clinical preventive action.

B There is **fair** evidence to recommend the clinical preventive action.

C The existing evidence is **conflicting** and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.

D There is **fair** evidence to recommend against the clinical preventive action.

E There is **good** evidence to recommend against the clinical preventive action.

I There is **insufficient** evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

Cochrane Collaboration (Protocol document)

Trial Selection:

1) Includes patients without known diabetes mellitus.
2) Compares screening for type 2 diabetes with diagnosis of type 2 diabetes during regular care.
3) Assess one or more relevant clinical outcome measure.
4) Uses random allocation to the comparison group.

Quality Assessment of Trials:

1) Minimization of selection bias:
- Randomization procedures will be scored adequate if the resulting sequences were unpredictable. When randomization was performed on a "group" level, the same criteria will apply.
- Allocation concealment will be scored adequate if participating patients and investigators could not forsee the assignment.

2) Minimization of performance bias:
- Method of blinding, if appropriate.

3) Minimization of attrition bias:
- Handling of drop-outs will be considered adequate when studies report a complete description of all patients failing to participate until the end of the trial and if the data were analyzed on intention-to-treat basis, that means with all randomized patients included.
- Overall drop-out rate less than 15% will be considered adequate.
- A difference in drop-out rate in the at risk groups less than 10% will be considered adequate.

4) Minimization of Detection Bias:
- Outcome assessment will be considered adequate if the outcome assessors were completely blind for the intervention.
- Method of blinding analysis will be considered adequate if the outcome assessors were completely blind for the intervention up to the point that all analyses were completed. Blinding of analyses is to date not a common practice in the conduct of randomized trials. Therefore only the possible influence in a sensitivity analysis will be explored, and this item will not be used for the overall quality assessment.

Quality Criteria Categories:

A All criteria met.

B One or more quality criteria only partially met.

C One or more quality criterion not met.

ADA

Level of Evidence

A Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:
- Evidence from a well-conducted multicenter trial;
- Evidence from a meta-analysis that incorporated quality ratings in the analysis;
- Compelling nonexperimental evidence, i.e.either a,; patients died before therapy and at least some survived with therapy or some patients died without therapy and none diead with therapy *(Center for Evidence Based Medicine, Oxford).*

Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:
- Evidence from a well-conducted trial at one or more institutions;
- Evidence from a meta-analysis that incorporated quality ratings in the analysis.

B Supportive evidence from well-conducted cohort studies, including:
- Evidence from a well-conducted prospective cohort study or registry;
- Evidence from a well-conducted meta-analysis of cohort studies.

Supportive evidence from a well-conducted case-control study.

C Supportive evidence from poorly controlled or uncontrolled studies, including:
- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results;
- Evidence from observational studies with high potential for bias;
- Evidence from case series or case reports.

D Conflicting evidence with the weight of evidence supporting the recommendation.

E Expert consensus of clinical experience.

USPSTF

Hierarchy of Research Design

I Evidence obtained from at least one properly randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Study Design Criteria and Internal Validity of Individual Studies

Good Study meets all criteria for that study design.

Fair Study does not meet all criteria but is judged to have no fatal flaw that invalidates its results.

Poor Study contains a fatal flaw.

Study design: Systematic reviews
Criteria:
Comprehensiveness of sources/search strategy used
Standard appraisal of included studies
Validity of conclusions
Recency and relevance

Study design: Case-control studies
Criteria:
Accurate ascertainment of cases
Nonbiased selection of cases/controls with exclusion criteria applied equally to both
Response rate
Diagnostic testing procedures applied equally to each group
Appropriate attention to potential confounding variables

Study design: Randomized controlled trials (RCTs) and cohort studies
Criteria:
Initial assembly of comparable groups: For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
Important differential loss to follow-up or overall high loss to follow-up
Measurements: equal, reliable, and valid (includes masking of outcome assessment)
Clear definition of interventions
All important outcomes considered
Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Study design: Diagnostic accuracy studies
Criteria:
Screening test relevant, available for primary care, adequately described
Study uses a credible reference standard, performed regardless of test results
Reference standard interpreted independently of screening test
Handles indeterminate results in a reasonable manner
Spectrum of patients included in study
Sample size
Administration of reliable screening test

Recommednations graded according to one of five classifications reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A Good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.

B At least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.

C At least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.

D At least fair evidence that [the service] is ineffective or that harms outweigh benefits.

I Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

APPENDIX D - Type 2 Diabetes and Complications Prevention Trials - Study Designs and Key Outcomes/Results

Study	*Type/Design*	*Description*	*Objectives*	*Entry Criteria*	*Key Outcomes/Results*	*Reference(s)*
DPP	Indirect RCT	Placebo-controlled. Conducted at 27 clinical centres in the U.S. Adaptive randomization procedure, stratified by clinical centre.	• Comparison of the efficacy and safety of three interventions (intensive lifestyle vs. standard lifestyle recommendations combined with Metformin or placebo) in preventing or delaying development of diabetes. • Assessing differences between the three treatment groups in the development of cardiovascular disease and its risk factors.	• ≥ 25 years old • BMI ≥ 24 kg/m² • No prior diabetes diagnosis (other than GDM) • Nondiabetic by 1997 ADA and 1985 WHO criteria • IGT based on a single 75-g OGTT • Elevated FPG 95-125 mg/dL	Compared to placebo: • Lifestyle intervention reduced the incidence of diabetes over an average 2.8 years years by 58%; • Metformin intervention reduced the incidence of diabetes over an average 2.8 years by 31%. To prevent one case of diabetes during a period of three years, 6.9 persons meeting study criteria would have to participate in he lifestyle intervention program, and 13.9 would have the receive Metformin.	The Diabetes Prevention Program Research Group. *Diabetes Care* , 1999;22(4):623-634 Knowler WC et al. *N Engl J Med* , 2002; 346(6):393-403.
DPP Washout Study	Indirect washout study	Medication intervention group (Metformin and placebo) of the RCT	To determine whether the observed benefit of treatment with Metformin in persons with IGT was a transient pharmacological effect or more sustained, i.e. after withdrawl from medication.	Participants assigned to medication intervention group (Metformin and placebo) who had not developed diabetes at the end of the trial.	• The DPP showed Metformin decreased risk of diabetes by 31%. The washout study showed 26% of this effect can be accounted for by the pharmacological effect of Metformin that did not persist after the drug was stopped. • After the washout study (followed for 1-2 weeks after withdrawal from Metformin, confirmatory OGTT conducted within 6 weeks for those diagnosied with diabetes), incidence of diabetes was still reduced by 25%. Thus, the Metformin benefit did not represent "masking" of the development of diabetes.	The Diabetes Prevention Program Research Group. *Diabetes Care* , 2003;26(4):977-980.
STOP-NIDDM	Indirect RCT	Double-blind, placebo-controlled. Conducted in Canada, Germany, Austria, Norway, Sweden, Denmark, Finland, Isreal, Spain	Assess the effects of acarbose in preventing or delaying conversion of IGT to diabetes	IGT AND FPG 5.6-7.7 mmol/L	• Acarbose can be used, either as an alternative or in addition to changes in lifestyle , to delay development of type 2 diabetes in patients with IGT. • 32% of participants treated with acarbose developed diabetes, whereas 42% of participants receiving placebo developed diabetes. • Treatment with placebo for 3 months was associated with an increase in conversion from IGT to diabetes. • Acarbose significantly increased reversal from IGT to normal glucose tolerance.	Chaisson J-L et al. *Lancet* , 2002;359:2072-7.
Finnish Diabetes Prevention Study	Indirect RCT	• Placebo-controlled. Randomization assigned by study physician using randomization list; stratification according to center, sex and mean plasma glucose concentration after 2hPG 75g OGTT. • Study was partly blinded: study physician, nurses and staff involved in delivering the intervention had to be aware of group assignment.	To determine the feasibility and effects of a program of changes in lifestyle designed to prevent or delay the onset of type 2 diabetes in subjects with IGT.	• Overweight (BMI ≥ 25 kg/m² • 40-65 years old • IGT • No diabetes diagnosis	• Cumulative incidence of diabetes after four years was 11% in intervention group vs. 23% in the control group. • During the trial, risk of diabetes was reduced by 58% in the intervention group, and was directly associated with changes in lifestyle.	Tuomilehto J et al. *N Engl J Med* , 2001; 344(18):1343-50.
Da Qing IGT and Diabetes Study (Lifestyle)	Indirect RCT	Placebo-controlled. Subjects were randomized by clinic.	To determine whether diet and exercise interventions in persons with IGT may delay the development of NIDDM (i.e. reduce the incidence of NIDDM, and thereby reduce the overall incidence of diabetes complications and mortality attributed to these complications.	•Resident of Da Qing city, China •Receiving care at one of the clinics in Da Qing city •IGT determined by 2hPG 75g OGTT • ≥ 25 years of age	• Cumulative incidence of diabetes at 6 years was 68% in the control group vs. 44% in the diet intervention group, vs. 41% in the exercise group, and vs. 46% in the diet + exercise intervention group. • In a proportional analysis adjusted for differences in baseline BMI and fasting glucose, the diet, exercise and diet+ exercise interventions were associated with 31%, 46% and 42% reductions in risk of developing diabetes, respectively.	Pan XR et al. *Diabetes Care* , 1997; 20(4):537-544.
Da Qing IGT and Diabetes Study (IR & IS)	Indirect	Diet, exercise and diet + exercise intervention groups of the RCT.	To investigate the effects of insulin resistance (IR) and insulin secretion (IS) on the development of diabetes mellitus in persons with IGT who underwent lifestyle interventions.	Participants assigned to diet, exercise and diet + exercise intervention groups.	• Interventions were more effective in persosn with less insulin resistance.	Li G et al. *Diabetes Research & Clinical Practice,* 2002:58(3):193-200.
Malmö Preventive Trial (6-year feasibility study)	Indirect	Non-randomized. Included an IGT intervention group, and IGT routine treatment group, a diabetic intervention group, and a normal glucose tolerance group.	To determine whether the beneficial effects of diet and exercise treatment over 6-12 month periods can be satisfactorily extended over longer periods, and with drop-out minimized.	•Male •48 years old (mean age 48) •Resident in the Malm ö region	• The diabetes and IGT intervention groups showed substantial improvements in glucose tolerance (2hPG 75-g OGTT) during the first 2-year intervention period. This improvement was maintained in the IGT group for the duration of the study, whereas mean 2hPG (75g OGTT) was unchanged for the diabetes group. • In the diabetes and IGT intervention groups mean 2-h insulin values were substantially reduced during the intervention period, concomitant with the fall in 2-h glucose. In the IGT routine treatment group and the normal glucose tolerance group, insulin values were unchanged. • In the diabetes group, 54% had improved and were in remission at follow-up (i.e. no longer had glucose levels diagnostic of diabetes). • In the IGTintervention group, glucose tolerance had improved in 75% of cases, and was below the 2-h value of 7.0 mmol/L in 52% of cases. 11% of the IGT intervention group had diabetes at follow-up. • In the IGT routine treatment group, glucose tolerance had deteriorated in 67%; 29% had developed diabetes. • Relative risk of diabetes development in the IGT intervention group compared to the IGT routine treatment group was 0.37. • No individuals in the normal glucose tolerance group had developed diabetes.	Eriksson KF and Lindgarde F. *Diabetologia* , 1991;34:891-8.
Malmö Preventive Trial (12-year mortality in male subjects)	Indirect	IGT intervention group compared to an IGT non-randomized routine treatment group, a diabetic intervention group, and a normal glucose tolerance group.	• To determine whether, at age 60, the IGT intervention group were still characterized by a survival rate comparable to that in the normal glucose tolerance group, as was the case at age 54. • To determine whether mortality in the IGT intervention group was lower than in the IGT routine treatment group. • To identify possible predictors of death in the IGT subgroups and in the cohort as a whole.	•Male cohort from Malm ö Preventive Trial. •Mean age 54 years (follow-up at mean age 60 years) •Resident in the Malm ö region	• Mortality rate for IGT intervention group was similar to that in the normal glucose tolerance group, with no difference at age 60. • Mortality rates for the IGT routine treatment group and the diabetes group were 2 times and 3 times greater than the normal glucose tolerance group, respectively. • Mortality rate for the IGT intervention group was significantly lower than that in the IGT routine group.	Eriksson KF and Lindgarde F. *Diabetologia* , 1998;41:1010-16.
Troglitazone in high-risk Hispanic women	Indirect RCT	Double-blind, placebo-controlled.	Whether chronic amelioration of insulin resistance would preserve pancreatic β-cell function and delay the onset of diabetes.	•Hispanic Females •Previous gestational diabetes	•During blinded treatment, average annual diabetes incidence rates were 12% and 5% in the placebo and troglitazone groups, respectively. •At 31-month follow-up, diabetes rates were 12% and 6% in the placebo and troglitazone groups, respectively.	Buchanan TA et al. *Diabetes* , 2002;51: 2796-2803.
UKPDS 33	Indirect RCT	10-year prospective study 20 hospital-based clinics in England, Scotland and Northern Ireland.	To compare the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial.	•58-60 years of age •Newly diagnosed diabetes •FPG 6.1-15.0 mmol/L after 3 months of diet treatment	•Over 10 years, A1c was 7% in the intensive group compared with 8% in the conventional group, an 11% reduction. •Compared with the conventional group, the risk in the intensive group was 12% lower for any diabetes-related endpoint; 10% lower for any diabetes-related death; and 6% lower for all-cause mortality. •Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction in microvascular endpoints. •There was no difference for any of the three aggregate endpoints between the three intensive agents (chlorpropamide, glibenclamide, or insulin).	UK Prospective Diabetes Study Group. *Lancet* , 1998;352(9131):854-53.
UKPDS 38	Indirect RCT	10-year prospective study 20 hospital-based clinics in England, Scotland and Northern Ireland.	To determine whether tight control of blood pressure prevents macrovascular and microvascular complications in patients with type 2 diabetes.	Hypertension Type 2 diabetes	•Mean BP during follow up was significantly reduced in the group assigned tight blood pressure control (144/82 mm Hg) compared with the group assigned to less tight control (154/87 mm Hg). •Reductions in risk in the group assigned to tight control compared with that assigned to less tight control were 24% in diabetes related end points, 32% in deaths related to diabetes, 44% in strokes, and 37% in microvascular end points. •There was a non-significant reduction in all cause mortality. •After nine years of follow up the group assigned to tight blood pressure control also had a 34% reduction in risk in the proportion of patients with deterioration of retinopathy by two steps and a 47% reduced risk of deterioration in visual acuity by three lines of the early treatment of diabetic retinopathy study (ETDRS) chart. •After nine years of follow up 29% of patients in the group assigned to tight control required three or more treatments to lower blood pressure to achieve target blood pressures.	UK Prospective Diabetes Study Group. *BMJ* , 1998;317:703-13.
Hypertension Optimal Treatment	Indirect RCT	Double-blind, placebo-controled. Subjects from 26 countries	To assess the optimum target diastolic blood pressure and the potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension.	•50-80 years of age •Hypertension and diastolic blood pressure between •100 mmHg and 115 mmHg	•Diastolic BP was reduced by 20.3 mm Hg, 22.3 mm Hg, and 24.3 mm Hg, in the ≤ 90 mmHg, ≤85mmHg, and ≤80 mmHg target groups, respectively. •The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 m Hg. •The lowest risk of cardiovascular mortality occurred at 86.5 mmHg. •In patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group ≤80 mmHg compared with target group ≤90 mmHg. •Acetylsalicylic acid reduced major cardiovascular events by 15% and all myocardial infarction by 36%, with no effect on stroke.	Hansson L et al. Lancet, 1998;352:837-53.
Lipid Study Group	Indirect RCT	Double-bling, randomized trial	To compare the effects of pravastatin (40 mg daily) with those of a placebo over a mean follow-up period of 6.1 years.	• 31-75 years of age •History or myocardial infarction or hospitalization for unstable angina •Initial plasma total cholesterol levels of 155-271 mg/dL measured 4 weeks before randomization.	•Death from coronary heart disease occurred in 8% of placebo subjects vs. 6% of the pravastatin group, a relative risk reduction of 24%. •Overall mortality was 14% in placebo subjects vs. 11% in the pravastatin group, relative risk reduction of 22%. • Incidence of all cardiovascular outcomes was consistently lower in the pravastatin group: relative risk reduction of 29% for myocardial infarction, 24% for death from coronary heart disease or nonfatal myocardial infarction, 19% for stroke, and 20% for coronary revascularization.	The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. *N Engl J Med* , 1998;339(19):1349-1357.

APPENDIX E – SEARCH METHODOLOGY AND YIELDS

Electronic searching

A.
General internet searching:
Terms:
Diabetes + guidelines
Diabetes + recommendations
Diabetes + association
Diabetes + society
[Country name] + diabetes + guidelines
[Country name] + diabetes + screening
[Country name] + diabetes + recommendations
[Country name] + diabetes + association
[Country name] + diabetes + society
Europe + diabetes + guidelines
Europe + diabetes + screening
Europe + diabetes + association
Europe + diabetes + society

B.
Searched for specified organizations/guidelines by name: CTFPHC, CDA, ADA, USFSTP, Cochrane Collaboration, WHO, IDF

C.
Medline:

Search Terms:	*Yield*
Diabetes	220115
Screening	211728
Guidelines	111798
Recommendations	60622
Impaired glucose tolerance	4505
Impaired fasting glucose	562
Screening + guidelines	6344
Screening + recommendations	3859
Diabetes + guidelines + screening	435
Diabetes + recommendations + screening	251
Impaired glucose tolerance + screening	373
Impaired fasting glucose + screening = 81	81

D.
Cochrane Library (via University of Alberta electronic library resources)
Search by topic: Metabolic & Endocrine Disorders
→ Search by sub-topic: Diabetes Mellitus and Related Disorders (yield: 48)
→Diabetes mellitus: 43
→Type 2 Diabetes Mellitus: 26 (visual scan of all entries)
→Screening for Type 2 Diabetes Mellitus (Protocol)

Hand searching
Reference sections of relevant articles reviewed.
Hard copy of CDA 2003 guidelines.