# The Efficacy and Cost of Alternative Strategies for Systematic Screening for Type 2 Diabetes in the U.S. Population 45–74 Years of Age

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**OBJECTIVE** — To simulate the outcomes of alternative strategies for screening the U.S. population 45–74 years of age for type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — We simulated screening with random plasma glucose (RPG) and cut points of 100, 130, and 160 mg/dl and a multivariate equation including RPG and other variables. Over 15 years, we simulated screening at intervals of 1, 3, and 5 years. All positive screening tests were followed by a diagnostic fasting plasma glucose or an oral glucose tolerance test. Outcomes include the numbers of false-negative, true-positive, and false-positive screening tests and the direct and indirect costs.

**RESULTS** — At year 15, screening every 3 years with an RPG cut point of 100 mg/dl left 0.2 million false negatives, an RPG of 130 mg/dl or the equation left 1.3 million false negatives, and an RPG of 160 mg/dl left 2.8 million false negatives. Over 15 years, the absolute difference between the most sensitive and most specific screening strategy was 4.5 million true positives and 476 million false-positives. Strategies using RPG cut points of 130 mg/dl or the multivariate equation every 3 years identified 17.3 million true positives; however, the equation identified fewer false-positives. The total cost of the most sensitive screening strategy was $42.7 billion and that of the most specific strategy was $6.9 billion.

**CONCLUSIONS** — Screening for type 2 diabetes every 3 years with an RPG cut point of 130 mg/dl or the multivariate equation provides good yield and minimizes false-positive screening tests and costs.

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In the United States, the costs of diabetes are staggering. In 2002, the direct and indirect costs of diabetes were estimated to be $132 billion (1). The enormous cost of diabetes and the ease of detecting type 2 diabetes in its preclinical stage led the American Diabetes Association (ADA) to recommend screening asymptomatic persons ≥45 years of age for diabetes (2). Although the ADA currently recommends screening with a fasting plasma glucose (FPG), it had recommended screening with a random plasma glucose (RPG) as recently as 2000 (3). Indeed, RPG remains clinicians' preferred method of screening. Among nondiabetic individuals ≥45 years of age enrolled in a large managed care organization, 95% of glucose testing involved RPG (4). Despite the frequent occurrence of RPG screening, substantial controversy remains as to the optimal cut point to define an abnormal test (5) and the optimal frequency of screening. To address these questions, we modeled several systematic approaches to screening the U.S. population 45–74 years of age for diabetes. We assessed screening with RPG cut points of 100, 130, and 160 mg/dl and screening using RPG and other risk factors in a multivariate equation (6). We assessed screening at 1-, 3-, and 5-year intervals over 15 years. We assumed that all positive screening tests were followed by a definitive diagnostic test: an FPG for those with RPG ≥200 mg/dl and a 2-h 75-g oral glucose tolerance test (OGTT) for those with RPG <200 mg/dl. We assessed the direct and indirect costs associated with each screening strategy and the cost per true-positive case identified. In these analyses, we sought to identify the screening strategy that would provide good yield, sufficient protection from false negative and false-positive results, and acceptable cost.

## RESEARCH DESIGN AND METHODS

— The study population for our simulation was a closed cohort representing the U.S. population 45–74 years of age without a previous diagnosis of diabetes. According to the 2000 U.S. census, 80.3 million people were 45–74 years of age (7). Based on the Third National Health and Nutrition Examination Survey, 7.7 million people 45–74 years of age were previously diagnosed with diabetes (8). Thus, 72.6 million individuals were eligible for screening.

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**Abbreviations:** ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; RPG, random plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

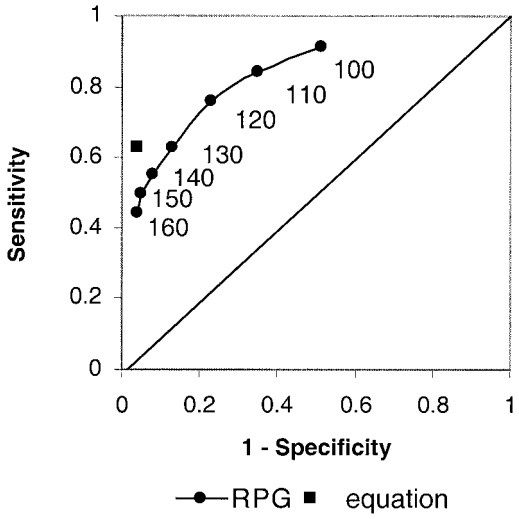


**Figure 1**—*ROC curve for static RPG cut points from 100 to 160 mg/dl and for the multivariate equation.*

### Screening and diagnostic strategies

We examined four screening tests: *1*) screening with an RPG cut point of 100 mg/dl, a highly sensitive test; *2*) screening with an RPG cut point of 160 mg/dl, a highly specific test; *3*) screening with an RPG cut point of 130 mg/dl, a test with intermediate sensitivity and specificity; and *4*) screening with a multivariate logistic equation that incorporated RPG, postprandial time (self-reported number of hours since last food or drink other than water), age, sex, and BMI (6). We also assessed three screening intervals over a 15-year period: *1*) baseline and every 5 years, *2*) baseline and every 3 years, and *3*) baseline and every year.

We assumed that individuals with positive screening tests but RPG <200 mg/dl (94% those with positive screening tests) would undergo an OGTT for definitive diagnosis and that individuals with positive screening tests and RPG ≥200 mg/dl (6% of those with positive screening tests) would have an FPG for definitive diagnosis (6).

### Estimating sensitivity and specificity

To estimate the sensitivity and specificity of each screening test, we applied the RPG cut points and the multivariate equation to a large dataset that included diabetes risk factors, RPG levels, and 2-h 75-g OGTTs performed on separate days. For RPG ≥100 mg/dl, sensitivity was 91% and specificity 49%; for RPG ≥130 mg/dl, sensitivity was 63% and specificity 87%; and for RPG ≥160 mg/dl, sensitivity was 44% and specificity 96%. The equation was 63% sensitive and 96% specific (6).

### Estimating the prevalence and incidence of diabetes

We estimated the prevalence of undiagnosed diabetes to be 10% at baseline and the prevalence of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) to be 22% (7). We assumed that the prevalence of IGT/IFG remained constant and estimated the rate of progression from IGT/IFG to diabetes to be 5.7% per year (9). Although the incidence of type 2 diabetes decreases by ~50% in persons ≥75 years of age compared with those 64–75 years of age, the incidence increases by 50% in persons 65–74 years of age compared with those 45–64 years of age (10). For this reason, we believe that over the time frame of 15 years, the incidence remains approximately constant.

### Screening efficacy

We measured the efficacy of each screening strategy by calculating the number of false-negative (screen-negative individuals with diabetes), true-positive (screen-positive individuals confirmed to have diabetes on definitive testing), and false-positive (screen-positive individuals without diabetes on definitive testing) screening tests at each screening examination and over the 15-year study period.

For each screening examination following baseline, we estimated the prevalence of undiagnosed diabetes. First, the total number of subjects eligible for screening was estimated by excluding the number of new true positives. Second, the number of new cases of undiagnosed diabetes was calculated by excluding the false negatives from the total number of eligible subjects in the population and by multiplying by 0.22 (IGT/IFG prevalence) and 0.057 (rate of progression from IGT to diabetes). Third, the total number of cases with undiagnosed diabetes was calculated by adding the number of false negatives to the number of new cases. Finally, the prevalence of undiagnosed diabetes was calculated by dividing the total number of cases with undiagnosed diabetes by the total number of eligible subjects remaining in the population. After each screening examination, the number of eligible subjects became smaller because those diagnosed with diabetes were removed from the population.

### Cost analysis

Direct medical costs included physician time ($51 per visit), RPG tests ($5.24), diagnostic FPGs ($5.24), and OGTTs ($17.22) (7). Indirect costs included the cost of patient time (1 h for an initial visit or diagnostic FPG, 2.5 h for OGTT, $8.00 per hour) and travel ($7.00 per trip) (7). In 2000, 54.4 million Americans 45–74 years of age without a diagnosis of diabetes sought medical care, and 18.2 million did not (7). For individuals who sought care, we assumed that screening was opportunistic and that the only direct medical cost was the cost of the screening test and, when required, the cost of a diagnostic FPG or OGTT. For those who had not sought medical care, we considered the direct medical cost of screening to include the cost of an outpatient visit, the screening test, and, when required, the diagnostic FPG or OGTT.

**RESULTS** — The sensitivities and specificities of various RPG cut points are plotted on a receiver operating characteristic (ROC) curve in which the 2-h 75-g OGTT served as the gold standard (Fig. 1). Each incremental improvement in sensitivity for RPG ≥130 mg/dl was associated with a substantial reduction in specificity. The multivariate equation was more sensitive than RPG alone at a given level of specificity and more specific than RPG alone at a given level of sensitivity.

Figure 2 illustrates the number of false-negative screening tests at each screening examination. The slope of the curves, particularly those with shorter screening intervals, becomes flat after several screening examinations. Except for the most specific strategy (screening with

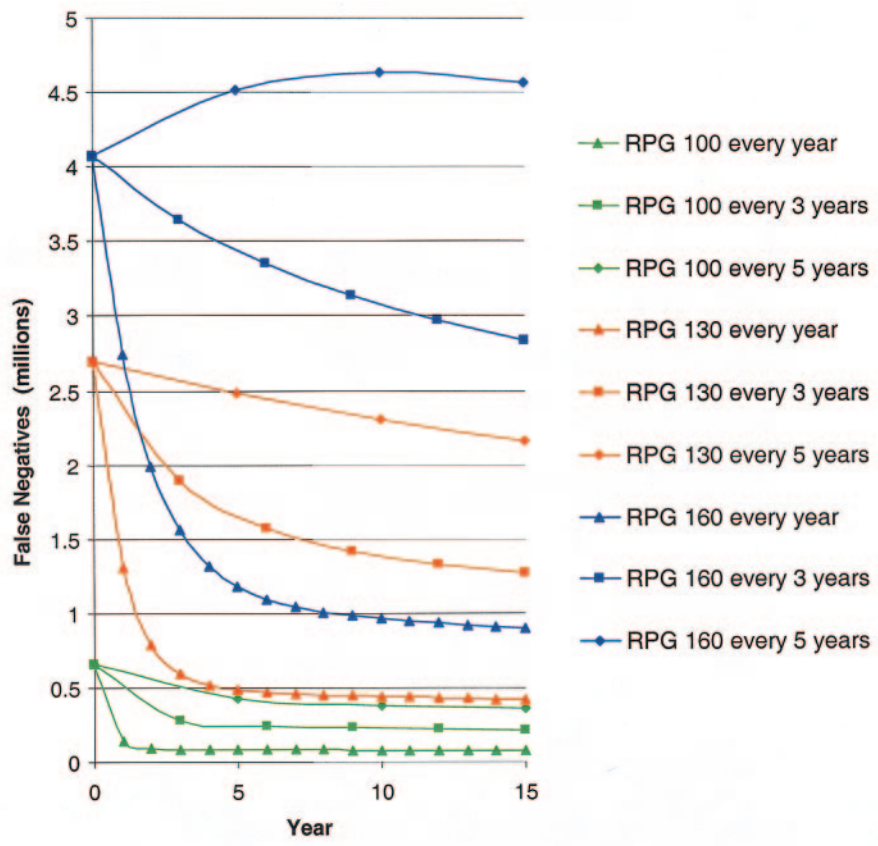


**Figure 2**—*False negatives at each time point as a function of cut point and frequency of screening.*

an RPG cut point of 160 mg/dl every 5 years), which does not keep pace with the number of diabetic patients entering the population each year, the number of false-negative tests falls substantially after several screening examinations. Because the sensitivities are the same, the equation generates the same number of false negatives as an RPG cut point of 130 mg/dl.

Table 1 shows the cumulative number of true-positive and false-positive screening tests for the entire 15-year screening period. The absolute difference in the number of true-positive screening tests between the most sensitive and least sensitive strategies is 4.5 million. The absolute difference in the number of false-positive screening tests between the most sensitive and least sensitive strategy is 476 million. Thus, a cut point with higher specificity minimally decreases the number of true-positive screening tests (the yield) but substantially decreases the number of false-positive tests.

Table 2 shows cost data for the entire 15-year screening period. The total cost for the most sensitive and least specific strategy, using an RPG cut point of 100 mg/dl every year, is $42.7 billion. The total cost for the least sensitive and most specific strategy, using an RPG cut point of 160 mg/dl every 5 years, is $6.9 billion. The cost per true positive identified for screening with a cut point of 100 mg/dl every 3 years is $916, with a cut point of 130 mg/dl is $642, with a cut point of 160 mg/dl is $626, and with the equation is $563. Costs are lower for opportunistic screening than for population screening. Considering a strategy using a cut point of 130 mg/dl every 3 years, the cost per true positive for opportunistic screening is $275. For population screening, the cost per true positive is $1,745.

**Table 1**—*Cumulative true-positive and false-positive screening tests*

| | True positives (millions) | False-positives (millions) |
|---|---|---|
| RPG ≥100 mg/dl | | |
| Every year | 18.5 | 485.9 |
| Every 3 years | 18.3 | 182.3 |
| Every 5 years | 18.2 | 121.6 |
| RPG ≥130 mg/dl | | |
| Every year | 18.1 | 124.2 |
| Every 3 years | 17.3 | 46.5 |
| Every 5 years | 16.4 | 31.3 |
| RPG ≥160 mg/dl | | |
| Every year | 17.6 | 38.1 |
| Every 3 years | 15.7 | 14.3 |
| Every 5 years | 14.0 | 9.5 |
| Equation | | |
| Every year | 18.1 | 38.1 |
| Every 3 years | 17.3 | 14.3 |
| Every 5 years | 16.4 | 9.5 |

**CONCLUSIONS** — The ADA recommends opportunistic screening for type 2 diabetes. At the same time, the ADA acknowledges that questions remain as to the optimal method and frequency of screening (2). We found that an approach that balances sensitivity and specificity—an RPG with a cut point of 130 mg/dl or a multivariate equation applied every 3 years—is optimal.

The sensitivity and specificity of the cut point used to define a positive test have a major impact on efficacy and cost. If one considers screening to be a one-time event, it is tempting to reduce the cut point in order to increase sensitivity so that no cases are missed. However, with repeated screenings, the number of false-negative individuals in the population decreases substantially regardless of the sensitivity (Fig. 2). An unfortunate consequence of using a lower and more sensitive cut point is that it decreases specificity and substantially increases the number of false-positive screening tests (Table 1). The difference in cut points does not have the same dramatic impact on the cumulative number of true positives identified (Table 1).

In addition to selecting an appropriate cut point, one must consider screening periodicity. For each screening strategy, increasing the frequency of screening from every 5 years to every year approximately quadruples the number of false-positive tests requiring definitive diagnostic testing (Table 1). Increasing the time between screenings does, however, increase the likelihood that diabetes complications may develop in the interval between screenings. The incidence of complications in type 2 diabetes is difficult to estimate because the onset and duration are unknown. In type 1 diabetes, proliferative retinopathy begins to develop 3–5 years after onset of diabetes

**Table 2—*Cumulative direct, indirect, and total costs (in billions of dollars) for opportunistic* (n = *54.4 million) and population screening* (n = *18.2 million) of the U.S. population 45–74 years of age and costs per true-positive screening test***

| | Direct medical costs | | | Indirect costs | | | Total costs | | | Cost per true positive | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Opportunistic | Population | Total | Opportunistic | Population | Total | Opportunistic | Population | Total | Opportunistic | Population | Total |
| RPG ≥100 mg/dl | | | | | | | | | | | | |
| Every year | 10.1 | 15.8 | 25.8 | 9.9 | 6.9 | 16.9 | 20.0 | 22.7 | 42.7 | 1,444 | 4,918 | 2,312 |
| Every 3 years | 4.0 | 6.1 | 10.1 | 4.0 | 2.7 | 6.7 | 7.9 | 8.9 | 16.8 | 576 | 1,934 | 916 |
| Every 5 years | 2.7 | 4.2 | 7.0 | 2.8 | 1.9 | 4.6 | 5.5 | 6.1 | 11.6 | 403 | 1,340 | 637 |
| RPG ≥130 mg/dl | | | | | | | | | | | | |
| Every year | 5.6 | 14.4 | 20.0 | 2.8 | 4.6 | 7.4 | 8.4 | 19.0 | 27.4 | 619 | 4,193 | 1,513 |
| Every 3 years | 2.3 | 5.7 | 8.0 | 1.3 | 1.9 | 3.1 | 3.6 | 7.5 | 11.1 | 275 | 1,745 | 642 |
| Every 5 years | 1.6 | 3.9 | 5.5 | 0.9 | 1.3 | 2.2 | 2.6 | 5.2 | 7.8 | 209 | 1,274 | 475 |
| RPG ≥160 mg/dl | | | | | | | | | | | | |
| Every year | 4.6 | 14.2 | 18.8 | 1.2 | 4.1 | 5.2 | 5.7 | 18.3 | 24.0 | 430 | 4,147 | 1,359 |
| Every 3 years | 1.9 | 5.7 | 7.6 | 0.6 | 1.7 | 2.3 | 2.5 | 7.3 | 9.8 | 213 | 1,865 | 626 |
| Every 5 years | 1.4 | 4.0 | 5.3 | 0.5 | 1.2 | 1.6 | 1.8 | 5.1 | 6.9 | 173 | 1,450 | 492 |
| Equation | | | | | | | | | | | | |
| Every year | 4.7 | 14.5 | 19.2 | 1.1 | 4.2 | 5.3 | 5.8 | 18.6 | 24.4 | 425 | 4,114 | 1,348 |
| Every 3 years | 1.9 | 5.5 | 7.4 | 0.6 | 1.7 | 2.3 | 2.5 | 7.2 | 9.7 | 195 | 1,665 | 563 |
| Every 5 years | 1.4 | 3.8 | 5.2 | 0.5 | 1.2 | 1.7 | 1.9 | 5.0 | 6.9 | 152 | 1,218 | 419 |

(11) and nephropathy begins to develop 6–10 years after onset (12). Therefore, screening every 3 years should not allow complications to develop among those remaining undiagnosed. Screening every 5 years may, however, allow for the development of undiagnosed and, hence, untreated retinopathy and nephropathy. The most sensitive RPG cut point has the highest total cost, driven by the large number of false-positive screening tests. The periodicity of screening affects the total cost even more than the choice of a cut point. The total cost of screening every year is more than twice that of screening every 3 years at each RPG cut point.

Incorporating screening into ongoing medical care also reduces cost. For opportunistic screening, the cost per true-positive case identified is less than one-third that associated with population-based screening (Table 1). In opportunistic screening, a higher proportion of the total cost is incurred after a positive screening test. This is particularly true of the indirect costs of opportunistic screening, because they are incurred only with follow-up diagnostic testing. Therefore, with opportunistic screening there is a substantially higher cost associated with the most sensitive strategies. Although the absolute costs associated with population screening are less, fewer people require population screening than opportunistic screening (18.2 million vs. 54.4 million). Studies of community screening have suggested that the yield of screening may be higher among those without regular health care (13). However, even if the yield is twofold higher in population-based screening, it remains less efficient.

When evaluating the cost of strategies with intermediate sensitivity and specificity, the multivariate equation has some advantages over RPG with a cut point of 130 mg/dl. Because both screening tests have the same sensitivity, they diagnose the same number of true positives. However, because the multivariate equation is more specific than RPG with a cut point of 130 mg/dl, it generates fewer false-positives. The total cost for the screening with equation is $9.7 billion versus $11.1 billion with an RPG with a cut point of 130 mg/dl. This translates into savings of $79 per case of undiagnosed diabetes identified. The benefits of using the multivariate equation must, however, be weighed against its logistical complexities and the feasibility and cost of obtaining

information on the additional risk factors included in the equation.

There are several limitations to our study. First, we have not modeled all potential screening tests or strategies. Although the ADA has recommended screening with FPG, it is not commonly performed in routine clinical practice (4), and concern has been raised that the FPG alone may not be sufficiently sensitive as a screening test (14). Studies have reported the sensitivity of an FPG cut point of 126 mg/dl to be 35–59% and the specificity to be 85–95%, comparable to the sensitivity and specificity of an RPG cut point of 160 mg/dl (15–17). Second, we cannot determine whether the costs of screening are balanced by clinical benefits of earlier diagnosis and treatment. Although recent clinical trials have demonstrated benefits associated with early treatment of IGT/IFG (18–22), prospective trials have not addressed the long-term impact of earlier diagnosis and treatment of type 2 diabetes.

In summary, we have shown that screening strategies that balance sensitivity and specificity, such as RPG with a cut point of 130 mg/dl or a multivariate equation, provide good yield and minimize false-positive tests and costs. A screening interval of 3 years is long enough to minimize false-positives, but should not allow complications to develop. Opportunistic screening is more efficient than population screening. Screening is warranted if identification of those with diabetes through screening, and their early treatment, is shown to delay or prevent complications.

**References**


1. American Diabetes Association: Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 26:917–932, 2003
2. American Diabetes Association: Screening for type 2 diabetes. *Diabetes Care* 27 (Suppl. 1):S11–S14, 2004
3. American Diabetes Association: Screening for type 2 diabetes. *Diabetes Care* 23 (Suppl. 1):S20–S23, 2000
4. Ealovega MW, Tabaei BP, Brandle M, Burke R, Herman WH: Opportunistic screening for diabetes in routine clinical practice. *Diabetes Care* 27:9–12, 2004
5. Rolka RB, Narayan KMV, Thompson TJ, Goldman D, Lindenmayer J, Alich K, Bacall D, Benjamin EM, Lamb B, Stuart DO, Engelgau MM: Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care* 24:1899–1903, 2001
6. Tabaei BP, Herman WH: A multivariate logistic regression equation to screen for diabetes: development and validation. *Diabetes Care* 25:1999–2003, 2002
7. Zhang P, Engelgau MM, Valdez R, Benjamin SM, Cadwell B, Narayan KMV: Costs of screening for pre-diabetes among U.S. adults: a comparison of different screening strategies. *Diabetes Care* 26:2536–2542, 2003
8. Centers for Disease Control and Prevention: Prevalence of diabetes and impaired fasting glucose in adults: United States, 1999–2000. *Morbid Mortal Weekly Rep* 833–837, 2003
9. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701–710, 1997
10. Kenny SJ, Aubert R, Geiss LS: Prevalence and incidence of non-insulin-dependent diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, p. 53
11. Klein R, Klein BEK: Vision disorders in diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, p. 293–338
12. Nelson RG, Knowler WC, Pettitt DJ, Bennett PH. Kidney diseases in diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, p. 349–400
13. Tabaei BP, Burke R, Constance A, Hare J, May-Aldrich G, Parker SA, Scott A, Stys A, Chickering J, Herman WH: Community-based screening for diabetes in Michigan. *Diabetes Care* 26:668–670, 2003
14. DECODE Study Group: Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. *Diabetologia* 42:647–654, 1999
15. Bortheiry AL, Malerbi DA, Franco LJ: The ROC curve in the evaluation of fasting capillary blood glucose as a screening test for diabetes and IGT. *Diabetes Care* 17: 1269–1272, 1994
16. Blunt BA, Barrett-Connor E, Wingard DL: Evaluation of fasting plasma glucose as screening test for NIDDM in older adults. *Diabetes Care* 14:989–993, 1991
17. Engelgau MM, Narayan KMV, Herman WH: Screening for type 2 diabetes. *Diabetes Care* 23:1563–1580, 2000
18. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
19. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
20. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51: 2796–803, 2002
21. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
22. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002