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 non-diabetic 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.
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).

**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 FPBs ($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
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 sev-
eral screening examinations. Because the
sensitivities are the same, the equation
generates the same number of false nega-
tives as an RPG cut point of 130 mg/dl.

Table 1 shows the cumulative num-
ber 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 ab-
olute 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 num-
ber 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 to-
tal 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.

**CONCLUSIONS** — The ADA recom-
mends opportunistic screening for type 2
diabetes. At the same time, the ADA ac-
knowledges that questions remain as to
the optimal method and frequency of
screening (2). We found that an approach
that balances sensitivity and specifici-
ty—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
doctrine in order to increase sensitivity so
that no cases are missed. However, with
repeated screenings, the number of false-
negative individuals in the population de-
creases substantially regardless of the
sensitivity (Fig. 2). An unfortunate conse-
quently of using a lower and more sensi-
tive 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 posi-
tives identified (Table 1).

In addition to selecting an appropri-
ate cut point, one must consider screen-
ing 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 di-
agnostic testing (Table 1). Increasing the
time between screenings does, however,
increase the likelihood that diabetes com-
lications may develop in the interval be-
tween screenings. The incidence of
complications in type 2 diabetes is diffi-
cult to estimate because the onset and du-
ration are unknown. In type 1 diabetes,
proliferative retinopathy begins to de-
velop 3–5 years after onset of diabetes

![Figure 2](image-url)

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

### 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

<table>
<thead>
<tr>
<th>Direct medical costs</th>
<th>Cost per true positive</th>
<th>Total costs</th>
<th>Cost per true positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPG ≥100 mg/dl</td>
<td>Every year</td>
<td>10.1</td>
<td>4.9</td>
</tr>
<tr>
<td>RPG ≥130 mg/dl</td>
<td>Every year</td>
<td>5.6</td>
<td>2.8</td>
</tr>
<tr>
<td>RPG ≥160 mg/dl</td>
<td>Every year</td>
<td>4.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Equation</td>
<td>Every year</td>
<td>4.7</td>
<td>2.3</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Indirect costs</th>
<th>Cost per true positive</th>
<th>Total costs</th>
<th>Cost per true positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPG ≥100 mg/dl</td>
<td>Every year</td>
<td>25.8</td>
<td>14.9</td>
</tr>
<tr>
<td>RPG ≥130 mg/dl</td>
<td>Every year</td>
<td>14.2</td>
<td>8.4</td>
</tr>
<tr>
<td>RPG ≥160 mg/dl</td>
<td>Every year</td>
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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
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