Screening for Type 2 Diabetes

MICHAEL M. ENGELGAU, MD, MS
K.M. VENKAT NARAYAN, MD, MPH, MBA
WILLIAM H. HERMAN, MD, MPH

In 1997, nearly 16 million people in the U.S. had diabetes (1,2). Of this population, ~10.3 million were diagnosed and 5.4 million were undiagnosed (1,2). In the future, these numbers are expected to increase substantially (3). Type 2 diabetes accounts for 90–95% of all cases of diabetes in the U.S. (4,5), making it and its attendant clinical and economic consequences a major public health problem (6,7).

What role should screening for undiagnosed type 2 diabetes in asymptomatic adults play in combating the epidemic of diabetes (8)? Despite a lack of firm evidence for the benefit of early detection of type 2 diabetes through screening (9–11), several health organizations have recommended it for several reasons (12–15). First, one-third to one-half of type 2 diabetes is undiagnosed and, hence, untreated (2,3,16–21). Second, diabetic complications are frequently present at clinical diagnosis (22–28). Finally, earlier diagnosis and treatment is believed to prevent or delay such complications and improve health outcomes (29).

Although the benefits of early detection and treatment of type 2 diabetes seem intuitive, the decision to screen should be based on the best available evidence. In this review, we examine the evidence for and against screening for type 2 diabetes to help focus the debate on whether screening asymptomatic adults for diabetes should be incorporated into public policies.

PRINCIPLES OF TYPE 2 DIABETES SCREENING

There is a major distinction between diagnostic testing and screening. When an individual exhibits symptoms or signs of the disease, diagnostic tests are performed and such tests do not represent screening. The purpose of screening is to differentiate an asymptomatic individual at high risk from an individual at low risk for diabetes. Screening may use a variety of methods (e.g., risk assessment questionnaires, portable capillary blood assessments, and laboratory-based assessments) and various thresholds or cutoff points. In general, though, a screening test is not part of the diagnostic test. Ideally, screening tests are rapid, simple, and safe (11,30–32). A positive screening test only means the subject is more likely to have the disease than a subject with a negative screening test. Separate diagnostic tests using standard criteria (15) are required after positive screening tests to establish a definitive diagnosis. Clinicians should continue to be vigilant in recognizing clinical presentations that may be related to diabetes and should determine plasma glucose levels in the evaluation of patients with a history or symptoms suggestive of diabetes; this is not screening, but rather appropriate clinical care and diagnosis.

Generally, screening is appropriate in asymptomatic populations when seven conditions are met (11,30–41): 1) the disease represents an important health problem that imposes a significant burden on the population; 2) the natural history of the disease is understood; 3) there is a recognizable preclinical (asymptomatic) stage during which the disease can be diagnosed; 4) treatment after early detection yields benefits superior to those obtained when treatment is delayed; 5) tests are available that can detect the preclinical stage of disease, and the tests are acceptable and reliable; 6) the costs of case finding and treatment are reasonable and are balanced in relation to health expenditures as a whole, and facilities and resources are available to treat newly detected cases; and 7) screening will be a systematic ongoing process and not merely an isolated one-time effort. We will critically review the available evidence with respect to each of these issues as they pertain to screening asymptomatic adults for type 2 diabetes.

Question 1: Does diabetes represent an important health problem that imposes a significant burden on the population?

In brief, the answer to Question 1 is yes. In 1995, the estimated prevalence of diabetes among adults was 7.4%, and it is expected to rise to 8.9% by 2025 (3). Diabetes is a major cause of visual impairment and blindness (42–45), end-stage renal disease (ESRD) (46,47), and non-traumatic lower-extremity amputations (48–51). It also contributes substantially to cardiovascular disease, stroke, peripheral vascular disease, disability, premature mortality, and congenital malformations and perinatal mortality among offspring of diabetic mothers (48,52–55). Despite potential under-reporting, diabetes is currently listed as the seventh leading cause of death among the general population, and it ranks even higher among some minority populations (56).

Diabetes consumes an extraordinary amount of medical resources in the U.S. One recent study found that although the prevalence of diabetes was 5%, care for patients with diabetes accounted for ~15% of health care expenditures (6,7). Diabetic individuals consumed health care resources at rates two to three times that of nondiabetic individuals (6). Indirect costs from losses in productivity, though poorly characterized, are also substantial (57).
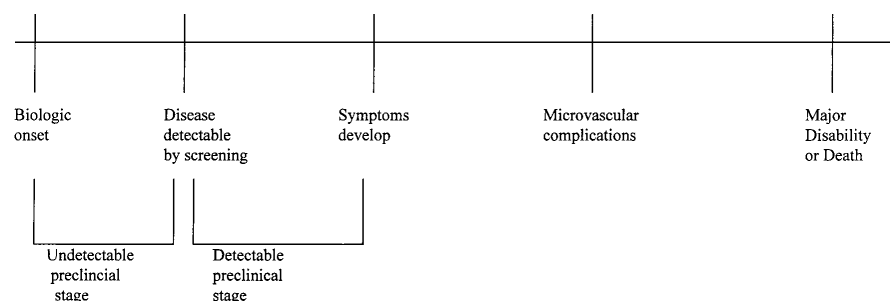
Figure 1—*The clinical stages relevant to screening in the natural history of type 2 diabetes.*

Question 2: Is the natural history of type 2 diabetes well understood?

The answer to Question 2 is yes. Diabetes progresses through several identifiable stages. Figure 1 outlines the clinical stages most relevant to diabetes screening. Biological onset is followed by a period during which the disease remains undiagnosed (2,4,17–20,58). Initially, postprandial hyperglycemia may be the primary defect. Subsequently, fasting hyperglycemia may develop. Early on, the disease may be difficult to detect with screening; then, as hyperglycemia increases, screening tests can more readily detect it. As a part of "routine" or incidental laboratory testing or in response to symptoms, a test is performed and the diagnosis is established. If not already present at diagnosis, diabetic complications develop in relation to the duration and degree of hyperglycemia and may result in major disability and, ultimately, death. Risk factors for diabetic complications are now fairly well characterized. Major risk factors for microvascular complications include duration of diabetes, poor glycemic control, and hypertension; major risk factors for macrovascular disease include hypertension, dyslipidemia, smoking, and possibly poor glycemic control.

Question 3: Does diabetes have a recognizable preclinical (asymptomatic) stage during which the disease can be diagnosed?

Again, the answer is yes. By using the same diagnostic criteria used for symptomatic individuals (Table 1) (15), diabetes can be diagnosed in asymptomatic individuals. Population-based studies designed to estimate the prevalence of diabetes have generally found that one-third to one-half of all diabetes is undiagnosed (2,4,17–20,58). The duration of the preclinical stage has been estimated by extrapolation from prevalence of complications at clinical diag-

nosis (59). Studies of people with newly diagnosed type 2 diabetes have found that 2–39% have retinopathy (22–26), 8–18% have nephropathy (27,60,61), 5–13% have neuropathy (4,22,62), and 8% have cardiovascular disease (60). Furthermore, the prevalence of cardiovascular and peripheral vascular disease and the incidence of premature death are similar to those of people with established diabetes (28,63,64). Using the assumptions that the prevalence of retinopathy is linear with duration of diabetes and that the prevalence is zero in the nondiabetic population, one study estimated the duration of preclinical diabetes to be 9–12 years before clinical diagnosis (26). Another study used a nonlinear regression model and estimated the preclinical duration to be between 7 and 8 years (65). Thus, depending on the investigators' assumptions and the populations studied, the preclinical phase may vary. In addition, while interpreting these studies, it is important to recognize that some, though probably not all, of the complications at diagnosis may arise from lesser degrees of hyperglycemia than those currently considered diagnostic for diabetes (66). If diabetic complications develop at glucose levels below the current diagnostic thresholds, the average duration of recognizable preclinical diabetes would tend to be reduced.

Question 4: Does treatment after early detection of type 2 diabetes yield benefits superior to those obtained when treatment is delayed?

The answer to question 4 is a qualified yes. Although the benefits of improved glycemic control in type 2 diabetes are now established, the benefits and risks of screening and early treatment are less clear. Very little is known about how well asymptomatic individuals who have been diagnosed after screening will comply with

advice about diet and exercise, or a medication regimen. If patients largely ignore advice about diet and exercise and if pharmacological therapy is associated with substantial side effects, the benefits of early detection through screening may be small. **Benefits and risks of screening for type 2 diabetes.** Randomized control trials (RCTs) would be the best means to evaluate the benefits and risks of diabetes screening and early treatment. RCTs are superior to case-control designs or observational studies because they measure the effect of the screening procedure alone and not other health behaviors that make an individual submit to screening (67). In an RCT, a control population receives routine clinical care; that is, the subjects are tested and treated for diabetes after clinical diagnosis, usually at the onset of symptomatic fasting hyperglycemia. This population is compared with an intervention population—a population periodically screened for diabetes and diagnosed before symptomatic hyperglycemia develops—and is treated from the time of diagnosis. Over the course of the clinical trial (and preferably over the lifetime of the patient), the benefits and risks of screening are assessed by comparing short- and long-term health outcomes.

Unfortunately, rigorous studies that apply currently available treatments to a screened group but not a control group have not happened and are unlikely to happen because of feasibility, ethical concerns, and costs (68,69). Random assignment to the control group might be seen as unethical because several health organizations have already recommended screening. In addition, because the incidence of diabetes is low and the benefits of screening may be small and accrue over many years, large numbers of participants and long-term follow-up would be required and would necessitate substantial resources. The unfortunate result of the lack of RCTs on screening for type 2 diabetes is that we have poor empirical data as to the quantifiable benefits and risks of screening.

The available studies on screening for type 2 diabetes can suffer from four types of bias that may lead to spurious conclusions: selection, lead time, length time, and over-diagnosis bias (Table 2) (31,34). Selection bias occurs if screen-detected individuals are more likely to have good health outcomes regardless of whether they are screened. For example, people who volunteer to participate in screening programs may be more likely to follow health recom-

Table 1—*Criteria for the diagnosis of diabetes*

Symptoms of diabetes* and a casual† plasma
  glucose level ≥200 mg/dl (11.1 mmol/l)
Fasting plasma glucose level ≥126 mg/dl
  (7.0 mmol/l)
2-h plasma glucose on an OGTT
  ≥200 mg/dl (11.1 mmol/l)

Only one criterion has to be met. The test must be repeated and remain positive on a separate day, except when symptoms of unequivocal hyperglycemia with acute metabolic decompensation are present. *Polyuria, polydipsia, and unexplained weight loss; †any time during day without regard to the time since the last meal. From the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (15).

mendations and to engage in preventive health practices than people who do not volunteer and are diagnosed through standard procedures. Thus, volunteers for screening may prevent or delay diabetic complications for reasons other than early detection. Lead time is the period between detection of disease by screening and diagnosis through standard procedures. A direct comparison between individuals detected through screening and those whose diabetes was diagnosed through standard procedures would demonstrate a longer interval before the development of diabetic complications in subjects detected through screening, even if early detection and treatment did not alter the natural history of the disease. This is an example of lead-time bias. Length-time bias occurs if screen-detected subjects have a slower natural progression of disease, which results in lower morbidity and mortality. The probability that a person is detected through screening depends on the duration of the preclinical disease state (31). Thus, a person who has a short preclinical state has a smaller chance of being detected before becoming symptomatic. On the other hand, a person with a long preclinical stage is more likely to be detected in a screening program. Thus, screening would tend to detect subjects with milder disease and slower progression, and follow-up would demonstrate better clinical outcomes in these individuals compared with clinically diagnosed individuals, regardless of any effect of treatment. Overdiagnosis bias can occur when rigorous screening efforts result in diagnoses being made among subjects who do not have the disease (34). In addition, overdiagnosis bias can occur during screening initiatives when subjects with positive screening tests are declared to have diabetes in the absence of complete diagnostic testing. Because such

individuals may not have the disease, they have a more favorable course and prognosis than people diagnosed through standard procedures, which results in an apparent, though not real, health benefit.

Because of the lack of RCTs, rigorous data about the risks of screening are also lacking. Nevertheless, several assumptions about risks may be made. Screening results falsely suggesting disease may expose patients to additional testing, follow-up, and treatment that may be inappropriate, bothersome, unpleasant, or hazardous. Currently, such negative effects are poorly understood, but may be considered in the broad categories of physical, psychological, and social harm (33,36). Exposure to diagnostic tests may result in physical harm (e.g., nausea and vomiting after ingestion of oral glucose load during an oral glucose tolerance test [OGTT]), and screening for other comorbidities may be associated with complications (e.g., hematoma after coronary angiography for ischemic heart disease). In addition, hypoglycemia might result from earlier and more aggressive treatment, as described later. The risks associated with drug or insulin therapy in screen-detected populations are not known, although it is clear that hypoglycemia occurs more frequently with intensive treatment. With respect to psychological and social harm, screening may increase worry and reduce health-related quality of life (QOL). In addition, both the sequellae of inappropriate labeling with diabetes and misdiagnosis after screening must be considered (70). After being diagnosed with diabetes, patients may have difficulty obtaining health insurance or employment. In addition, people without diabetes who have positive screen-

ing tests (false positives) are subject to the risks and costs of unnecessary evaluations. On the other hand, people with diabetes who have negative screening tests (false negatives) will not receive appropriate diagnostic testing and will be falsely reassured that they are disease-free.

Benefits and risks of improved glycemic control. Even though scant empirical data exist about the risks and benefits of screening per se, people with newly diagnosed diabetes typically have glucose levels that warrant treatment. For example, in the U.K. Prospective Diabetes Study (UKPDS), the average HbA_{1c} value among people with newly diagnosed type 2 diabetes at recruitment was 9.0% (71). Therefore, it is relevant to this review to examine the benefits (i.e., microvascular, macrovascular, and mortality outcomes) and the risks (i.e., hypoglycemia, weight gain, and QOL) associated with improved glycemic control in type 2 diabetes. Here, the data from relevant RCTs and disease models are much stronger and suggest a favorable benefit-to-risk ratio among subjects who are diagnosed through standard clinical practice.

Two RCTs have demonstrated the benefits of improved glycemic control on microvascular outcomes. The Kumamoto Study investigated 110 nonobese Japanese subjects with insulin-treated type 2 diabetes over 6 years (72) and found that intensive glycemic control yielded a 30–60% reduction in development and progression of microvascular complications. The Diabetes Control and Complications Trial (DCCT) found similar reductions among people with type 1 diabetes (73). The UKPDS compared a conventional dietary treatment policy with two intensive treatment policies based on sulfonylurea

Table 2—*Types of bias and effect on screening evaluations (31,34)*

Type	Effect
Selection	Having healthy participants leads to better outcomes in screen-detected individuals
Lead time	Earlier diagnosis results in screen-detected individuals living longer with disease than those diagnosed through standard procedures
Length time	Subjects detected through screening have a slower natural progression of disease and a better prognosis than those detected through standard procedures
Overdiagnosis	Enthusiasm for screening leads to erroneous diagnosis among people who do not have true disease, which leads to better apparent outcomes

Table 3—*Effectiveness of screening for type 2 diabetes from a lifetime simulation model among the total population and the African-American population*

	Lifetime cumulative incidence					Cost ($)	
	ESRD	Blindness	Lower-extremity amputation	Life-years gained	QALYs gained	Per life-year gained	Per QALY gained
Total population aged ≥25 years				0.02	0.08	236,449	56,649
Without screening	3.5%	9.1%	4.6%				
With screening	2.6%	5.9%	3.6%				
Absolute risk reduction	0.9%	3.2%	1.0%				
Number needed to treat*	111	31	100				
Total population aged 25–34 years				0.12	0.35	35,768	13,376
Without screening	19.2%	32.4%	19.0%				
With screening	15.9%	25.9%	16.0%				
Absolute risk reduction	3.3%	6.5%	3.0%				
Number needed to treat*	30	15	33				
African-Americans aged 25–34 years				0.15	0.40	2,219	822
Without screening	27.1%	38.9%	27.6%				
With screening	22.5%	30.1%	23.4%				
Absolute risk reduction	4.6%	8.8%	4.2%				
Number needed to treat*	22	11	24				
Total population aged ≥65 years				0.00	0.01	NA	575,241
Without screening	0.3%	1.7%	1.0%				
With screening	0.2%	1.1%	0.7%				
Absolute risk reduction	0.1%	0.5%	0.3%				
Number needed to treat*	1,000	200	333				
African-Americans aged ≥65 years				0.00	0.01	2,410,599	331,415
Without screening	0.9%	3.3%	2.1%				
With screening	0.7%	2.4%	1.5%				
Absolute risk reduction	0.3%	0.9%	0.6%				
Number needed to treat*	333	111	167				

Evaluation for cost-effectiveness is based on reference 77. NA, not applicable because denominator is zero. *Number needed to treat is over the lifetime.

and insulin (3,867 people aged 25–65 years, with newly diagnosed type 2 diabetes, fasting plasma glucose levels of 6.1–15.0 mmol/l after 3 months of dietary therapy, and no symptoms of hyperglycemia) (71). The absolute difference in the median HbA$_{1c}$ value between the intensive (both sulfonylurea and insulin) and conventional treatment groups was 0.9%, which was less than the ~2% difference observed between groups in the Kumamoto Study and the DCCT. Compared with conventional treatment, intensive therapy significantly reduced any diabetes-related end point (40.9 vs. 46.0 events/1,000 person-years) (71). Secondary analysis demonstrated that intensive therapy resulted in a significant reduction in microvascular end points (8.6 vs. 11.4/1,000 person-years) compared

with conventional treatment (71). In general, the relative risks of retinopathy, nephropathy, and neuropathy were all significantly reduced.

These two RCTs have also examined the relationship between glycemic control and macrovascular disease and mortality. In the Kumamoto Study, the number of major cerebrovascular, cardiovascular, and peripheral vascular events in the intensive treatment group was half of that in the conventional treatment group, but the event rate was low and the differences were not statistically significant (72). In the UKPDS, intensive versus conventional treatment showed nonsignificant reductions in the risk of myocardial infarction and in diabetes-related and all-cause mortality (71).

With improved glycemic control, the risk of hypoglycemia may increase. In

the Kumamoto Study, there was no significant difference in rates of hypoglycemia between groups (72). In the UKPDS, the rates of major hypoglycemic episodes per year were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin (71). Patients in the intensive treatment group had significantly more hypoglycemic episodes than those in the conventional treatment group ($P < 0.0001$) (71). Major hypoglycemic episodes occurred in 0.6% of overweight patients in the metformin-treated group (74).

Improved glycemic control may also be associated with weight gain. In the Kumamoto Study, there was a slight increase in BMI in both groups from baseline to 6 years; this increase, though, was

not statistically significant (intensive treatment group 20.5–21.2 vs. 20.3–21.9 kg/m^2, respectively, in the intensive vs. conventional treatment groups) (72). However, in the UKPDS, weight gain was significantly greater in the intensive treatment group than in the conventional treatment group with a mean increase of 2.9 kg ($P < 0.001$) (71). Compared with the conventional treatment group, patients assigned to insulin treatment had a greater gain in weight (4.0 kg) than those assigned to chlorpropamide (2.6 kg) or glibenclamide (1.7 kg) (71). Overweight patients randomly assigned to intensive treatment with metformin had a change in body weight similar to those subjects receiving conventional treatment and a lower increase in mean body weight compared with those subjects receiving intensive treatment with sulfonylureas or insulin (74).

Improved glycemic control may require more intensive self-care and substantial lifestyle changes. Thus, QOL may be affected by these treatment regimens. The UKPDS assessed disease-specific and generic measures of QOL in two large cross-sectional samples at 8 years ($n = 2,431$) and 11 years ($n = 3,104$) after randomization and disease-specific QOL in a small cohort of subjects ($n = 374$) at 6 months and annually thereafter for 6 years (75). The serial cross-sectional studies showed that the type of therapy was neutral in effect; there was neither improvement nor decline in QOL scores for mood, cognitive mistakes, symptoms, work satisfaction, or general health. Besides the observation of slightly more symptoms in patients allocated to conventional versus intensive therapy, the longitudinal study also showed no differences in QOL scores for the specific domains assessed.

QOL was affected by the occurrence of hypoglycemia in the UKPDS (75). Patients treated with insulin who had two or more hypoglycemic episodes during the previous year reported more tension, more overall mood disturbance, and less work satisfaction, as measured by the disease-specific questionnaire, than those with no hypoglycemic attacks. Although it was unclear whether frequent hypoglycemic episodes affected QOL or whether patients with certain personality traits or symptoms simply reported increased numbers of hypoglycemic attacks, the investigators concluded that therapeutic policies that reduce the risk of complications do not affect QOL.

Recently, two diabetes disease models have been used to estimate the benefits of glycemic control in type 2 diabetes. The first, a Markov model, examined the potential benefits of control for newly diagnosed complication-free members of a health maintenance organization (76). The model was constructed using the disease states (retinopathy, nephropathy, and neuropathy) and rates for early development of microvascular disease from the DCCT and values from the literature for the end-stage outcomes. Mortality estimates were based on U.S. vital statistics and were not adjusted for levels of glycemic control. The lifetime benefits were determined for a hypothetical intervention that reduced the HbA$_{1c}$ value from 9 to 7%. For a person diagnosed with diabetes at age 45 years, a reduction in the HbA$_{1c}$ value from 9 to 7% was estimated to decrease the lifetime risk of blindness by 2.3 percentage points (from 2.6 to 0.3%) and to lengthen life by 1.3 years. Benefits depended strongly on age and the baseline level of glycemic control.

Another study used a Monte Carlo simulation model to compare the lifetime benefits associated with early detection and treatment of type 2 diabetes based on one-time opportunistic (clinic-based) screening with diagnosis and treatment as it occurs in current clinical practice (77). Data for the model were obtained from clinical trials, epidemiological studies, and population surveys. A hypothetical cohort of 10,000 people from the U.S. population aged ≥ 25 years were followed from the onset of disease (assumed to be 10.5 years before clinical diagnosis and 5.5 years before screening diagnosis) until death. The lifetime incidence of ESRD, blindness, and lower-extremity amputation was reduced in the screened group by 26, 35, and 22%, respectively (Table 3). The mean duration free of these three major complications increased 0.08, 0.27, and 0.15 years, respectively. The absolute lifetime risk reduction was greatest for blindness, for which the number needed to treat was just 31 (i.e., to prevent one case of blindness). The benefits of early detection and treatment were found to accrue more from postponement of complications and the resulting improvement in the QOL than from additional years of life gained.

This simulation model did not include any potential benefit from early initiation of glycemic control on the incidence of cardiovascular disease (77). It also did not include any possible benefits from the

opportunity to influence macrovascular disease risk factor management. A model incorporating decreases in cardiovascular disease resulting from treatment to the more aggressive targets now recommended for patients with diabetes and hypertension (77a–c) and lipids (77d) might show a greater benefit. The model was moderately sensitive to assumptions about the performance of the screening test (sensitivity and specificity), the length of the preclinical diagnosis interval (a shorter interval was less cost-effective), the prevalence of undiagnosed diabetes (a higher prevalence was more cost-effective), and the intensity of glycemic management.

In summary, no RCTs of screening have been conducted. Moreover, there are no empirical data to demonstrate the benefits of screening, and there are few data on risks. RCTs have demonstrated that improving HbA$_{1c}$ levels from those levels typically found among subjects after a routine clinical diagnosis of type 2 diabetes can decrease microvascular and neuropathic complications; the effects on macrovascular disease are not as clear. Early diagnosis after screening may provide an opportunity to prevent morbidity by both improved glycemic management and earlier recognition and treatment of complications. Indeed, timely laser therapy may prevent or delay visual loss (78–80), instituting ACE inhibitor therapy may prevent or delay ESRD (81,82), and initiating comprehensive foot care may prevent lower-extremity amputations (83,84). However, clinical trials of treatment of diabetes diagnosed through current clinical practice and screening models provide modest evidence to support the benefit of early detection and improved glycemic control in type 2 diabetes.

Question 5: Are there tests that can detect preclinical (asymptomatic) diabetes that are reliable and acceptable?

For the most part, the answer is yes. It is clear, however, that current screening recommendations are not entirely consistent with available evidence and that a number of important operational questions require further research.

Ideally, a screening test should be both sensitive (have a high probability of being positive when the subject truly has the disease) and specific (have a high probability of being negative when the subject does not have the disease). Generally, however, a trade-off must be made between sensitivity and specificity. Increasing sensitivity reduces

Table 4—*Sensitivity and specificity and predictive positive value of various biochemical tests and combinations of tests for detecting undiagnosed type 2 diabetes*

Test	Metabolic state	Cutoff point	Sensitivity (%)	Specificity (%)	PPV prevalence 6%	12%	Reference
Urine glucose*							
	Fasting	≥trace	16	98	11	12	108
	Fasting	≥trace	35	100	26	26	105
	Random	≥trace	18	99	13	14	106
	Random	≥trace	64	99	36	37	107
	1-h postprandial	≥trace	43	98	25	27	109,112
	2-h OGTT	≥trace	48	96	23	27	105
	2- to 4-h postprandial	≥trace	39	98	23	25	105
Venous glucose†							
	Fasting	≥5.8	85	84	19	28	130
	Fasting	≥6.1	65	93	24	30	115
	Fasting	≥6.1	80	96	33	98	116
	Fasting	≥6.1	95	90	27	35	107
	Fasting	≥6.1	66	96	29	34	128
	Fasting	≥6.5	74	93	26	32	113
	Fasting	≥6.7	44	98	25	28	105
	Fasting	≥6.7	32	97	18	21	121
	Fasting	≥6.9	48	97	25	28	136
	Fasting	≥7.0	56	98	30	33	126
	Fasting	≥7.0	40	99	26	27	127
	Fasting	≥7.0	59	96	27	31	129
	Fasting	≥7.8	52	99	31	33	114
	1-h OGTT	≥11.1	87–93	89–90	24–26	33–35	116
	2-h OGTT	≥11.1	90–93	100	47–48	47–48	116
	2- to 4-h postprandial	≥7.2	50	99	30	32	105
Capillary glucose†							
	Fasting	≥5.5	90	94	31	38	108
	Fasting	≥6.7	65	94	25	31	131
	Fasting	≥6.7	90	90	26	34	132
	Random	Age- and postprandial time–specific	50–60	90	16–19	22–26	151
	Random	≥7.2	80	80	16	24	132
	Random	≥8.0	69	95	28	34	106
	2-h OGTT	≥11.1	69	98	34	38	117
	2-h OGTT	≥8.6	90	93	30	37	108
	2-h OGTT	≥9.7	98	98	42	46	132
Glycosylated hemoglobin‡	—	≥5.6	35	100	26	26	136
	—	≥5.8	92	89	25	33	107
	—	≥6.0	60	91	20	27	114
	—	≥6.03	85	91	26	34	137
	—	≥6.1	78	79	15	23	130
	—	≥6.3	48	100	32	32	135
	—	≥8.0	87	87	22	31	132
	—	≥8.1	37	96	19	22	138
	—	≥8.3	48	100	32	32	135
	—	≥8.3	43	96	21	25	145
	—	≥8.42	27	88	9	13	139
	—	≥8.5	15	100	13	13	141
	—	≥8.6	67	97	31	35	146

specificity, and increasing specificity reduces sensitivity. Screening tests should also be reliable and reproducible. Consistent results should be obtained when the test is performed more than once on the same person under the same conditions (85). Uniform procedures and methods, standardized techniques, properly functioning equipment, and quality control are necessary to ensure both reliability and reproducibility.

When considering a test or evaluating studies, one frequently examines the positive predictive value (PPV), which is defined as the probability of having diabetes when the screening test result is positive (11,85–87). The determinants of the PPV are the sensitivity and specificity of the screening test and the prevalence of disease in the population. When sensitivity and specificity are constant, the higher the prevalence of a disease and, thus, the higher the PPV of the screening test. Because an increase in PPV translates into more cases detected for each diagnostic test, it has important implications for resource use. Information about the type of population (e.g., volunteers and clinic-based patients) and the distribution of risk factors for diabetes (age, race or ethnicity, family history, obesity, and physical activity) can be used to target groups with a higher prevalence of diabetes and thereby enhance the PPV.

When evaluating studies of the performance of screening tests for type 2 diabetes, four issues must be considered: characteristics of the study population, the selection of cutoff points, referral policies for positive screening tests, and the nature of the definitive diagnostic test. The population's characteristics are important because the prevalence of diabetes in the population affects the PPV. The nature of the population may also affect the apparent performance of the screening test. For example, both sensitivity and specificity will be higher in populations that include subjects with severe hyperglycemia, which is also the case when subjects with diagnosed diabetes are included in the screened population. Distinguishing between subjects with decompensated diabetes who are experiencing frank fasting hyperglycemia and those without disease is easier than distinguishing between those with asymptomatic diabetes with mild hyperglycemia and those without diabetes. Thus, studies that include individuals with diagnosed diabetes should be interpreted cautiously.

Table 4—*Continued*

Test	Metabolic state	Cutoff point	Sensitivity (%)	Specificity (%)	PPV prevalence 6%	12%	Reference
Fructosamine†							
	—	≥1.18	19	99	14	15	121
	—	≥1.78	19	97	11	13	141
	—	≥1.92	74	95	29	35	147
	—	≥2.50	67	96	29	34	146
	—	≥2.90	23	98	15	17	136
Combination tests							
Fasting glucose plus HbA$_{1c}$		≥7.8 mmol/l ≥6.0%	40	99	26	27	114
Fasting glucose plus HbA$_{1c}$		≥5.6 mmol/l ≥5.5%	83	83	18	27	130
Fasting glucose plus fructosamine		≥5.4 mmol/l ≥235 μmol/l	82	83	18	27	130
Fasting glucose plus HbA$_{1c}$		≥6.1 mmol/l ≥6.1%	69	96	30	35	134

*Cutoff point expressed as qualitative dipstick determination; †cutoff point expressed as millimoles per liter; ‡cutoff point expressed as percent HbA$_{1c}$.

The issue of cutoff points is important and must be explicit, particularly in relation to sensitivity and specificity (11,85). A high cutoff point for a positive test ultimately results in a low sensitivity and high specificity, and a low cutoff point results in a high sensitivity and low specificity. Ideally, receiver operating characteristic (ROC) curve analyses, which can evaluate performance over the entire range of cutoff points, should be used to compare tests (86,88–93). Unfortunately, few studies have performed such analyses. Although not ideal, choosing a common specificity for each test allows for comparisons of the sensitivity, and choosing a common sensitivity allows for comparisons of specificity.

Referral policies used during evaluation studies are also extremely important. If only participants with positive screening tests are referred to receive verification by the gold standard test, then work-up bias occurs (i.e., diagnostic tests for type 2 diabetes are done only in those who screen positive, not in the entire study population). Work-up bias may substantially distort estimates of sensitivity and specificity if it is assumed that all people with negative screening tests do not have diabetes and that the screening test is 100% specific.

The final issue of the validity of the diagnostic test is important because some studies have not used definitive diagnostic testing with a recognized gold standard, thus making the assessment of sensitivity and specificity problematic.

Types of screening tests and their performance. We review two major methods used to screen for preclinical asymptomatic type 2 diabetes: questionnaires and biochemical tests.

Questionnaires. With questionnaires, self-reported demographic, behavioral, and medical information is used to assign a person to a higher or lower risk group for diabetes. Questionnaires are popular and are usually less expensive than biochemical tests, but, when used alone, they generally perform poorly.

In 1993, the ADA disseminated a questionnaire, titled "Take the Test. Know the Score" (95). This questionnaire assessed both symptoms and historical risk factors. Points were given for certain responses; a score of ≤5 points was considered low risk for diabetes, and a score of >5 points was considered high risk. Subsequent testing among both U.S. (96) and U.K. (97) populations found that the test performed rather poorly. For example, in the U.K., when a score of >5 was used to predict subjects with random capillary glucose measurements of >6.5 mmol/l, the sensitivity was just 46% and the specificity was 59%. Regardless of the capillary glucose mea-

surement, participants commonly reported symptoms of diabetes. Overall, approximately one-third of participants reported frequent urination, extreme fatigue, and blurred vision, and nearly one-fifth reported excessive thirst.

Two years later, another questionnaire was developed in the U.S. with data from the Second National Health and Nutritional Examination Survey (98). A test of the questionnaire in the population from which it was developed found a sensitivity of 79%, a specificity of 65%, and a PPV of 10% for detecting undiagnosed diabetes when using World Health Organization (WHO) criteria (99). By ROC curve analysis, the second questionnaire performed better than the ADA's 1993 questionnaire. Groups at high risk of diabetes were defined with five risk factors (older age, obesity, sedentary lifestyle, family history of diabetes, and delivering a baby weighing >4 kg). The questionnaire did not rely on past medical history to ensure its applicability to all populations, including the medically underserved, and to avoid depending on prior medical evaluations or care (100). The ADA has adapted this instrument for use in community-based diabetes screening programs (101). In doing so, some modifications were made to the validated questionnaire. Subsequently, this adapted risk test was used in a community screening program in Onondaga County, New York, where it had an overall sensitivity of 80%, a reduced specificity of 35%, and a PPV of 11.9% (100,102).

Another questionnaire, developed in the Netherland's Hoorn Study population, incorporated symptoms (thirst, pain, and shortness of breath during walking), demographic and clinical characteristics (age, sex, obesity, family history of diabetes, and hypertension), and exercise preferences (such as reluctance to use a bicycle for transportation) (103). When it was subsequently evaluated in a separate subgroup of the Hoorn Study population, this questionnaire was found to have a sensitivity of 56%, a specificity of 72%, and a performance slightly better than the ADA questionnaires for this population (as determined by ROC analyses).

In summary, diabetes screening questionnaires perform rather poorly as standalone tests. It is possible that they may be useful educational tools and may promote public awareness in low-risk populations, but their effectiveness has not been rigorously assessed (102,104).

Biochemical tests. Measurements of glucose and highly correlated metabolites (e.g., HbA_{1c} and fructosamine levels) have been used extensively for diabetes screening (105–151). Urine glucose and venous and capillary blood glucose may be measured under various conditions—fasting, at random, postprandial, or after a glucose load—to represent different metabolic states. For some tests, such as those for glycosylated hemoglobin (total, HbA_1 fraction, and the HbA_{1c} fraction), fructosamine, and anhydroglucitol, the immediate metabolic state is of relatively little importance. The characteristics of several biochemical screening tests and the PPV for a hypothetical population with a low prevalence (6%) and a high prevalence (12%) of undiagnosed diabetes are summarized in Table 4.

Measurement of glycosuria using a cutoff point greater than or equal to a trace value has a low sensitivity and a high specificity (Table 4). Performance is usually better with random, postprandial, or glucose-loaded measurements than with fasting measurements, perhaps in part because the renal threshold for glucose is reached more often in the nonfasting state. Thus, the usefulness of urine screening is limited.

Studies of fasting venous glucose screening tests often have used fasting measurements obtained as part of the diagnostic test. The 2-h glucose concentration from the OGTT from the same diagnostic test process has served as the gold standard test. In studies of populations in which subjects with previously diagnosed diabetes have been excluded and the populations have not been enriched with high-risk subjects (105,114,115,126,127), sensitivity has ranged from 40 to 65% at a specificity of >90%. Other studies have reported higher sensitivities (up to 95%) at specificities >90% (107,113,116,128–130), but some included subjects with diagnosed diabetes or populations with an increased proportion of individuals with abnormal glucose tolerance. Studies of fasting capillary glucose screening have reported performances similar to those for fasting venous glucose tests.

In studies that excluded subjects with overt diabetes, random and postprandial venous and capillary glucose tests performed better than fasting tests. This result occurs because subjects with undiagnosed diabetes are more likely to meet the 2-h OGTT diagnostic criterion versus the fasting criterion and have postprandial hyperglycemia versus fasting hyperglycemia (151). To obtain optimal performance from tests during random and postprandial states, higher cutoff points are needed to account for the postprandial state (and, in some cases, for age) (119,151).

Glycosylated hemoglobin measurements are becoming more widely available (152). With the use of various cutoff points, sensitivity of 15–67% has been reported at a specificity of >90% (Table 4). At a high specificity, higher sensitivities have been reported, but these were from studies in populations that included subjects with diagnosed diabetes or a high level of glucose intolerance (107,137).

In the past, problems with glycosylated hemoglobin measurements included a lack of standard reference materials and variations in the reference methods of different assays. These problems have been addressed by the National Glycohemoglobin Standardization Program, which produced substantial improvements in both the precision and comparability of methods (152). Unfortunately, considerable variability remains, and some issues, such as comparability of samples containing hemoglobin variants, also remain. In addition, HbA_{1c} levels, the most commonly used glycosylated hemoglobin measurement, may be unsuitable for diabetes screening: a study in a small cohort of subjects with normoglycemia (no diabetes) failed to find a relationship between fasting venous glucose and HbA_{1c} values (153). Other research has found that only 2–30% of the nondiabetic variance in glycosylated hemoglobin can be explained by fasting or postload blood glucose; the remainder is presumably related to other factors independent of glycemia, such as the rate of glycation and differences in red blood cell survival (154,155).

Both anhydroglucitol, a polyol sugar alcohol found in reduced serum concentrations in diabetic subjects, and fructosamine, a measure of glycosylated total serum proteins, have been evaluated for diabetes screening (Table 4). Like glycosylated hemoglobin measurements, measurements of anhydroglucitol and fructosamine are independent of fasting status, but neither measurement has performed better than other available tests.

Combinations of biochemical tests have also been evaluated (Table 4). Using multiple tests in series (with second and subsequent screening tests performed only when the preceding test is positive) can enhance the PPV by increasing the prevalence of disease in the population receiving the second screening test. For example, a second screening test performed only in the population of individuals who had positive initial screening tests yields a "double-positive" population that will have a higher prevalence of disease than either test administered alone. Screening programs can initially use a less expensive and more sensitive test and then use the more complicated, more specific, and more expensive test (e.g., a questionnaire followed by capillary glucose measurement). Strategies that use multiple screening tests will not detect more undiagnosed cases (i.e., will not improve sensitivity) but may allow for more efficient use of resources.

In summary, review of the performance of various screening methods for detecting undiagnosed type 2 diabetes shows that questionnaires tend to perform poorly, whereas biochemical tests perform better. Venous and capillary glucose measurements perform better than urinary glucose or HbA_{1c} measurements, and postprandial or post–glucose load glucose levels have advantages over fasting levels. Performance of all screening tests is dependent on the cutoff point selected. Currently, there are no uniform cutoff points to define positive screening tests. A two-stage screening test strategy may assist with a more efficient use of resources, although such approaches have not been rigorously tested. Because test performance typically depends on the population being evaluated, interpretation within and across studies can be difficult. Another confounding factor is that the blood glucose tests used to screen for diabetes are the same tests used to diagnose diabetes. Therefore, providers often do not see a distinction between screening and diagnosing diabetes; thus, different cut points may be confusing.

Questions 6: Are the costs of case finding and treatment reasonable and balanced in relationship to health expenditures as a whole, and are facilities and resources available to treat newly detected cases?

The answer to the first part of this question is unclear; for the second part, the answer is a qualified yes. Limited information concerning the cost of screening is available, but the information that does exist indicates that screening for undiagnosed diabetes in asymptomatic adults may be problematic depending on the setting at which screening occurs.

Screening may be done at the community level or in the context of medical

care. Three approaches to diabetes screening have been used: population-based, selective, and opportunistic. Population-based approaches attempt to screen every person in the entire population. Epidemiological studies designed to assess diabetes prevalence often use this approach. However, because it is costly and potentially inefficient (due to the low prevalence of diabetes in the general population), this method is not widely favored (except in populations with a very high prevalence of diabetes). Selective screening targets subgroups of the population with a high prevalence of risk factors for diabetes (101,156,157). Opportunistic screening involves screening individuals during routine encounters with the health care system, such as primary care visits or periodic health appraisals (158–164). Both selective and opportunistic screenings require fewer resources to reach high-risk groups, to conduct screening tests, and to perform follow-ups (160). Both may have poor coverage and a tendency to be misdirected—some people get too many tests too often, others get too few tests too infrequently (160).

Although community screening with the use of a selective method is both popular and common (70,165), fragmented health insurance coverage and variable access to health care may make it difficult to ensure both proper referrals for subjects who screen positive and appropriate repeat testing for subjects who screen negative (166). Although there is no evidence that the U.S. has too few health care providers to treat the additional cases of diabetes, access to providers is not universal because of the large number of people without health insurance. Furthermore, screening outside of clinical settings may mean that abnormal tests are never discussed with the primary care provider, that compliance with treatment recommendations is low, and that a positive long-term impact on health is unlikely (167).

The resources demanded by diabetes screening include those associated with screening itself, diagnostic tests for people with positive screening tests, and additional years of care due to earlier diagnosis, which may result in higher lifetime costs compared with patients detected through current clinical practice. Use of equipment for self-monitoring of glucose levels and testing strips for screening are relatively inexpensive per test (less than $1.00), but the cost of plasma glucose ($5.00) and HbA$_{1c}$ measurements ($13.50) are sub-

stantially higher (according to 1998 Medicare costs). The costs of personnel time for consent, test performance, counseling, and especially follow-up are unknown but are clearly substantial.

Determining program costs and the burden on the health care system require a knowledge of the prevalence of undiagnosed diabetes, the methods of case finding, and the operations of the health care delivery system. In the U.S., up to 40 million people (nearly 18% of the population) have either no medical care coverage or inadequate medical coverage (168). Besides self-directed changes in health behaviors, for early detection to provide significant benefits, there must be ongoing receipt of diabetes care (9,40). If those individuals confirmed to have diabetes do not receive care, there can be little or no benefit in earlier diagnosis, and the cost of screening, no matter how small, cannot be justified (169).

The best case can probably be made for opportunist screening. The screening simulation model discussed earlier (77) is considered an opportunistic screening program for the general U.S. population aged ≥25 years. The identified cost per case was $1,200, which included a fasting plasma glucose screening test, an OGTT for those with a positive screening test, and physician time for test interpretation. Diabetes was diagnosed ~5.5 years earlier with the screening program, and the estimated average annual cost for treatment of newly diagnosed patients was $1,007. The lifetime cost of diabetes treatment (routine care and treatment of complications) was $3,400 higher with screening ($49,600 vs. $46,200). The cost per life-year gained was $236,400, and the cost per quality-adjusted life-year (QALY) gained was $56,600 (Table 3). Greater benefits and more favorable cost-effectiveness ratios were found if screening was conducted for younger compared with older people (because younger people lived longer with diabetes and had great reductions in lifetime complications) and for African-Americans compared with the general population (primarily because of the higher complication rates among African-Americans).

Compared with other interventions for diabetes (e.g., intensive glycemic control, blood pressure and lipid management, and detection and treatment of diabetic retinopathy and nephropathy), screening for diabetes is not as cost-effective (170). Among type 2 diabetic patients, intensive glycemic control

costs $16,000 per QALY (172), tight blood pressure control costs $700 per additional life-year (173), improved lipid control with statins costs $2,100 per QALY (174), detecting and treating diabetic retinopathy costs $3,190 per QALY (175), and treatment with ACE inhibitors to delay progression of kidney disease is cost-saving (176). However, when compared with screening for other conditions, diabetes screening is less favorable than some and more favorable than others. For example, detecting mild thyroid failure in persons aged ≥35 years during a periodic health examination costs $9,000 per QALY for women and $23,000 per QALY for men (176a). Screening and treating persons with no cardiac history with statins ranges from $54,000 per QALY to $1,400,000 per QALY, depending on age, sex, and the level of LDL (176b). Screening for breast, colon, and cervical cancers, respectively, have been estimated at $150,000 per QALY (annual mammography for women 50–65 years of age), $16,000 per QALY (FOBT screening for persons 50–75 years of age), and $16,000 per QALY (pap smear every 4 years for women 20–75 years of age; for every year the figure is >$1,600,000/QALY) (176c). Expert consensus from reviews of guidelines and cost-effectiveness studies of interventions for various diseases suggest that interventions having cost-effectiveness ratios less than $20,000 per QALY should be readily adopted and that those having ratios between $20,000 and $100,000 per QALY are usually provided, even though availability may be somewhat limited. Those interventions that have cost-effectiveness ratios greater than $100,000 per QALY have weak evidence for adoption (177).

How diabetes screening complements efforts to control other diseases should also be considered. Screening for diabetes can be combined with efforts to detect other conditions, such as hypertension and dyslipidemia (9,40). The mix of screening tests that produce the most benefit at the lowest cost could thus be determined (40,68,178). However, even though conditions or behaviors that accelerate diabetic complications (such as hypertension, dyslipidemia, or smoking) might also be detected at diabetes screening (40), these conditions can be detected without diabetes screening. Furthermore, directly screening for, identifying, and treating these other conditions in the population may be more efficient (9). Although measurement of fasting glucose is recom-

Table 5—*Population-based, selective, and opportunistic screening program strategies and yields*

Type	Setting	Target population	Number of tests performed	Screening test used	Number of positive screening tests	Number of new cases detected	PPV (%)	Reference
Population	Community awareness campaign	Volunteers	NR	Self-referral after ad campaign	41	7	17	180
	Community sample for diabetes study	Volunteers responding to invitation	320	Risk score*	21	4	19	205
			320	Risk score	18	3	17	205
	Community education and outreach	Volunteers	3,031	CG	72	52	72	185
	Community screening	Volunteers	2,016	CG	148	6	4	96
	Community health fair	Volunteers	3,212	VG	120	25	21	206
	Community outreach	Volunteers	253,190	VG	9,682	5,370	55	207
	Community diabetes detection drive	Volunteers	559	VG, CG, urine	164	42	26	208
	Community diabetes promotion	Volunteers	23,228	CG	860	64	7	209
	Community outreach	Volunteers	396	Risk score	264	28	11	102
Selective								
	Hospital waiting room	Volunteers	548	CG	NR	5	—	181
	Dental clinic	All patients	119	VG	24	6	25	183
	Pharmacy (distributed 35,000 urine kits)	Volunteers (preference to high risk: >40 years old, obese, family history, large baby)	3,409	Urine	164	22	13	184
	Community outreach (mailed 7,426 risk questionnaires to households	Volunteers aged >60 years	349	Risk score	181	11	6	210
	Community physician's patients	20% sample of patients aged >40 years	1,767	BG	48	19	40	169
	Clinic population (mailed urine glucose kits)	Volunteers aged 45–70 years	2,984	Urine	73	17	23	192
	Clinic population (mailed urine glucose kits)	Volunteers aged 45–70 years	3,231	Urine	52	10	19	156
	Clinic population (mailed urine glucose kits)	Volunteers aged 45–70 years	13,795	Urine	343	99	29	112
	Motor vehicle department license renewal	Volunteers aged >70 years	410	CG	11	NR	—	186
	Industry workers	Volunteers aged 18–74 years	4,048	CG	267	13	5	211
	Clinic registries	Volunteers aged 50–69 years	367	CG	28	5	18	182
Opportunistic								
	Clinic population	Volunteers	3,268	CG, urine	234	66	28	125
	Health insurance beneficiaries aged >25 years	Volunteers	8,818	VG	176	30	17	167

*Use of questionnaire or risk classification scheme. BG, blood glucose; CG, capillary glucose; NR, not reported; PPV, positive predictive value; VG, venous glucose.

mended as part of the evaluation of patients with diagnosed hypertension and lipid disorders because knowledge of diabetic status helps to determine treatment targets and to guide appropriate drug therapy (77c, 178a). Thus, examination of studies that might support diabetes screening should primarily consider the benefit gained from improved glycemic control until there is additional evidence that knowledge of diabetes actually leads to more aggressive cardiovascular risk reduction and that this risk reduction is itself cost-effective in asymptomatic patients with diabetes.

For a health care system to implement diabetes screening, it must obtain new resources or direct resources away from other activities. Because health care budgets are finite, redirection is more common; thus, there is an "opportunity" cost in taking on a new activity (i.e., other activities may have to be reduced or eliminated) (178). Health care policy leaders need to assess the current situations and priorities to determine how diabetes screening should take precedence. Cost-effectiveness studies can help, but the absolute cost of the effort must be considered.

In summary, both population-based and selective community screenings consume considerable resources and are unlikely to have a positive long-term impact on health. Opportunistic screening consumes fewer resources and provides better follow-up, but there is little empirical information about the benefits of such screening within current health care systems. Computer simulation modeling suggests that clinic-based opportunistic screening is less cost-effective than other diabetes interventions but is in the range of other screening procedures recommended for several other conditions.

Questions 7: Will screening be a systematic ongoing process?
The answer to question 7 is probably not, at least not as currently conducted. Screening inevitably misses some individuals with disease (sensitivity <100%) because many people do not present themselves for screening, and incident cases replenish the pool of undiagnosed cases. Thus, to fully address the problem of undiagnosed disease, screening programs must be ongoing. For ongoing screening to occur, there must be a commitment to develop and sustain screening activities, which, for community screen-

ing, include program coordination, support, and evaluation. If opportunistic screening is made part of routine preventive care, screening could be conducted in clinical settings at designated intervals. If conducted outside of usual clinical care, the logistical barriers are more substantial. In addition, the optimal time interval between screenings is not clear. Few studies have examined the appropriate frequency of screening. In one U.K. study (179), repeat diabetes screening was performed at 30 months using self-testing of postprandial glycosuria in 3,200 patients registered at a general clinic. The repeat screening response rate was slightly lower than the initial response rate (73 vs. 79%, $P < 0.0001$), but the yield was not significantly different (0.44 vs. 0.72%, $P = 0.2$). The optimal interval between screenings is one at which the prevalence of undiagnosed cases reaches the prevalence of such cases at the previous screening, and the cost-effectiveness is the same for each screening. Thus, several unresolved issues remain as to how to ensure periodic screening and how often screening should occur.

THE YIELD OF DIABETES SCREENING PROGRAMS —
Evaluations of diabetes screening programs have focused on the programs' abilities to detect undiagnosed cases. Published results of these evaluations listed according to the type of program used are presented in Table 5. Classification of the studies is based on the information from each report and an assessment of what appeared to be the dominant mode of the screening used.

Many screening programs have combined population-based and selective screening strategies (Table 5). Some programs, for example, began with population-based health promotion and diabetes awareness programs that targeted entire communities and then screened volunteers with diabetes risk factors. Testing strategies have included questionnaires and fasting, random, postprandial, and glucose-loaded biochemical measurements. Some programs have conducted public awareness campaigns that have resulted in increased patient requests for screening when making visits to health care providers (180), whereas others have advocated increasing professional awareness (166). The yields are highly variable and dependent on the screening test cutoff

point. They have ranged from 4 to 72%.

Selective screening has occurred in a wide variety of settings, such as hospital and clinic waiting rooms (181), doctors' offices and medical clinics (182), dental clinics (183), pharmacies (184), shopping centers (185), community centers (185), driver's license registration centers (186), worksites, and churches (187). Groups with rates of diabetes higher than the general population have been targeted using known risk factors for disease, such as older age, family history of diabetes, and obesity (186,188). Yields for selective screening have ranged from 5 to 40%.

The only rigorous study of the effectiveness of screening, which used simulation models (and is subject to limitations of this method), used an opportunistic screening approach (77). Few actual programs have used such an approach. Those programs involve such approaches as the sponsorship by health insurance companies of multichannel chemistry screening through widespread phlebotomy centers (167) and the use of clinic registries (106). The yields of opportunistic programs ranged from 17 to 28%.

SCREENING PRACTICES, POLICIES, AND RECOMMENDATIONS — In the
U.S., some of the first organized diabetes screening was conducted among insurance applicants during the early 1900s (189). Later, during World Wars I and II, diabetes screening was conducted among enrollees in the armed services. The development of automated glucose measurement techniques led to even more widespread screening (189). Despite rather broad implementation, little was known about what these efforts accomplished.

Qualitative assessments of diabetes screening test performances in the U.S. during the 1950s found high false-positive and false-negative rates (189), but a call for the evaluation of diabetes screening efforts did not occur until the 1970s (190). In the 1970s and 1980s, problems were noted with indiscriminate mass screening, and the value of such initiatives was questioned (183,191–193). Two of the major issues concerned the criteria for a positive screening test and the need for standardized diagnostic criteria for diabetes. Diagnostic criteria were more firmly established in the early and mid-1980s (99,194). In the late 1980s and early 1990s, after wide-

Table 6—*Current screening recommendations for type 2 diabetes for health agencies, task forces, and professionals*

Agency, task force, or organization	Strategy	Specimen	Type of collection	Positive test (mmol/l)	Repeat interval	Year published	Reference
WHO	Selective, target risk factors	Urine, blood (plasma)	NS		NS	1994	12
			Fasting	≥6.5			
			Random	≥7.0 to 8.0			
BDA	Selective, target risk factors	Urine, blood (plasma)	2- h postprandial	≥trace	5 years	1993	14
			Fasting	≥6.7			
			2-h 75-g OGTT	≥8.0			
USPSTF	Selective, target risk factors	Blood (plasma)	Fasting	NS	Clinical dissertation	1996	70
CTFPHE	Selective, target risk factors	Urine, blood	NS	NS	NS	1979	196
			Fasting, random	NS			
ADA	Selective, using risk assessment questionnaire	Blood (plasma)	Fasting (≥8 h)	≥7.0	3 years	1998	15 and 101
			Random (<8 h)	≥8.9			
			2-h 75-g post–oral glucose load	≥11.1			
			Capillary (whole blood)				
			Fasting (≥8 h)	≥6.1			
			Random (<8 h)	≥7.8			
ACP	Selective, target risk factors	Blood (plasma)	Fasting	NS	NS	1991	195
AAFP	All children, adolescents, and adults	None	Counsel to engage in regular physical activity		NS	1998	197

AAFP, American Academy of Family Physicians; ACP, American College of Physicians; BDA, British Diabetic Association; CTFPHE, Canadian Task Force on the Periodic Health Examination; NS, not stated.

spread acceptance of standard diagnostic criteria for diabetes and reports that as much as half of the total diabetes burden was undiagnosed, some health organizations began to recommend screening.

Currently, several health agencies, task forces, and professional organizations have published recommendations for screening for type 2 diabetes (Table 6) (70,101,195–197). Some of the recommendations were published several years ago, but none have been revised since the publication of the results of the UKPDS (71) or the cost-effectiveness simulation model (77). The most recent ADA recommendations were included in the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (15). The preliminary WHO report on the diagnosis and classification of diabetes did not address screening (13).

Because definitive studies on the benefits of screening have not been available, all of the recommendations have relied on epidemiologic and other indirect evidence, expert opinion and consensus. None of the studies encourage population-based screening. Some suggest a selective or opportunistic approach in populations with diabetes risk factors. The WHO, the British Diabetic Association, and the ADA all pro-

vide screening strategies and recommend repeat-screening intervals. None of the strategies have been formally evaluated.

The current recommendations of the U.S. Preventive Services Task Force (USPSTF), which were published in 1996 and endorsed by the American Medical Association (198), cite insufficient evidence to recommend for or against routine screening (70). Major limitations cited by the USPSTF are the lack of practical screening tests that are sufficiently sensitive and specific and insufficient evidence that detection during the preclinical phase will improve long-term outcomes. Because evidence of benefit from early detection was not available, however, the USPSTF suggests that clinicians may nevertheless decide to screen high-risk individuals on other grounds and for the potential, albeit unproven, benefit that early treatment may provide. The report suggested that if the UKPDS demonstrated important clinical benefits from more intensive interventions in patients with minimally symptomatic diabetes (a subgroup study from the UKPDS that has not been performed as yet), then UKPDS data may provide support for screening in asymptomatic adults. The USPSTF recommendations are cur-

rently under revision.

The current ADA recommendations (101), which were published in 1998, state that early detection and thus early treatment may reduce the burden of diabetes and its complications; accordingly, screening may be appropriate in certain circumstances. The ADA suggests that screening be considered at any age if risk factors for diabetes (i.e., family history; obesity; belonging to high-risk racial or ethnic group; history of abnormal glucose tolerance, hypertension, hyperlipidemia, or gestational diabetes; or delivery of a baby weighting >4 kg) are present. In addition, the ADA recommends screening all individuals >45 years of age, regardless of their risk factor status. It also recommends repeat screening at 3-year intervals. The rationales for this recommendation are that the incidence of type 2 diabetes increases sharply after age 45 years, the likelihood of developing any significant complications of diabetes within 3 years of a negative test is negligible, and the risk factors included in ADA's recommendations are firmly established.

In light of these recommendations, just how common is screening for type 2 diabetes? Little information describing the level

of screening is available. A 1989 U.S. population-based survey found that ~40% of individuals who did not have diabetes reported being tested for the disease during the previous year by a doctor or other health professional (157). Unfortunately, this report did not describe the location or the circumstances of the testing. In 1998, a population-based survey in Montana found that 39% of individuals without diabetes had been screened during the previous year (199). Several health organizations and agencies recommend diabetes screening, and screening is undoubtedly taking place, but it seems unlikely that it is being systematically applied and left up to patients, health care providers, and public health workers. A good deal of "accidental" diabetes screening may be occurring in the health care setting because the widespread use of multichannel chemistry tests means that glucose is frequently measured from laboratory tests conducted for other reasons.

SUMMARY—Definitive studies of the effectiveness of screening for type 2 diabetes are currently not available. RCTs would be the best means to assess effectiveness, but several barriers prevent these studies from being conducted. Prospective observational studies may characterize some of the benefits of screening by creating screened and unscreened groups for comparison. The availability of better data systems and health services research techniques will facilitate such comparisons. Unfortunately, the interpretation of the results of such studies is extremely problematic.

Several screening tests have been evaluated. Risk assessment questionnaires have generally performed poorly as stand-alone tests. Screening with biochemical tests performs better. Venous and capillary glucose measurements may perform more favorably than urinary glucose or HbA$_{1c}$ measurements, and measuring postprandial glucose levels may have advantages over measuring fasting levels. However, performance of all screening tests is dependent on the cutoff point selected. Unfortunately, there are no well-defined and validated cutoff points to define positive tests. A two-stage screening test strategy may assist with a more efficient use of resources, although such approaches have not been rigorously tested. The optimal interval for screening is unknown. Even though periodic, targeted, and opportunistic screening within the existing health care system seems to offer the greatest yield and likelihood of appropriate follow-up and

treatment, much of the reported experience with screening appears to be episodic poorly targeted community screening outside of the existing health care system.

Statistical models have helped to answer some of the key questions concerning areas in which there is lack of empirical data. Current models need to be refined with new clinical and epidemiological information, such as the UKPDS results (200). In addition, future models need to include better information on the natural history of the preclinical phase of diabetes. Data from ongoing clinical trials of screening and treatment of impaired glucose tolerance, such as the Diabetes Prevention Program, may eventually offer more direct evidence for early detection and treatment of asymptomatic hyperglycemia (201). It will be important to use comprehensive cardiovascular disease modules that assess the conjoint influence of glucose and cardiovascular risk factor reduction, information on QOL, and refined economic evaluations using common outcome measures (cost per life-year or QALY gained) (11,178,202–204). Such studies should consider all of the costs associated with a comprehensive screening program, including, at a minimum, the direct costs of screening, diagnostic testing, and care for patients with diabetes detected through screening. Finally, combinations of screening tests and different screening intervals should be evaluated within economic studies to allow selection of the optimal approach within the financial and resource limitations of the health care system.

CONCLUSIONS—The effectiveness of screening for diabetes has not been directly demonstrated. Indirect examination of the potential benefits of screening using data from observational studies, data on treatment effectiveness from RCTs, and data on disease progression from simulation models suggests that early detection of type 2 diabetes and improved glycemic control may modestly reduce the lifetime occurrence of microvascular disease. There is little convincing evidence that the incidence of macrovascular disease will be reduced by improved glycemic control alone, but it may be improved by more aggressive treatment of hypertension and hyperlipidemia. The physical, psychological, and social effects of screening and early diagnosis remain unclear. One cost-effectiveness study, which was conducted using simula-

tion models, assessed an approach that involved screening of individuals who had contact with the health care system for reasons other than diabetes evaluation. In general, such opportunistic screening of the adult population is cost-prohibitive, although opportunistic screening of high-risk subgroups was in a cost range considered economically feasible by some health care systems. Also, targeted opportunistic screening appears as cost-effective as many other screening procedures that are considered appropriate in the U.S.

In conclusion, population-based and selective screening programs in community settings (outreach programs, health fairs, or shopping malls) have uniformly demonstrated low yield and poor follow-up. Such screening entails a substantial opportunity cost and, under most circumstances, does not represent a good use of resources and therefore cannot be recommended. Periodic screening of high-risk individuals as part of ongoing medical care may be warranted, understanding that the evidence is incomplete. Questions remain as to the optimal methods, cutoff points, and screening frequency. As stated earlier, clinicians should continue to be vigilant in recognizing clinical situations with a history, sign, or symptom suggestive of diabetes that warrant testing.

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