Rethinking Diabetes Screening and Case Finding Strategies in Clinical Practice: Who's Really at Risk?

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Biography:

Dr. Bowen is a general internist, pediatrician, and outcomes and health services researcher in the Departments of Medicine, Pediatrics, and Clinical Sciences. After finishing his residency in Internal Medicine and Pediatrics at Vanderbilt University Medical Center, he completed the VA National Quality Scholars Fellowship Program which is an interdisciplinary fellowship focused on quality improvement, systems-based practice, and implementation science. He is the chair elect of the Society of General Internal Medicine Evidence-based Medicine Task Force and a member of the Community Leadership Board of the North Texas Chapter of the American Diabetes Association. He is currently supported by a career development award in patient-oriented research (K23) from the National Institutes of Diabetes, Digestive, and Kidney Diseases. His research focuses on the development of novel case finding strategies and clinical decision support to identify patients with undiagnosed type 2 diabetes and prediabetes using random glucose values and diabetes risk factors routinely available within the electronic medical record.

Purpose and Overview:

This presentation reviews the principles of population-based screening in the context of type 2 diabetes. In the absence of evidence supporting population-based screening, opportunistic screening and case finding strategies are discussed in the context of clinical practice. Approaches to identifying patients at high risk for diabetes including screening guidelines and risk scores are examined. We define and discuss the glucose history in the context of electronic medical record data and explore its potential use in developing EMR-based diabetes risk scores integrated with clinical decision support.

Educational Objectives:

At the conclusion of this lecture, the listener should be able to:

1) Describe the evidence for and against population-based screening for type 2 diabetes
2) Understand key differences in US diabetes screening guidelines and how their performance varies in different clinical populations
3) Understand the utility of diabetes risk scores and barriers to the use of current risk scores in clinical practice
4) Define glucose history and its association with undiagnosed diabetes

Overview

Type 2 diabetes is a major public health problem that meets many of the World Health Organization (WHO) criteria for population-based screening. However, evidence demonstrating that individuals with screen-detected diabetes have better health outcomes than those diagnosed in routine clinical practice is lacking. As a result, current recommendations support opportunistic screening of individuals at high risk for diabetes in the context of routine clinical practice. However, the optimal approach to identifying individuals at high risk for diabetes remains unclear. This presentation reviews the criteria for diabetes screening, current screening guidelines, the potential utility of diabetes risk scores, and a novel approach to identifying individuals at high risk for diabetes using random glucose data in clinical practice.

Epidemiology

Type 2 diabetes is a major cause of morbidity and mortality in the United States with an estimated cost of $245 billion in 2012.[1] Diabetes is the leading cause of blindness, renal failure, and non-traumatic lower-limb amputations in the US.[2] An estimated 29.1 million people, or 9.3% of the US population, have type 2 diabetes. However, 8.1 million people with diabetes in the US are currently undiagnosed. The prevalence of diabetes increases with age, with adults age 65 and older having nearly twice the prevalence of diabetes compared with those age 45 years or younger (33% vs. 17.5%). The age-adjusted prevalence of diabetes is significantly higher in Hispanics (22.6%), non-Hispanic blacks (21.8%) and non-Hispanic Asians (20.6%) compared with non-Hispanic whites (11.3%).[3]

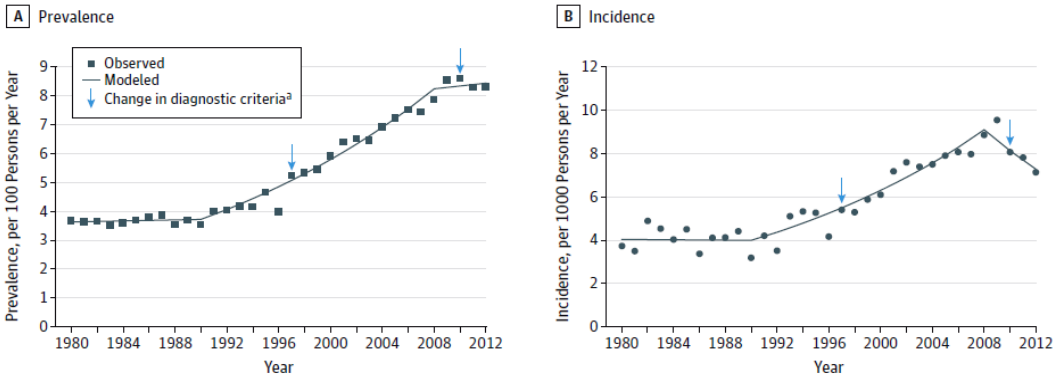
Prediabetes, which is blood glucose that is higher than normal but not high enough to be diagnosed as diabetes, is a high risk state for developing diabetes. Diabetes risk increases across the glycemic continuum as glucose levels rise from normal, to prediabetes, and ultimately to diabetes. An estimated 86 million US adults in the US have prediabetes, accounting for over 37% of the population. Alarmingly, 77 million of those with prediabetes remain undiagnosed.

Trends in Diabetes Incidence and Prevalence

The incidence and prevalence of diabetes nearly doubled between 1980 and 2008, with the most striking increases between 1990 and 2008. The increase in obesity, which is a major risk factor for type 2 diabetes, during this time has largely paralleled the increase in diabetes. However, the dramatic increases in diabetes incidence and prevalence are multifactorial resulting from not only an increased burden of risk factors in the population, but also improved case detection, improved survival rates, changing demographics in the US population, and changes to diabetes diagnostic criteria.[4]

The incidence and prevalence of diabetes plateaued between 2008 and 2010 and subsequently declined significantly from 8.5 to 6.6 per 1,000 population. However, in spite of declines in the general population, incidence and prevalence continued to increase in population subgroups including Hispanics, non-Hispanic blacks, and those with less than a high school education.[4,5]

Figure 1. Trends in Age-Adjusted Diagnosed Diabetes Prevalence and Incidence Among Adults Aged 20-79 Years, 1980-2012



Data are from the National Health Interview Survey. Joinpoint regression was conducted using the natural logarithm of the age-adjusted rate as the dependent variable and year as the independent variable.

[a] In 1997, the diabetes diagnostic criteria for fasting plasma glucose was lowered from 140 mg/dL or more to 126 mg/dL or more; in 2010, hemoglobin A_{1c} was adopted for the diagnosis of diabetes. To convert glucose to mmol/L, multiply by 0.0555.

Although these decreases in diabetes incidence and prevalence are encouraging, the causes and implications remain uncertain. The change in diabetes rates over time results in part from data artifacts related to changing diagnostic criteria over time. Incidence and prevalence rates are assessed using population-based, self-reported survey data and reflect changes in clinical practice over time. In 1997, the American Diabetes Association shifted their approach to diagnosing diabetes in clinical practice by advocating use of fasting glucose in place of the oral glucose tolerance test. During this time, the diagnostic threshold for diabetes was lowered from ≥ 140mg/dL to ≥ 126 mg/dL, increasing the population of patients diagnosed with diabetes. However, incidence rates were increasing steadily prior to this diagnostic change, so this alone is unlikely to account for the observed changes.[4]

In 2010, the ADA recommended the use of hemoglobin A_{1C} (HbA_{1c}) for screening and diagnosis of diabetes. As a screening and diagnostic test, HbA_{1c} has a lower sensitivity than fasting glucose and identifies fewer individuals with diabetes. Since HbA_{1c} does not require fasting, it is often the preferred test in clinical practice for both patients and clinicians. However, the extent to which clinicians utilize HbA_{1c} for screening and diagnosis is unknown, making it difficult to quantify the impact of a potential shift from fasting glucose to HbA_{1c} for screening and diagnosis.[4] Given that HbA_{1c} is now commonplace, it is possible that a new baseline for incidence and prevalence will be established and serve as a reference point going forward.

Screening and Case Finding

Screening is the process of testing asymptomatic individuals with unrecognized disease in the general population for the purpose of distinguishing those with high and low probabilities of disease.[6] Screening is a multi-step process that identifies those in need of screening, determines if screening is appropriate, invites individuals for screening, performs the screening test, follows up results, notifies the patient of results, and initiates further evaluation and treatment as indicated.[7] Screening tests, which aim to differentiate well individuals with unrecognized disease from those that do not have disease, are designed to test large numbers of asymptomatic individuals, are generally simple, acceptable to patients, and relatively low risk. Cut-points for screening tests are generally selected to prioritize sensitivity and detection of disease. Diagnostic tests seek to establish the presence or absence of disease in individuals with a positive screening test. Diagnostic tests, on the other hand, are targeted, favor specificity, may be invasive and expensive, but have an acceptable risk-benefit ratio.

Although screening and case finding are often used interchangeably, important differences exist. In screening, the entity conducting the testing invites healthy volunteers from the population to undergo screening tests with an implicit that they will benefit. In case finding, patients initiate contact with the healthcare system for reasons unrelated to screening and undergo testing that may identify unrecognized disease. As such, case finding does not carry an implied guarantee that the patient will benefit, but rather that they will receive the highest standard of care available.[6] Case finding is commonly referred to as 'opportunistic screening.'

Principles of population based screening

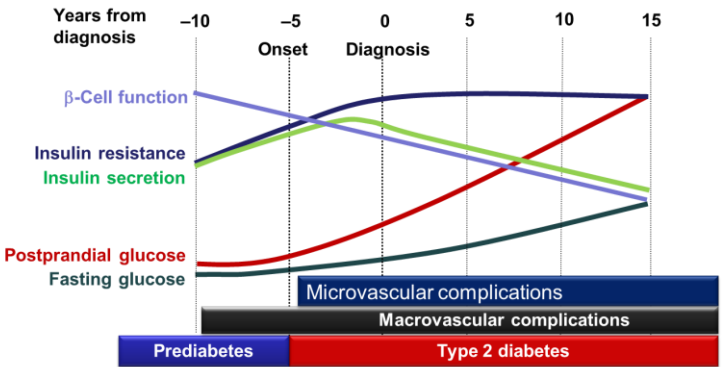
In 1968, the World Health Organization (WHO) outlined principles to assess the risks, benefits, and costs of population based screening programs.[8] These criteria are broadly applicable to screening programs irrespective of the underlying condition. Recommendations for or against a screening program are influenced by the best available evidence for each of these criteria. Evidence that early disease detection improves health outcomes relative to the risks and benefits of the screening program is the most important factor in justifying screening policy. The public health importance of type 2

WHO Principles of Population-based Screening	
Screening Condition	Is it an important health problem?
	Is the natural history of disease well understood?
	Is there a long time between the presence of risk factors/sub-clinical disease and progression to overt disease?
	Does early intervention improve health outcomes?
Screening Test	Is the test valid?
	Is the test simple, reliable, and affordable?
	Is the test acceptable to patients and staff?
Diagnosis and Treatment	Is access to diagnostic facilities available and timely?
	Is treatment effective and accessible?
	Are screening, diagnosis and treatment cost-effective?
	Is the screening program sustainable and ongoing?
	Do benefits outweigh harms?

diabetes and its impact on population health were discussed earlier. The supporting other key screening criteria will be reviewed below.

Natural History of Diabetes

In normal individuals, glucose is a tightly regulated function of insulin production and insulin sensitivity. Early in metabolic dysregulation, beta cells increase insulin production to maintain glucose in a normal range as insulin resistance increases. However as insulin resistance continues to increase, beta cells are unable to produce enough insulin to overcome insulin resistance and glucose begins to rise.[9]



AACE Diabetes Resource Center

Is there an asymptomatic, pre-clinical state for diagnosis?

Progressive loss of beta cell function results in glucose levels that increase over time. As glucose rises, the risk for diabetes increases across the glucose continuum from normal glycemia, to prediabetes, to pre-clinical diabetes, and ultimately clinically apparent diabetes. Data suggest that the onset of type 2 diabetes may occur 9-12 years before clinical diagnosis, providing a sufficient window for early detection.[10] This window is independent of the prediabetes state, which is considered a distinct, high risk state for developing diabetes rather than pre-clinical diabetes. This is because many individuals with prediabetes never proceed to frank diabetes, especially those at lower end of the glycemic spectrum.[11] In the United Kingdom Prospective Diabetes Study (UKPDS), 50% of those with newly diagnosed diabetes had evidence of diabetes complications.[12] This supports not only the existence of a preclinical phase but also evidence of end-organ damage occurring prior to clinical diagnosis. At clinical diagnosis, the estimated prevalence of microvascular complications is retinopathy (2-39%), nephropathy (8-18%), and neuropathy (5-15%).[13]

Are there acceptable, reliable tests to detect diabetes in the preclinical disease state?

In type 2 diabetes, the screening and diagnostic tests are identical. Three tests [(fasting plasma glucose, hemoglobin A_{1C} (HbA_{1c}), and oral glucose tolerance test (OGTT)] are endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, and the International Diabetes Federation. Currently, guidelines do recommend use of one test over the other. In addition, a random glucose

≥ 200 mg/dL in the presence of hyperglycemic symptoms such as polyuria and polydipsia is considered diagnostic of diabetes. Currently, random glucose has no defined role in diabetes screening.[14]

Although no single screening test is recommended or preferred for the screening and diagnosis of diabetes in clinical practice, it is important that clinicians understand the strengths and weakness of each test. For practical purposes, HbA_{1c} is often preferred by patients and clinicians because it can be done at any time of the day without necessitating fasting. OGTT is the least practical because it requires substantial time and effort for both patients and staff. Technical features and glycemic classifications by test are shown in the table below.

Screening and Diagnostic tests for Diabetes						
Test	**Technical Features**	**Pros**	**Cons**	**Normal**	**PreDM**	**DM2**
HbA_{1c}	• No fasting required • Sample highly stable • Coefficient of variation (COV): assay allows up to 5% • If result 6.5%, possible range (6.0-7.0%)	• Convenient • low within-patient variability • National standard monitored for accuracy • Highly correlated with outcomes	• Lower sensitivity • Interference from Hb Variants, disease processes • Expensive	<5.7%	5.7-6.4%	≥6.5%
Fasting Glucose	• Requires 8H fast • Low sample stability (30 min) • COV: 5.7% in same person • If result 126mg/dL (110-142)	• Low cost • Widely available	• Affected by short term changes • High within-patient variability • Lower correlation with outcomes and complications	<100 mg/dL	100-125 mg/dL	≥126 mg/dL
2H glucose on OGTT	• Requires 8H fast; 2H follow-up • Low stability (30 min) • Require intake ≥150g CHO for 3 days before	• Most sensitive	• Inconvenient, expensive • High within-patient variability • Poor reproducibility	<140 mg/dL	140-199 mg/dL	≥200 mg/dL

Two key aspects of diabetes screening and diagnostic tests are often underappreciated. First, the coefficient of variation for screening tests is higher than one might expect. HbA_{1c} assays are certified by the National Glycohemoglobin Standardization Program (NGSP), which standardizes HbA_{1c} test results to those of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) which established the relationship between glycemic control via HbA_{1c} the risk of diabetes outcomes.[15] HbA_{1c} assays certified by the NGSP have a coefficient of variation up to 5% such that a result of 6.5% is in reality anywhere between 6.0-7%; however, local lab variation is likely much less than this. Fasting glucose and OGTT are not standardized to outcome data, but are monitored by strict laboratory guidelines. Accounting for the average 5.7% variation on repeat sampling of a fasting glucose within the same individual, a value of 126 mg/dL could be anywhere

between 110-142 mg/dL. OGTT has even higher variation. Thus, initial screening tests should be repeated to confirm correct glycemic classification if the result is abnormal.[16] Secondly, clinicians often underappreciate that the 3 recommended diabetes screening tests often classify patients differently. Only 23% of patients with undiagnosed diabetes will test positive by all 3 tests. The 2 hour glucose from the OGTT is the most sensitive, identifying 90% of undiagnosed diabetes, followed by fasting glucose, which identifies 46% of undiagnosed disease, and then HbA_{1c}, which identified 30% of undiagnosed disease. It is important to note that this does not include repeat, confirmatory testing, so the within-patient variability of the OGTT and FBG is not accounted for in these estimates. Generally, the initial screening test should be selected based on the acceptability to the patient.[17]

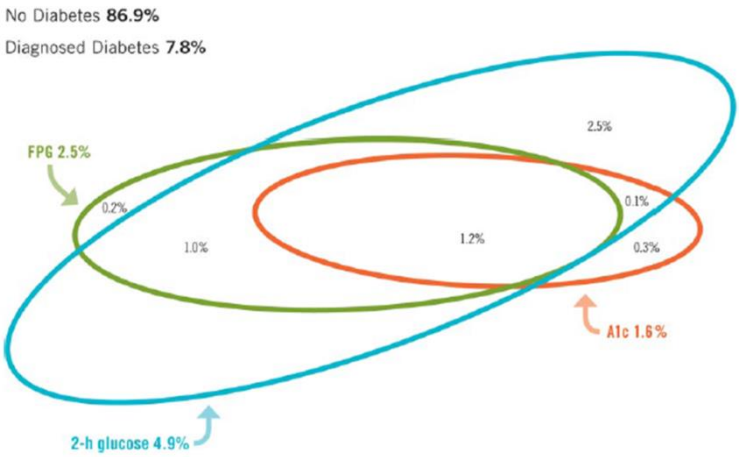


Figure 1—*Undiagnosed diabetes in the U.S. population aged ≥20 years by three diagnostic criteria—NHANES 2005–2006. C*

What are the potential harms of diabetes screening?

Because screening tests are intended for use in asymptomatic individuals, the potential benefits of administering screening tests should outweigh the potential harms of testing. Since diabetes screening involves a routine phlebotomy procedure and laboratory test, the procedural risks of diabetes screening are no greater than those encountered by patients in routine clinical care. Limited studies have examined the harms of screening, and no studies have examined the potential harms associated with false positive screening tests.[18] The ADDITION study found no difference in anxiety between those participating in a screening program and those in routine care. However, those screening positive for diabetes, reported slightly higher rates of anxiety, depression, and worry about diabetes compared with those who screened negative.[19]

Does treatment of screen detected individuals improve health outcomes compared with those detected and treated in clinical practice?

Data from United Kingdom Prospective Diabetes Study

The bulk of data supporting early identification and treatment of type 2 diabetes comes from intervention studies examining the impact of early treatment on diabetes outcomes among patients diagnosed in routine clinical practice. The UKPDS enrolled

5100 patients with newly diagnosed type 2 diabetes who were not on insulin. After a dietary run-in phase, patients were randomized 1) to standard care with diet; 2) intensive control (sulfonylurea/insulin or metformin in obese patients). During the 10 year followup period, the median HbA_{1c} was lower in the intensive intervention group vs. control (7.0% vs. 7.9%; p<0.0001). Intensive treatment reduced the risk of any microvascular disease (RR 25% (7-40%); p=0.009) and any diabetes endpoint (12% (1-21%); p=0.029). At the end of the 10 year trial, no differences in all-cause mortality, diabetes related death, or fatal/non-fatal MI were observed.[20] Ten years after completion of the trial, outcomes were re-examined.[21] Although glycemic differences between the intensive and standard of care groups were lost within 12 months (HbA_{1c} 8.0% vs. 8.1%), significant reductions in all-cause mortality (13%; p=0.007), fatal/non-fatal MI (15%; p=0.01), microvascular disease (24%; p=0.001), and any diabetes endpoint (9%; p=0.04) were observed in the intensive control group compared with the conventional treatment group. These findings demonstrated the importance of early, intensive glycemic control (compared with conventional diet) on health outcomes – even after glycemic control worsens. These findings support evidence of a "legacy effect" of early diabetes treatment – mainly that early, intensive glycemic control improves health outcomes even if there is a subsequent regression in glycemic control.[21]

ADDITION-Cambridge Trial

The ADDITION-Cambridge trial[22] was a pragmatic, cluster-randomized trial that randomized general practices in England to stepwise screening followed by intensive treatment or routine care versus no screening. Patients age 40-60 scoring in the highest 25% of a diabetes risk score were invited for screening. The screening group included 16,047 participants and the no-screening control group had 4,137 participants. Median follow-up was 9.6 years. In the screening group, 3% of participants were diagnosed with diabetes. No difference in all-cause mortality (HR 1.06 (0.90-1.25), cardiovascular mortality (HR 1.02 (0.75-1.38) , diabetes-related mortality (HR 1.26 (0.75-2.10), or cancer mortality (HR 1.08 (0.75-1.38) was observed between the screening vs. no screening group.[22] Five year follow-up in the ADDITION-Europe trial examining cardiovascular outcomes of protocol-driven diabetes, hypertension, cholesterol management vs. routine clinical care in those with screen-detected diabetes found no difference in the time to first cardiovascular event (HR 0.83 (0.65-1.05).[23]

The ADDITION-Cambridge Trial is the highest quality study examining the effect of screening on population mortality. Of note, this study was unable to compare outcomes in patients with screen-detected diabetes vs. clinically-diagnosed diabetes because it lacked data on opportunistic diabetes screening, diagnosis, and outcomes in the population control group. Additional limitations of this study include a low baseline prevalence of undiagnosed diabetes and limited screening uptake, with those at highest risk not responding to the screening invitation. If diabetes screening reduces mortality,

this is probably mediated by concurrent, evidence-based therapies such as statins, blood pressure control, and smoking cessation that have been shown to decrease cardiovascular risk and mortality. Although this study does not strengthen the case for widespread, population-based diabetes screening, it is unlikely that there will be future randomized controlled trials of screening vs. no screening.

Is diabetes screening potentially cost effective?

Multiple studies suggest that diabetes screening may be cost effective.[18] However, like all cost effectiveness studies, findings are highly sensitive to model assumptions. The true cost effectiveness of diabetes screening programs is likely to be determined by the prevention of cardiovascular outcomes and diabetes complications, which in turn depend on the effectiveness of treatments to improve disease outcomes. Unlike many cancer screening programs where early detection increases treatment options, cure rates, and survival, early diagnosis of diabetes still means lifelong, daily self-management tasks for the majority of patients. Although diabetes medications are quite effective, suboptimal diabetes self-management can significantly limit the impact of diabetes treatments.

Strategy	Discounted QALY of screening vs. no screening after 50 years	Diagnosis lead time, years gained
Age 30, every 3 years	$10,512	6.3
Age 45, every years	$15,509	5.98
Age 45, every 3 years	$9,731	5.33
Age 45, every 5 years	$9,786	4.72
Age 60, every 3 years	$25,738	1.83
HTN, every years	$6,287	2.84
HTN, every 5 years	$6,490	2.43
Maximum screening (every 6 months starting age 30)	$40,778	7.84

The Archimedes model, which has been validated against clinical and epidemiological studies demonstrating good calibration, used US data to simulate diabetes screening and treatment over a 50 year time horizon. This study examined 8 hypothetical screening strategies compared with a no-screening control strategy. Using fasting glucose as the screening test, they concluded that screening was cost effective when started between the ages of 30-45 and repeated every 3-5 years. Screening individuals with hypertension was the most cost effective strategy because it resulted in the highest estimate of preventable events for the modeled outcomes (diabetes incidence, myocardial infarcion, stroke, microvascular complications).[24]

Models examining the cost effectiveness of screening for prediabetes using a random capillary glucose + fasting glucose or OGTT followed by lifestyle intervention found an ICER ranging $8,181-9,511/QALY compared with no screening over a lifetime time horizon. However, these estimates were highly sensitive to the effectiveness of the lifestyle intervention and the cost to deliver the intervention.[25]

Summary

Although screening for type 2 diabetes meets many of the WHO population-based screening criteria,[8] it remains unclear whether or not early detection and treatment of type 2 diabetes via screening programs improves outcomes compared with those detected in routine clinical care. As a result, current evidence does not support universal, population-based diabetes screening. In lieu of this, current guidelines recommend opportunistic screening or case finding strategies targeted at population subgroups at high risk for diabetes.

Diabetes Case Finding in Clinical Practice

Current diabetes screening guidelines from the American Diabetes Association (ADA), US Preventative Services Task Force (USPSTF) and the International Diabetes Federation recommend opportunistic screening of individuals at high risk for diabetes.[14,26,27] Opportunistic screening – also known as case-finding – is screening that occurs when patients present to the healthcare system for a purpose other than screening. A key consideration in opportunistic screening is how to best execute screening in the context of a busy clinical environment with time constraints and multiple competing demands. Selective screening is a process by which screening is targeted to subgroups of the population at high risk based on epidemiological evidence. The key consideration in selective screening is defining the population at risk.

Diabetes screening guidelines define diabetes risk very differently making it difficult for clinicians to select patients for screening. The IDF recommends using a diabetes risk score such as FINDRISK to assess diabetes risk and identify individuals in need of glycemic testing based on projected future development of diabetes.[27] In contrast, US guidelines recommend screening based on the presence of various risk factors as shown in the table. For those with normal screening results, repeat screening is recommended in 3 years based on expert opinion and rationale that diabetes complications are unlikely to develop during this time. For

2016 American Diabetes Association Guideline[14]
All adults age 45 and older
Adults age 18 or older who are overweight (BMI ≥ 25 kg/m^2 or ≥ 25 kg/m^2 in Asian Americans with one or more additional risk factors:
• Physical inactivity • First-degree relative with diabetes • High-risk race/ethnicity (African American, Latino, Native American, Asian American, Pacific Islander) • Women with baby weighing > 9 lb or prior diagnosis of gestational diabetes • Hypertension (≥140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL • Women with polycystic ovarian syndrome • Prediabetes (A1c≥5.7-6.4%, impaired glucose tolerance, or impaired fasting glucose on previous testing) • History of cardiovascular disease • Other clinical conditions associated with insulin resistance (acanthosis nigricans, severe obesity)
2015 USPSTF Guideline[26]
Adults age 40-70 who are overweight or obese (BMI ≥ 25 kg/m^2)

those with prediabetes, repeat screening is recommended in 1 year given the increased risk of transitioning from prediabetes to diabetes.[14]

Performance of ADA and USPSTF Screening Guidelines in the US Population

The ADA and USPSTF guidelines define risk very differently. The ADA guideline is designed to be highly sensitive with a goal of identifying as many people with diabetes as possible. Using data from the National Health and Nutrition Examination Survey (NHANES), 76% of the adult population in the US meets ADA screening criteria. However, only 46% of those eligible report undergoing diabetes screening in the past 3 years. The USPSTF guideline defines risk much more narrowly and recommends screening for 34% of the US adult population, with only 50% of those eligible completing screening.[28,29] Using HbA_{1c} as the gold standard diagnostic test, the ADA criteria are highly sensitive to detect undiagnosed diabetes and dysglycemia. However, specificity is poor meaning that many individuals are identified as "at risk for diabetes" but have normal glycemic testing when screened. Using a more narrow risk definition, the 2015 USPSTF guideline is equally sensitive and specific to detect undiagnosed diabetes, but is more specific than sensitive to detect undiagnosed dysglycemia. Overall discrimination, as assessed by the Area Under the Receiver Operator Curve (AROC), and number needed to screen (NNTS) was similar the ADA and USPSTF criteria.[28]

Performance of Diabetes Screening Guidelines in NHANES

Screening Strategy	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AROC (95% CI)	NNTS
Identification of Diabetes Cases, HbA_{1C} ≥ 6.5%				
ADA	99.2 (98.4–100.0)	23.0 (20.9–25.1)	0.59 (0.58–0.60)	35
2015 USPSTF	65.2 (58.4–71.9)	66.5 (64.4–68.5)	0.64 (0.61–0.67)	32
Identification of Dysglycemia, HbA_{1C} ≥ 5.7%				
ADA	96.0 (94.8–97.3)	28.8 (26.1–31.4)	0.61 (0.60 – 0.61)	4
2015 USPSTF	50.2 (47.4–53.0)	71.2 (69. –73.4)	0.61 (0.60 – 0.62)	6

Performance of the ADA and USPSTF Screening Guidelines in Clinical Practice

The performance of diabetes screening guidelines in clinical practice is likely to differ from performance in population-based samples because patients engaged in clinical care have more medical conditions and diabetes risk factors relative to the general population. Additionally, eligibility for guideline-indicated screening and guideline performance vary across populations. In a large (N=50,515) population of adults cared for in a Community Health Center network in the Midwest and Southern US, only 25.1% of adults were eligible for screening according to the 2015 USPSTF guideline. In this study, 37% of the study population was under than age of 40, making them ineligible for screening by the 2015 USPSTF guideline. Overall, 59% of the population underwent opportunistic screening, with 72% of results being normal, 20% having prediabetes, and 8% having incident diabetes. Among those screened

(n=29,946), the USPSTF guideline was 45% sensitive, 72% specific, PPV 39%, and NPV of 77% for the detection of dysglycemia, which was defined as the combination of diabetes and prediabetes.[30] Overall, performance was similar to that observed in the population-based NHANES sample.

Using electronic medical record data from Parkland Health and Hospital System outpatient primary care clinics, we identified 44,186 patients ages 18-64 without diagnosed diabetes or prediabetes who had not been screened for diabetes. The study population had a high burden of diabetes risk factors with 55% being over the age of 45, 80% having a BMI≥25 kg/m^2, 55% with a family history of diabetes, and 51% having hypertension. Over 80% of the population was uninsured, and racial/ethnic diversity was high (47% Hispanic; 34% black; 5% Asian).

Diabetes Screening Guideline Performance in Parkland Primary Care (N=26,733)

Outcome	Sensitivity	Specificity	PPV	NPV
2015 USPSTF Guideline				
Undiagnosed Diabetes	82.1%	39.7%	20.4%	93.6%
Undiagnosed Prediabetes	73.0%	42.8%	43.7%	72.3%
Undiagnosed Dysglycemia	75.3%	49.4%	60.6%	65.9%
ADA Guideline				
Undiagnosed Diabetes	99.1%	8.6%	14.0%	98.6%
Undiagnosed Prediabetes	97.0%	10.4%	39.7%	85.0%
Undiagnosed Dysglycemia	97.6%	12.9%	53.7%	83.7%
Dysglycemia: combination of diabetes and prediabetes				

Overall, 26,733 patients (60.5%) underwent opportunistic diabetes screening. Screening results classified 49.1% of patients as having normal glycemia, 37.8% as having incident prediabetes, and 13.1% as having incident diabetes. Overall, 51% of the population had newly diagnosed dysglycemia. In the Parkland system, HbA_{1c} was the most frequently ordered screening test (50%) followed by fasting glucose (23%) and OGTT (0.6%).[31] Using ADA screening guidelines, 89.3% of the sample was eligible for screening, with guideline performance as shown in the table. Using 2015 USPSTF guidelines, 57% were eligible for screening. The sensitivity and specificity in the Parkland population was substantially higher than that in the Community Health Center Network, demonstrating substantial variability in guideline performance across different populations.

In summary, overall opportunistic screening rates in clinical practice seem to be higher than those reported on national, population-based surveys, but approximately 40% of patients eligible for guideline-indicated diabetes screening remain untested. In clinical practice, HbA_{1c} is the most frequently used diabetes screening test. In populations with a high burden of diabetes risk factors, the ADA guideline recommends near universal diabetes screening which poses significant challenges in resource-limited environments. The performance of diabetes screening guidelines varies substantially across populations with different levels of diabetes risk factors in the underlying population. Efficient, practical approaches to help clinicians to identify patients at highest risk for diabetes and facilitate screening in clinical practice are needed.

Screening Smarter: A Role for Risk Scores in Diabetes Case Finding?

Diabetes risk scores are tools designed to objectively assess of the probability of an individual patient having diabetes. Thus, they provide a mechanism of identifying high risk patients for diabetes testing in case finding strategies. Risk scores can be particularly useful when risk is determined by complex interactions of patient level risk factors, genetics, and environmental influences that vary in strength and direction across different populations. Well-designed risk scores can capture this complexity and present information to patients and clinicians in an actionable manner capable of changing clinical practice and outcomes.[32]

Risk scores can be designed to detect both incident and prevalent disease depending on the time horizon of the prediction. Incident risk scores predict the future development of diabetes in individuals that currently do not have diagnosed diabetes. In contrast, prevalent risk scores detect undiagnosed diabetes with an immediate time horizon. In case finding, prevalent risk scores can serve as instruments to select high risk individuals to undergo diabetes testing. Risk scores can be designed for patients to self-assess their diabetes risk, or they can be designed for use by clinicians. The key factor differentiating patient vs. clinician targeted risk scores is the type of data needed to calculate the score. Patient-oriented risk scores utilize data known to patients (for example age, race, sex, family history, BMI) and do not require calculations beyond addition. Clinician oriented risk scores often include invasive data (laboratory results, vital parameters, and biologic data) that are not known to patients. Clinician-oriented risk scores can also harness automated computerized algorithms to allow a larger number of predictors and more complex modeling.

Patient-oriented Diabetes Risk Scores

Patient-oriented risk scores are completed in the community or prior to encounters with healthcare providers so that patients can quantify their diabetes risk and engage their healthcare provider in a conversation about diabetes screening. Barriers to the use of patient-oriented risk scores include a low perceived risk for diabetes, difficulty understanding and using the score, concern about potential results, and uncertainty about how best to utilize the score and link high risk patients to clinical care for screening.[33] Two commonly used patient-oriented risk scores are the ADA Diabetes Risk test[34], which is utilized in the current Type 2 Diabetes Prevention Campaign sponsored by the CDC, ADA, and AMA in partnership with the Ad Council (http://www.adcouncil.org/Our-Campaigns/Health/Type-2-Diabetes-Prevention) and the Finnish Diabetes Risk Score (FINDRISC)[35], which is recommended by the International Diabetes Federation for use in identifying high risk individuals for screening.[27] In the derivation and validation datasets, the ADA risk score classified 35-40% of the population as being at high risk, which was much lower than the ADA diabetes

screening guideline (82-100%). The ADA risk score had a higher PPV (8-10%) than the ADA screening guidelines (5%) using the same data. A concise version of the FINDRISC without physical activity and intake of fruits/veggies/berries was validated with similar performance.

	ADA Diabetes Risk Test[34]	FINDRISC[35]
Purpose	Detect undiagnosed prevalent diabetes	Predict future development of drug-treated diabetes
Risk Factors in Score	• Age • Sex • BMI • Family History • Hypertension • Physical inactivity	• Age • BMI • Waist Circumference • History of high blood glucose • Use of blood pressure medication • Physical inactivity • Daily intake fruit/veggie/berries
Performance range in derivation/validation samples		
Sensitivity	72-82	78-81
Specificity	62-67	76-77
PPV	8-10	5-13
NPV	98-99	99

The ADA risk test is available in Epic 2015 and currently installed at UT Southwestern. However, the performance of this risk score in the UTSW population is unknown. It is well recognized that diabetes risk scores often perform poorly in populations that differ from the population in which the score was derived, and risk scores should be recalibrated and validated in the target population prior to use.[36,37] A significant challenge in implementing the ADA risk test as an automated, EMR-based risk calculator in Epic is that the score was developed to be used by patients as a self-report tool. In the EMR, physical activity is not frequently documented in a structured field, and the absence of family history of diabetes may indicate that either the family history is truly negative – or it just was not asked. If missing, this score will underestimate the patient's diabetes risk due to missing data.

Clinician-oriented Diabetes Risk Scores

A number of clinician-oriented diabetes risk scores have been developed; however, relatively few have been implemented for use in clinical practice. [32,33] These risk scores often utilize multiple predictors and involve complex algorithms that limit their use. Patient level risk factors are the most commonly included variables followed by clinical information such as vital signs, comorbidities, and uncommon laboratory tests.[38] Inclusion of genetic profiling has not been shown to improve diabetes risk score performance.[36]

The Framingham Diabetes Risk Score,[39] which was developed to predict incident diabetes over a 7-year time horizon, is an example of a relatively parsimonious model developed using US data. A patient-oriented score including age, sex, family history of diabetes, and BMI had an AROC=0.724. By adding commonly available clinical variables to this model, including hypertension, HDL, triglycerides, BMI, and fasting glucose 100-125 mg/dL AROC improved to 0.852. The addition of further variables to

the risk score including 2-hour post prandial glucose, insulin level, c-reactive protein, and HOMA insulin resistance index failed to improve discrimination further. A systematic review of diabetes risk scores found similar discrimination among scores containing 3-8 risk factors. This suggests that the selection of risk factors to include in the risk score is likely more important than the number of risk factors.[37] Importantly, in models predicting future diabetes, the strongest predictor is the presence of existing prediabetes as evidenced by an odds ratio 7.25 in the Framingham score.[39]

Developing Diabetes Risk Scores to Detect Prevalent Diabetes Using EMR Data

To identify cases of undiagnosed diabetes, clinicians have two key decisions to make: 1) if a patient has never been screened for diabetes, should they be screened and 2) if a patient has been previously screened, should they be screened again. For patients who have been previously screened and have known prediabetes, guidelines indicate repeat screening in 1 year based upon high rates of transition from prediabetes to diabetes. This is captured in many existing risk scores that incorporate prediabetes as a risk factor. However, deciding if a patient merits screening if they have not been previously screened is a much more challenging decision.

The detection of undiagnosed diabetes in clinical practice may be improved by the development of parsimonious, EMR-powered diabetes risk scores that are integrated into clinical workflow. Selection of risk factors that are consistently available, accurate, and captured in discrete EMR fields is critical to EMR risk score development

Glucose History

Although patients may not have been previously screened with a gold-standard diabetes test, the majority of patients in clinical practice have random glucose data available. We refer to a patient's collection of glucose values over time as their glucose history. Random glucose – simply defined as non-fasting glucose – can be challenging for clinicians to interpret. Although values greater than 200 mg/dL in the setting of diabetes symptoms are diagnostic of diabetes, little guidance is provided to help clinicians interpret values <200 mg/dL. Random glucose values vary depending on dietary intake, time since last meal, adrenergic state, and underlying glucose metabolism. In normal individuals, glucose regulation is tightly controlled such that post prandial excursions are relatively small. However, as dysregulations in glucose metabolism begin to develop, post-prandial glucose begins to rise, and this is reflected in random glucose values.[9] Random glucose elevations and increased glucose variability may provide an early, detectable signal of glycemic dysregulation capable of identifying individuals at high risk for diabetes.

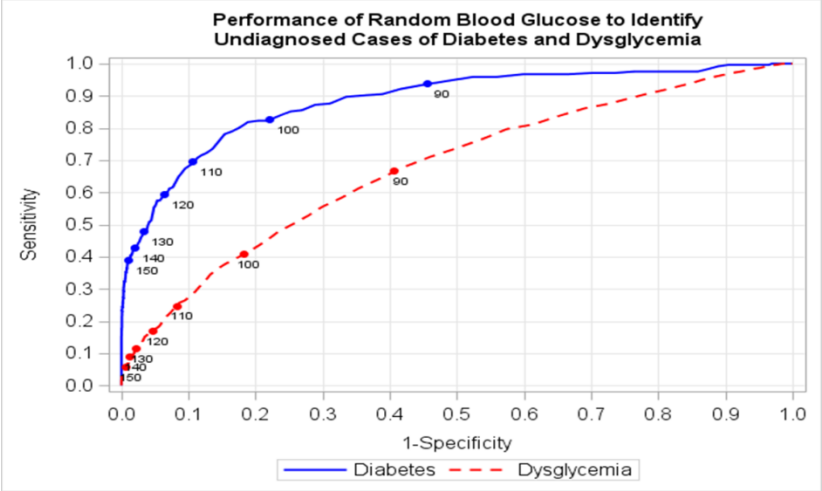
Using nationally representative NHANES data, we demonstrated that in patients without diagnosed diabetes, a single random glucose is strongly associated with undiagnosed diabetes after adjusting for common diabetes risk factors. Even relatively modest random glucose elevations (100-119 mg/dL) increase the odds of undiagnosed diabetes 7-fold. However, the relationship between random glucose and undiagnosed prediabetes and dysglycemia is less robust. This is likely related to more modest glucose elevations and less glucose variability in the early stages of glycemic dysregulation, which may be missed if only a single glucose value is examined.[40]

Table 3. Dose Response Relationship between Random Blood Glucose (RBG) and Undiagnosed Diabetes, Prediabetes, and Dysglycemia (Prediabetes + Diabetes)

	Adjusted Odds Ratio (95% CI)		
Glucose Range	Undiagnosed Prediabetes	Undiagnosed Diabetes	Dysglycemia
RBG < 100 mg/dL	Reference	Reference	Reference
RBG 100–119 mg/dL	2.2 (1.9–2.5)	7.1 (4.4–11.4)	2.3 (2.0–2.7)
RBG 120–139 mg/dL	3.3 (2.6–4.2)	30.3 (20.0–46.0)	3.8 (3.0–4.9)
RBG ≥ 140 mg/dL	3.5 (2.2–5.5)	256.0 (150.0–436.9)	8.4 (5.7–12.3)

All values adjusted for age, sex, race, BMI, hypertension, hyperlipidemia, cardiovascular disease, and family history of diabetes. Random glucose (mg/dL) × 0.5551 = mmol/L.

In the Screening for Impaired Glucose Tolerance Trial,[41] random glucose was shown to be a stronger predictor of undiagnosed diabetes than age, race/ethnicity, and BMI.[42] A random glucose value of 125 mg/dL was 40% sensitive, 93% specific and had PPV of 22% to identify undiagnosed diabetes. Using nationally representative data from NHANES, we have shown that a single random glucose ≥ 100 mg/dL is 82% sensitive, 78% specific with an AROC of 0.80 to identify undiagnosed diabetes. The performance of a single value to detect dysglycemia is modest (sensitivity 39%, specificity 82%, AROC 0.61) (Figure).[28] We are currently conducting studies using Parkland EMR data to examine the role of the glucose history in identifying patients in need for formal diabetes testing.



Piloting EMR-based Clinical Decision Support for Diabetes Screening

Based on data from the SIGT study that identified a random glucose of 125 mg/dL as a strong predictor of undiagnosed diabetes, we developed clinical decision support (CDS) at UT Southwestern that was designed to promote visit-based diabetes screening in patients without diagnosed diabetes who had an elevated random glucose or a previously abnormal $HbA1_c$ that was not repeated in >12 months. We evaluated the effectiveness of CDS to promote diabetes screening in a 12-month cluster

randomized trial in which primary care providers were randomized to either CDS or usual care. The CDS appeared within the Epic visit navigator for clinicians in the intervention group when they had a clinic visit with one of their primary care patients meeting CDS criteria. The primary outcome was a resulted $HbA1_c$ within 90 days of the CDS firing. Over 90% of patients triggering CDS satisfied ADA screening criteria. In the CDS intervention, 40% of patients had a resulted diabetes test vs. 8% in the usual care group. Patients seeing clinicians randomized to the CDS intervention were much more likely to complete diabetes screening (OR=9.4 (4.9-18.3) compared with usual care. CDS identified 16 incident cases of diabetes and 99 cases of incident/prevalent prediabetes. This pilot study demonstrates that that a simple diabetes risk tool based on the glucose history can improve case finding by activating visit-based CDS that prompts clinicians to order diabetes screening during routine clinical encounters.

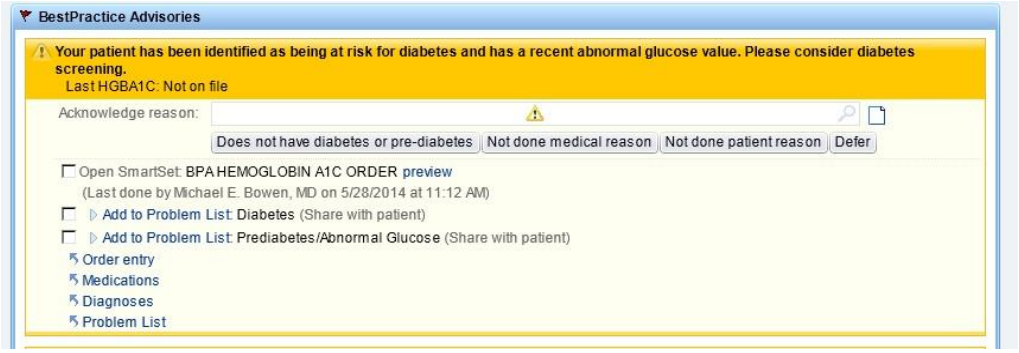


Table 2. Study Outcomes

	Control (N=312)	CDS (N=435)	P-value
Primary Outcome: Completion of A1C within 90 days of CDS			
Unadjusted Odds Ratio	Reference	8.5 (4.4-16.6)	<0.001
Adjusted Odds Ratio	Reference	9.4 (4.9-18.3)	<0.001
Secondary Outcomes: Cases of Diabetes and Prediabetes Identified			
A1C Resulted, n (%)	24 (7.7)	172 (39.5)	<0.001
Normal, n	9	57	<0.001
Prediabetes, n	12	99	<0.001
Diabetes, n	3	16	<0.001

Conclusions

Type 2 diabetes and prediabetes are significant public health problems in the US. Although diabetes satisfies most of the criteria for population-based screening, evidence demonstrating that patients with screen detected diabetes have better health outcomes than those diagnosed in routine clinical practice is lacking. It is unlikely that future studies will definitively answer this question. In lieu of population-based screening, case finding strategies targeted at high risk patients is recommended. The optimal approach to identifying high risk patients is unclear. Only 60% of patients eligible for guideline-indicated screening undergo diabetes testing in clinical practice. Current ADA and USPSTF screening guidelines have significantly different sensitivity and specificity; however, overall discrimination by AROC for undiagnosed diabetes is similar. Risk scores that identify patients at high risk for diabetes using data available in routine clinical practice may help improve case identification. Strong arguments can be made that we may not need to screen more, we just need to screen smarter.

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