Prediabetes: Pre- Does Not Mean Preordained

Up to 70% of people with prediabetes eventually go on to develop type 2 diabetes. But dietary changes and increased physical activity can slow or even prevent progression to full-fledged diabetes.

By Jack McCain

Although the number of U.S. adults diagnosed with diabetes has decreased in recent years, about 1.4 million new cases of diabetes were diagnosed in Americans aged 18 to 79 in 2014, and that number remains near historic highs. But the prevalence of diagnosed diabetes in the United States is dwarfed by the prevalence of undiagnosed diabetes and prediabetes (Figure 1). As of 2012, about 21 million Americans had diagnosed diabetes. More than 4 times as many—86 million—had prediabetes and an additional 8 million had diabetes that hadn't been diagnosed (CDC 2014).

Prediabetes is an intermediate stage between normal, healthy glucose tolerance and the more severe glucose intolerance that characterizes type 2 diabetes. Without appropriate lifestyle interventions, about 15% to 30% of U.S. adults with prediabetes will go on to develop full-fledged type 2 diabetes within 5 years; on an annual basis, 11% of prediabetic adults who fail to improve their diet and increase their physical activity will develop type 2 diabetes (CDC 2013).

Prediabetes encompasses impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. It can also be defined with the results from a glycated hemoglobin (HbA1c) test: prediabetes is 5.7% to 6.4% and diabetes is 6.5% or higher (Table 1). Prediabetes does not always lead to type 2 diabetes, although a majority of people with prediabetes—up to 70%—eventually progress to type 2 diabetes. Over the short term (3 to 5 years), about 25% of people with IFG or IGT progress to diabetes, 25% revert to normal glucose tolerance, and 50% remain in the IFG or IGT category (Nathan 2007).

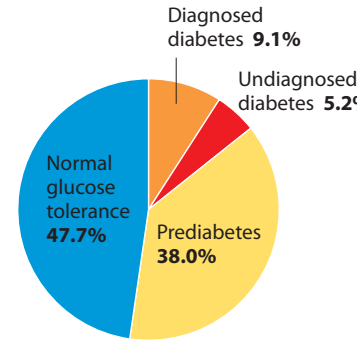
Prediabetes that does not progress to diabetes is associated with a modestly increased risk for cardiovascular disease (HR, ~1.1–1.4). But the main reason to be concerned about prediabetes is the risk of it developing into diabetes. Among those who develop type 2 diabetes, the risk for cardiovascular disease doubles or even quadruples compared with those in the prediabetes category (Nathan 2007). Furthermore, microvascular complications (retinopathy, neuropathy) that develop subclinically while someone is in the prediabetes phase may become more serious and start producing symptoms by the time type 2 diabetes is diagnosed.

In addition to reducing morbidity and mortality and improving patients' quality of life, an economic argument can be advanced for identifying and treating people with prediabetes, given the prevalence of type 2 diabetes and the high cost of treating episodes of its macrovascular and microvascular complications (Figure 2). In 2012, medical costs associated with diabetes and prediabetes amounted to $244 billion, but medical costs associated only with prediabetes accounted for just 18% of that amount (Figure 3) (Dall 2014).

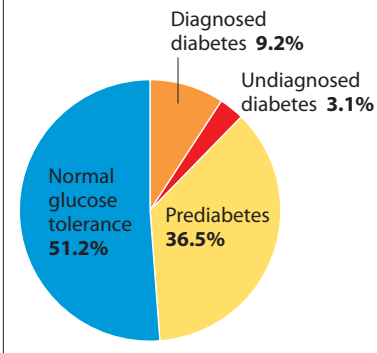
On the other hand, the prediabetes label may cause undue alarm if physicians and other clinicians fail to help patients understand that prediabetes does not necessarily lead to diabetes. Only in rare cases is treatment with medication warranted, and people can have a positive influence on their

FIGURE 1
Distribution of defects in glucose metabolism in the U.S., 2011–2012

Panel A
HbA1c, FPG, or 2-hr PG



Panel B
HbA1c or FPG



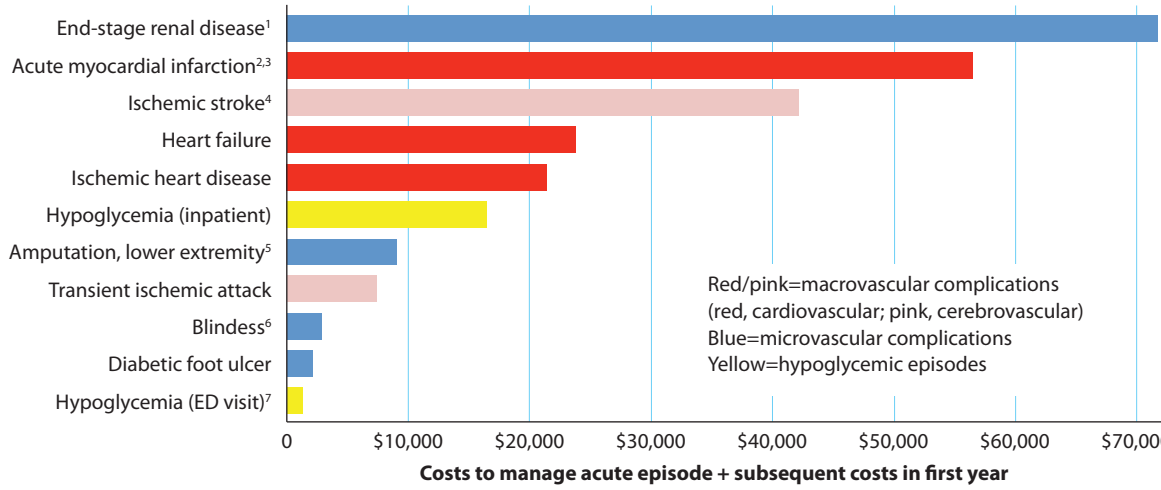
When glucose values are assessed by glycated hemoglobin, fasting plasma glucose, or 2-hour plasma glucose tests, 14.3%* of adults aged ≥20 years in the U.S. general population are found to have diabetes. When only HbA1c and fasting plasma glucose tests are used, the proportion with diabetes is slightly lower, 12.3%*. By both sets of measures, only about half the adult population has normal glucose values and more than one third has prediabetes.

Source: Menke 2015

* Includes diagnosed and estimated undiagnosed populations. FPG=fasting plasma glucose, PG=plasma glucose.

FIGURE 2

Estimated event-year costs per patient of diabetes complications



The estimated cost of diagnosed diabetes in the United States in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in indirect costs. The complications depicted above are ranked by the cost of managing an acute episode and its subsequent costs in the first year. Among the many other complications that people with diabetes may develop are neuropathy, nonalcoholic fatty liver disease, periodontal disease, hearing loss, erectile dysfunction, and depression.

[1]In 2011, 228,924 people with kidney failure from diabetes depended on chronic dialysis or a kidney transplant. In the same year, diabetes was listed as the primary cause of kidney failure in 44% of all new cases.

[2]Hospitalization rates for AMI in 2010 were 1.8 times higher among adults aged ≥20 years with diagnosed diabetes than among adults without diagnosed diabetes.

[3]Cardiovascular disease death rates in 2003–2006 were 1.7 times higher among adults aged ≥18 years with diagnosed diabetes than among adults without diagnosed diabetes.

[4]Hospitalization rates for stroke in 2010 were 1.5 times higher among adults aged ≥20 years with diagnosed diabetes than among adults without diagnosed diabetes.

[5]About 73,000 nontraumatic lower-limb amputations were performed in 2010 in adults aged ≥20 years with diagnosed diabetes.

[6]Among adults ≥40 years with diagnosed diabetes in 2005–2008, 4.2 million (28%) had diabetic retinopathy.

[7]About 282,000 ED visits in 2011 were for adults aged ≥18 years with hypoglycemia as the first-listed diagnosis and diabetes as another diagnosis.

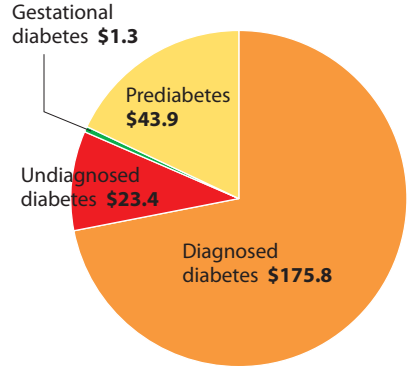
SOURCES: CDC 2014, Ward 2014

FIGURE 3

U.S. medical costs ($ billions) associated with diabetes and prediabetes, 2012

Prediabetes accounted for 18% of the $244 billion in U.S. medical costs from diabetes and related conditions in 2012. If nonmedical costs associated with diagnosed and undiagnosed diabetes are included, total 2012 costs were $322 billion. Annual medical costs per case in 2012 amounted to $10,970 for patients with diagnosed diabetes; undiagnosed diabetes, $4,030; and prediabetes, $510.

Source: Dall 2014



chances of progressing to diabetes by improving their diets and becoming more physically active. In the wrong circumstance, categorizing people as having prediabetes could lead to overtreatment and added expense.

Screening and diagnosis

The American Diabetes Association (ADA) recommends glucose screening for all adults aged 45 years and for adults of any age who are overweight or obese and have additional risk factors (Table 2).

In a 2015 update of its 2008 recommendation, the United States Preventive Services Task Force (USPSTF)

TABLE 1
Screening and diagnostic tests for prediabetes and diabetes

Test	Test values			Advantages	Disadvantages
	Normal	Prediabetes[1]	Diabetes		
Fasting plasma glucose	<100 mg/dL	100–125 mg/dL (impaired fasting glucose)	≥126 mg/dL	• More convenient for patients than OGTT • Less costly than OGTT	• Requires fasting ≥8 hours • Subject to day-to-day within-patient variability • Acute illness or stress may increase glucose levels • Unstable at room temperature
Oral glucose tolerance	<140 mg/dL	140–199 mg/dL (impaired glucose tolerance)	≥200 mg/dL over 2 hours		• Requires fasting ≥ 8 hours • Requires 2 hours between blood draws • Subject to day-to-day within-patient variability • Acute illness or stress may increase glucose levels
HbA1c	<5.7%	5.7–6.4%	≥6.5%	• More convenient than glucose tests (no fasting, no timed measurements) • Not subject to day-to-day within-patient variability • Provides retrospective view of last 2–3 months of glucose level	• Severe illness may reduce life of red blood cells, resulting in value below true level

[1]Risk for diabetes can extend below the ranges listed. Within the ranges, risk increases in curvilinear fashion, such that the risk predicted when test results are in the high end of the range is considerably higher than the risk predicted by results in its low end.

Sources: ADA 2016a, ADA 2016b, Siu 2015

recommended screening asymptomatic nonpregnant adults, ages 40 to 70, for glucose abnormalities and type 2 diabetes if their body-mass index (BMI) is 25 or greater (Siu 2015). The task force previously recommended screening asymptomatic adults for diabetes if they had sustained blood pressure >135/80 mmHg (treated or untreated) (Selph 2015b).

The ADA today recognizes three blood tests to screen for and diagnose prediabetes and diabetes: the oral glucose tolerance test (OGTT), which is also known as the 2-hour plasma glucose test; fasting plasma glucose (FPG); and HbA1c (Table 1). The FPG test measures the amount of plasma glucose after a fast of at least 8 hours. The OGTT begins with an FPG test, after which the patient ingests 75 g of glucose, which stimulates insulin secretion; plasma glucose is measured 2 hours after the glucose is swallowed. The HbA1c test measures the percentage of hemoglobin A (the predominant form of hemoglobin)

TABLE 2
Screening for prediabetes and diabetes: Current ADA and USPSTF recommendations

	ADA (ADA 2016a, ADA 2016b)	**USPSTF** (Siu 2015)
Target population	• Asymptomatic adults of any age who are overweight or obese (BMI ≥25; ≥23 for Asian-Americans) and have additional risk factors[1] • All adults age ≥45	• Adults aged 40–70 years who are overweight or obese
Screening interval	• Every 3 years (minimum) if tests are normal • Annually if patient has prediabetes or elevated risk	• Every 3 years if initial test normal
Confirmation of diagnosis	• Repeat same test without delay (with new blood sample) • If different test is used and both results are above diagnostic threshold, diagnosis is confirmed • If different test is used and results are discordant, the test whose result is above the diagnostic threshold should be repeated	• Repeat with same test on different day
Interventions	• Intensive counseling on diet and physical activity • Metformin to be considered for patients with BMI >35, age <60 years, or history of gestational diabetes	• Repeated counseling on diet and physical activity

[1]Risk factors: prior test showing HbA1c ≥5.7%, IFG, or IGT; physical inactivity; first-degree relative with diabetes; belonging to race or ethnic group with high risk for diabetes; blood pressure ≥140/90 mmHg; current therapy for hypertension; HDL-cholesterol <35 mg/dL; triglyceride level >250 mg/dL; history of cardiovascular disease; diagnosis of gestational diabetes; delivery of baby >9 lb.

TABLE 3
Differences in metabolic abnormalities in IFG and IGT

	Impaired fasting glucose (IFG)	Impaired glucose tolerance (IGT)
Insulin resistance, hepatic	Severe	Modest
Insulin resistance, skeletal muscle	Normal or near normal	Severe
Beta-cell insulin secretion, first phase	Severe impairment	Severe impairment
Beta-cell insulin secretion, second phase	Near normal	Severe impairment

Source: Kanat 2012

to which glucose has bound, forming glycated hemoglobin. Once formed, HbA1c persists in a red blood cell until the cell dies. Because red blood cells live about 2 or 3 months, measuring the percentage of HbA1c provides a long-term picture of glycemic levels, in contrast to snapshots provided by glucose tests taken on a single day. These tests should not be regarded as just different ways to measure the same phenomenon, however.

The ADA notes that each test is equally appropriate but that a given test may fail to detect diabetes or prediabetes in an individual (ADA 2016a). That can happen because the physiologic mechanisms underlying IFG and IGT are different. IFG is characterized by hepatic insulin resistance, while IGT is characterized by insulin resistance in skeletal muscle and greater beta-cell dysfunction (Table 3, Figure 4).

Interventions

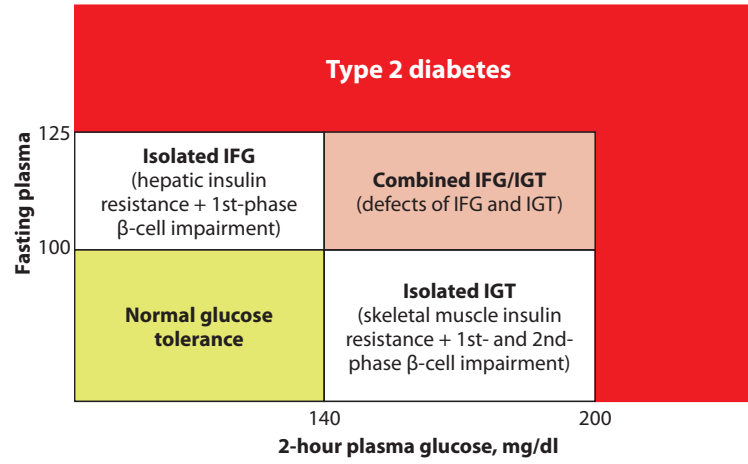
The goal for patients with prediabetes is to stave off progression to full-blown diabetes. The ADA recommends intensive counseling about diet and physical activity that aims for losing 7% of body weight. The term *physical activity* includes but is not restricted to structured exercise. For certain patients (BMI >35, age <60 years, history of gestational diabetes), metformin therapy also should be considered in addition to lifestyle modification (ADA 2016b).

The USPSTF found that a substantial body of evidence supports similar behavioral intervention because at-risk patients tend to have multiple risk factors. Eating healthy foods and becoming more physically active address elevated blood sugar, excessive weight, high blood pressure, and elevated lipid levels all at once, in contrast to drug treatment narrowly focused on individual risk factors (Siu 2015).

Research shows that lifestyle modifications modestly reduce the risk for CVD in populations with multiple risk factors such as excessive weight, hypertension, lipid disorders, and IFG or IGT. But in studies of patients with IFG or IGT, lifestyle interventions were found to decrease the risk of progression to diabetes by 45% (pooled RR, 0.55; CI, 0.43–0.70) (Selph 2015a). The USPSTF notes that while metformin and other drugs are effective in reducing progression to diabetes in patients with glucose abnormalities, lifestyle modifications (dietary changes and increased physical activity) are more effective.

Yet in its review, the USPSTF found little evidence from randomized controlled trials (RCTs) showing that treating IFG, IGT, or diabetes detected via screening results in mor-

FIGURE 4
Glucose defects in IFG, IGT by current ADA definitions



Impaired fasting glucose (IFG) initially was defined, in 1997, as fasting plasma glucose (FPG) ≥110 mg/dL to 125 mg/dL. In 2003, the range was lowered to 100 mg/dL. In the fasting state, the rate of hepatic glucose production is the key factor determining the plasma glucose level; insulin-resistant hepatocytes release glucose into the bloodstream, resulting in elevated plasma glucose concentrations. Despite 2-hour glucose <140 mg/dL, patients with isolated IFG are at higher risk of progressing to diabetes, possibly because of diminished β-cell function.

Source: ADA 2016a, Abdul-Ghani 2008, Faerch 2016

tality benefits. The USPSTF said the best (and only) evidence available for such a benefit comes from a Chinese study in which 6 years of lifestyle intervention after 23 years of follow-up resulted in a 29% reduction in risk for all-cause mortality (HR, 0.71 [CI, 0.51–0.99]) and a 41% reduction in risk for cardiovascular mortality (HR, 0.59 [CI, 0.36–0.96]) compared with usual care (Selph 2015a). After 20 years of follow-up, however, no statistically significant difference in all-cause mortality and cardiovascular mortality had been observed. This study enrolled overweight adults (mean BMI, 25.8) with IGT. Neither was any mortality benefit found in similar trials with shorter follow-up than the Chinese study.

Trials of drug treatment—with or without lifestyle intervention—in people who are overweight or obese with IFG, IGT, or early diabetes have shown no mortality benefit and few differences in other health outcomes (Selph 2015a). For eight studies of glucose-lowering drugs, the pooled odds ratio for all-cause mortality was 1.1 (CI, 0.87–1.18); for cardiovascular mortality, 1.06 (CI, 0.84–1.35). Because of the high cost, large number of subjects, and lengthy follow-up required, it is doubtful that an RCT ever will be conducted to find out if there is a mortality benefit from screening for prediabetes.

The dearth of evidence from RCTs is offset to some extent by the substantial amount of evidence showing that lifestyle interventions can delay—and possibly prevent—prediabetes from worsening into diabetes. Moreover, there is little, if any chance, of harm from improved diets or greater physical activity. For these reasons, the USPSTF sees a moderate net benefit in screening for abnormal glucose metabolism.

Debate about definitions

Over the past 3 decades, the concept of prediabetes and the appropriate method for identifying it has been the subject of extensive debate and revision. The National Institute of Diabetes and Digestive and Kidney Diseases assembled a small group of diabetes experts in the late 1970s called National Diabetes Data Group (NDDG). In 1979, the NDDG defined diabetes in 3 ways: by the presence of classic symptoms, by FPG ≥140 mg/dL, or by 2-hour plasma glucose ≥200 mg/dL. At the same time the NDDG also introduced *impaired glucose tolerance* as an intermediate stage between normal glucose tolerance and diabetes. IGT was defined as FPG <140 mg/dL at the start of the OGTT and 2-hour plasma glucose ≥140 to 199 mg/dL. The OGTT was widely regarded as the gold standard for diagnosing diabetes.

An argument supporting the initial range defining IGT was that microvascular complications of diabetes were thought to be relatively rare within the range. In 1997, however, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus challenged this notion by citing studies of diabetic retinopathy in three populations: Pima Indians, Egyptians, and the general U.S. population. Those studies used OGTT, FPG, and HbA1c tests; retinopathy was determined via fundus photography or ophthalmoscopy. In all three populations, similar thresholds for 2-hour plasma glucose, FPG, and HbA1c were identified, below which the prevalence of retinopathy was low

Online risk calculators: Plug in your numbers

A number of free online calculators can help people learn about their prediabetes and diabetes risk. About 90% of American adults with prediabetes are unaware of their condition (CDC 2013). In an effort to correct that situation, the Ad Council, with sponsorship from the American Diabetes Association (ADA), the American Medical Association, and the CDC, recently launched a campaign of public service announcements and a website (DoIHavePrediabetes.org) with a calculator that helps people learn if they are at high risk for prediabetes and, if they are, to see a physician so that blood work can be done.

The risk factors for prediabetes are the same as those for diabetes, and the DoIHavePrediabetes calculator uses 7 of them: age ≥40 years, male sex, history of hypertension, history of gestational diabetes, physical inactivity, excessive weight, and family history of diabetes.

A different online calculator (www.framinghamheartstudy.org/risk-functions/diabetes), designed with data from the Framingham Offspring Study, allows people, ages 45 to 64, to assess their risk of developing diabetes in the next 8 years (Wilson 2007). The calculator's algorithm gives the greatest weight to IFG (10 points), BMI ≥30 (5 points), and low HDL-cholesterol (5 points). But IFG by itself leads to an 8-year risk of developing diabetes of 3% or less, according to this calculator. The more risk factors present in addition to IFG, the greater the risk of progression, and in the absence of risk factors other than IFG, the risk of progression can be low despite IFG. Most patients with IFG also have additional risk factors and, like IFG, these risk factors tend to be components of the metabolic syndrome, which are important for determining a person's risk of diabetes, along with cardiovascular disease.

A similar calculator (http://aricnews.net/DiabRisk/DiabRC1.html) is based on the Atherosclerosis Risk in Communities (ARIC) study and provides a 9-year risk estimate (Schmidt 2005).

and above which it was much higher. The FPG cutpoint in those studies was well below the 140 mg/dL level that triggered a diabetes diagnosis according to the 1979 NDDG definition. As a result, the committee recommended that diabetes be diagnosed at a lower FPG concentration, 126 mg/dL, and this recommendation was adopted by the ADA.

In addition, the committee recommended that *impaired fasting glucose*, defined as FPG ≥110 mg/dL to 125 mg/dL, be used to describe the intermediate state between normal glucose tolerance and diabetes. The ADA also adopted this recommendation. The previous conventions for OGTT and IGT stayed in place. The World Health Organization, which concurred with the 1979 definitions, went along with most of what the expert committee said in 1997 except for continuing to regard OGTT as the gold standard and recommending that it be used whenever feasible to make sure patients with IFG didn't have diabetes.

In 2003, the expert committee made a further adjustment, lowering the threshold for IFG from 110 mg/dL to 100 mg/dL so that IFG would be more comparable with IGT, from a numerical perspective, with respect to prevalence.

The most recent change, setting the current testing triad in place, came from a recommendation from a third group, the International Expert Committee (IEC), whose members were appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation. The IEC added HbA1c testing as a tool for diagnosing prediabetes and diabetes (IEC 2009), arguing that the correlation between HbA1c and retinopathy was stronger than the correlation between FPG and retinopathy, and that a measure that captures long-term glucose levels is superior to the measure of a single point. In 1997, the Expert Committee had cited the lack of assay standardization as a reason for not adopting HbA1c as a diagnostic tool. Although this objection had been overcome by 2003, the expert committee still recommended against using HbA1c to diagnose diabetes. The ADA adopted the IEC recommendation, however, and added HbA1c testing to its 2010 standards of medical care (ADA 2010), with HbA1c ≥6.5% designating diabetes and with HbA1c in the range of 5.7% to 6.4% identified as prediabetes.

In its 2009 report, the IEC went beyond simply endorsing HbA1c testing, however. It rejected the notion that any test is the gold standard, with respect to microvascular and macrovascular complications of diabetes and took issue with the concepts of prediabetes, IFG, and IGT:

> While there appears to be an approximate glycemic threshold above which the risk for retinopathy escalates, there does not appear to be a specific level at which risk for diabetes clearly begins. A continuum of risk for the development of diabetes across a wide range of subdiabetic A1c levels may make the classification of individuals into categories similar to IFG and IGT equally problematic for A1c, as it implies that we actually know where risk begins or becomes clinically important. The continuum of risk in the subdiabetic glycemic range argues for the elimination of dichotomous subdiabetic classifications, such as "pre-diabetes," IFG, and IGT.

But the committee's prediction that, with the arrival of HbA1c testing, "the categorical clinical states prediabetes, IFG, and IGT ... will be phased out" has not yet happened (and neither has HbA1c testing replaced the fasting glucose test). As of 2016, these terms continue to be prominent in the ADA's annually revised standard of care for diabetes.

The takeaway

Determining whether a person has prediabetes could be a starting point for helping patients to adopt a healthier lifestyle, but an assessment of the person's risk for progressing to type 2 diabetes requires identifying the many other risk factors at play. A great advantage of the recommended intervention, lifestyle modification, for prediabetes is that it presents little or no drawbacks while addressing multiple risk factors—not just glucose levels but also high blood pressure, high triglycerides, low HDL-cholesterol, and excess weight, all of which are also risk factors for cardiovascular disease. Furthermore, improvements in diet and physical activity provide many benefits not easily captured by data entered into a medical record but which are commonly recognized by people who pursue such changes.

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