Using a Quantitative Measure of Diabetes Risk in Clinical Practice to Target and Maximize Diabetes Prevention Interventions

Paul A. Rich, MD, Charles F. Shaefer, MD, FACP, Christopher G. Parkin, MS, and Steven V. Edelman, MD

An estimated 79 million American adults are at risk for developing type 2 diabetes, based on a condition referred to as prediabetes.[1] Although there is currently no cure for type 2 diabetes, studies have definitively shown that the progression from prediabetes to diabetes can be delayed or prevented through lifestyle modifications and pharmacological treatment.[2–4] Unfortunately, the vast majority of people with prediabetes are undiagnosed. Indeed, a recent study by Geiss et al.[5] found that < 8% of U.S. adults with prediabetes are aware of their condition.

Given the growing diabetes epidemic and the alarming prevalence of unawareness among those at risk for developing this disease, the American Diabetes Association (ADA) recommends screening of all patients who are at risk for prediabetes or who may have undiagnosed diabetes (Table 1).[6]

Individuals meeting the criteria in Table 1 should have their glycemic status assessed by fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or A1C. As shown in Table 2, the diagnosis of prediabetes is based on glucose or A1C values that are higher than normal but not at levels diagnostic of diabetes.[6]

According to ADA recommendations, individuals who are identified as having prediabetes should be referred to an ongoing support program that targets weight loss and increased physical activity, and these programs should be covered by third-party payers.[6] The ADA further recommends that treatment with metformin be considered for at-risk patients who have a BMI ≥ 35 kg/m^2, are < 60 years of age, and/or are women with prior gestational diabetes.[6]

Given the significant clinical and economic costs associated with type 2 diabetes, it is crucial that diabetes prevention be a priority for the health care system. However, it is also important to consider that a relatively small percentage of individuals who have prediabetes will progress to overt type 2 diabetes within 5 years. The 5-year conversion rate from prediabetes to type 2 diabetes ranges from 10%[7] to 23%[8] depending on the diagnostic criteria used.

Because considerable resources are required to provide diabetes prevention programs to the ever-

Table 1. Criteria for Testing Adult Patients for Prediabetes or Diabetes[6]

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m^2*) and who have one or more of the following additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, or Pacific Islander)
   - Women who delivered a baby weighing ≥ 9 lb or who were diagnosed with gestational diabetes
   - Hypertension (blood pressure ≥ 140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level > 35 mg/dl and/or a triglyceride level > 250 mg/dl
   - Women with polcystic ovarian syndrome
   - A1C ≥ 5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity or acanthosis nigricans)
   - History of cardiovascular disease
2. In the absence of the above criteria, testing for diabetes should begin at 45 years of age.
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

**At-risk BMI may be lower in some ethnic groups.*

Table 2. Criteria for Diagnosis of Prediabetes or Diabetes[6]

Measure	Normal	Prediabetes*	Diabetes
FPG (mg/dl)	< 100	100–125 (IFG)	≥ 126
2-hour plasma glucose 75-g OGTT (mg/dl)	< 140	140–199 (IGT)	≥ 200
A1C (%)	< 5.7	5.7–6.4	≥ 6.5

**For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.*

increasing number of patients with prediabetes, accurate tools are needed to identify prediabetic individuals who are most likely to progress to type 2 diabetes. This should allow for more efficient and effective use of health care resources and optimize health care outcomes.

This article discusses the clinical application of a validated prognostic test (PreDx, Tethys Bioscience, Inc., Emeryville, Calif.) that provides clinicians with an estimate of the 5-year likelihood of progression to type 2 diabetes for patients who have been identified through screening as having prediabetes.[9–12] Patient cases are presented to demonstrate how the PreDx test can be used within various clinical scenarios to facilitate implementation of diabetes prevention therapies (lifestyle-based and pharmacological) and then monitor the effectiveness of those interventions.

Barriers to Diabetes Prevention

Although efforts have been made to address the significant and growing epidemic of diabetes, strategies to activate clinicians to aggressively screen for and treat individuals with prediabetes have been minimally successful. We have identified two major obstacles to these diabetes prevention efforts: *1*) limitations of current assessment tools and *2*) constraints on clinicians' time and resources.

Limitations of current prediabetes assessment tools

Screening for prediabetes is the essential first step in diabetes prevention, and although current tools and assessment protocols are relatively effective for the initial identification of at-risk individuals, they do not adequately address the need to identify individuals who are at the highest risk for progressing to diabetes in the near term. These tools and approaches are either difficult to implement in clinical practice or lack the specificity required for accurate detection of high-risk individuals.

The OGTT is a specific indicator of diabetes risk and is considered to be the gold standard for detection of prediabetes.[13] However, its complexity, poor reproducibility, associated costs, time requirements, and patient inconvenience often inhibit routine use in clinical practice.[6,14,15] The OGTT is rarely performed for purposes other than clinical research and to assess glycemia status in women during pregnancy.

A fasting plasma glucose test to assess for impaired fasting glucose (IFG) can be performed easily in most clinical settings. However, this method of screening for prediabetes casts a very wide net, identifying ~ 26% of the adult population as at risk (prediabetes),[16] with minimal stratification for level of risk of progressing to type 2 diabetes.

Furthermore, although A1C testing has recently been added to the armamentarium of prediabetes detection options,[6] use of A1C levels often fails to identify most adults with prediabetes.[17–19] A recent study by Fajans et al.[17] found that ~ 33% of individuals with early diabetes or impaired glucose tolerance (IGT) have A1C levels < 5.7%. Moreover, there is growing evidence questioning the reliability of the A1C test. Many factors can influence glycation and, thus, the test's accuracy.[17,20] These include weaknesses in analytical methods, ethnicity, and various medical conditions such as presence of hemoglobinopathies, iron deficiency, any type of anemia, chronic liver disease, and fast or slow glycation.[20]

Other methods, such as measuring components of the metabolic syndrome or calculating risk scores based on clinical measures (e.g., lipid levels, blood pressure, and waist circumference), have also been used to identify patients most likely to develop diabetes.[21] However, these approaches require multiple measures and also suffer from low specificity.[8,22]

Limitations of treatment approaches

Lifestyle interventions such as dietary modification, physical exercise, and modest weight loss have been shown to prevent or delay the progression from prediabetes to frank type 2 diabetes.[2,23,24] Because these interventions often involve significant changes in eating habits and physical activity, patients need initial counseling to help them understand the changes they are being asked to make, as well as ongoing support and encouragement from their health care providers to sustain those new behaviors.

Unfortunately, many patients do not receive the level of care they need to make and sustain these changes; barely half of patients receive the preventive, chronic disease, and acute care services recommended by

national health care organizations and agencies.[25]

A key contributor to this suboptimal care is lack of physician time.[26,27] Yarnell et al.[27] determined that clinicians would require 21.7 hours/day to effectively meet the needs of a typical patient population of 2,500. Looking specifically at diabetes prevention interventions used in the Diabetes Prevention Program,[2] it is noteworthy that these interventions required ~ 75% of staff time to treat the 25% of patients randomized to the intensive lifestyle intervention group.

Pharmacological treatment with metformin has also been shown to delay or prevent progression to diabetes. However, treatment with metformin in elderly patients has shown limited effectiveness.[28] Furthermore, use of metformin is not approved by the U.S. Food and Drug Administration (FDA) in individuals with prediabetes,[29] and many clinicians are reluctant to prescribe this medication without strong evidence for its necessity.

Given the growing, worldwide diabetes epidemic, there is an ever-increasing need for new testing methodologies that can accurately diagnose individuals who have the highest likelihood of developing diabetes and that can support both clinicians and patients in initiating and sustaining effective prevention strategies. The PreDx test is a relatively new prognostic blood test that may help clinicians address these issues.

PreDx Test

The PreDx test is a multimarker blood test that can be used in primary care practices to help determine the 5-year likelihood of a patient progressing from prediabetes to type 2 diabetes.[9] Early detection of these highest-risk individuals may facilitate more effective patient management by enabling clinicians to focus health care resources earlier and to more effectively initiate and monitor diabetes prevention interventions.

The multimarker PreDx test is based on seven biomarkers (glucose, A1C, insulin, C-reactive protein, ferritin, interleukin-2 receptor α, and adiponectin) that are independently associated with diabetes risk.[22] The test measures these markers in a fasting blood sample, and its results, along with patients' sex and age, are placed into an algorithm that generates an objective and quantitative score to distinguish among people at high, moderate, and low 5-year probability of developing type 2 diabetes.[10–12] This information enables clinicians to focus interventions on the relatively few patients who are genuinely at a high 5-year risk of developing diabetes, thus avoiding unnecessary treatment and expenses for patients who are less likely to develop diabetes within the next 5 years.

A study by Kolberg et al.[10] demonstrated that the performance characteristics of the PreDx test were similar to those of the OGTT but superior to all other methodologies, including FPG, A1C, fasting insulin, and the HOMA-IR (homeostasis model of assessment—insulin resistance) for predicting the 5-year likelihood of type 2 diabetes. The PreDx test was also found to be superior to metabolic syndrome components and clinical risk scores for detection of near-term conversion to diabetes.[9,11] Furthermore, unlike the OGTT, the PreDx test requires only a single blood draw and does not involve monitoring patients over a 2-hour time period.

In a recent analysis of the European Diabetes Prevention Study, Tuomilehto et al.[30] demonstrated that the test not only identifies those who are most likely to develop diabetes, but also facilitates monitoring the efficacy of therapeutic interventions through follow-up testing, thus enabling clinicians to modify the intervention if the PreDx test indicates that it has not been successful.

The PreDx test report (Figure 1) provides a single numerical score from < 1 to 9.9 (lowest to highest risk) that indicates each patient's likelihood of progressing to type 2 diabetes within the next 5 years. On the first page, the PreDx score, which is categorized as "low" (green), "moderate" (yellow), or "high" (red), is presented, as is the patient's absolute 5-year diabetes risk (%). The patient's risk relative to the general population is also provided. For example, a score of 5.8 corresponds to a 4.6% 5-year risk of developing type 2 diabetes, which represents a 1.4-fold increase in risk compared to the 5-year risk in the general population (3.4%).[9] The second page of the report provides results and reference ranges of the individual biomarkers used to determine the PreDx score.

Because the PreDx test requires a simple fasting blood draw using standard sample collection and handling procedures, it is relatively easy to incorporate into routine clinical practice. However, cost-effectiveness is also an important factor when considering adoption of new diagnostic technology. In a recent health economic analysis by Sullivan et al.,[31] use of the PreDx test in combination with fasting glucose measurement showed an incremental cost-effectiveness ratio (ICER) of $17,000 per quality-adjusted life year (QALY) gained at 5 years and produced a cost savings at 10 years. Without using the PreDx test, detection of high-risk patients based only on FPG resulted in an ICER of $235,000 per QALY gained at 5 years and $94,600 per QALY gained at 10 years. Based on this analysis,

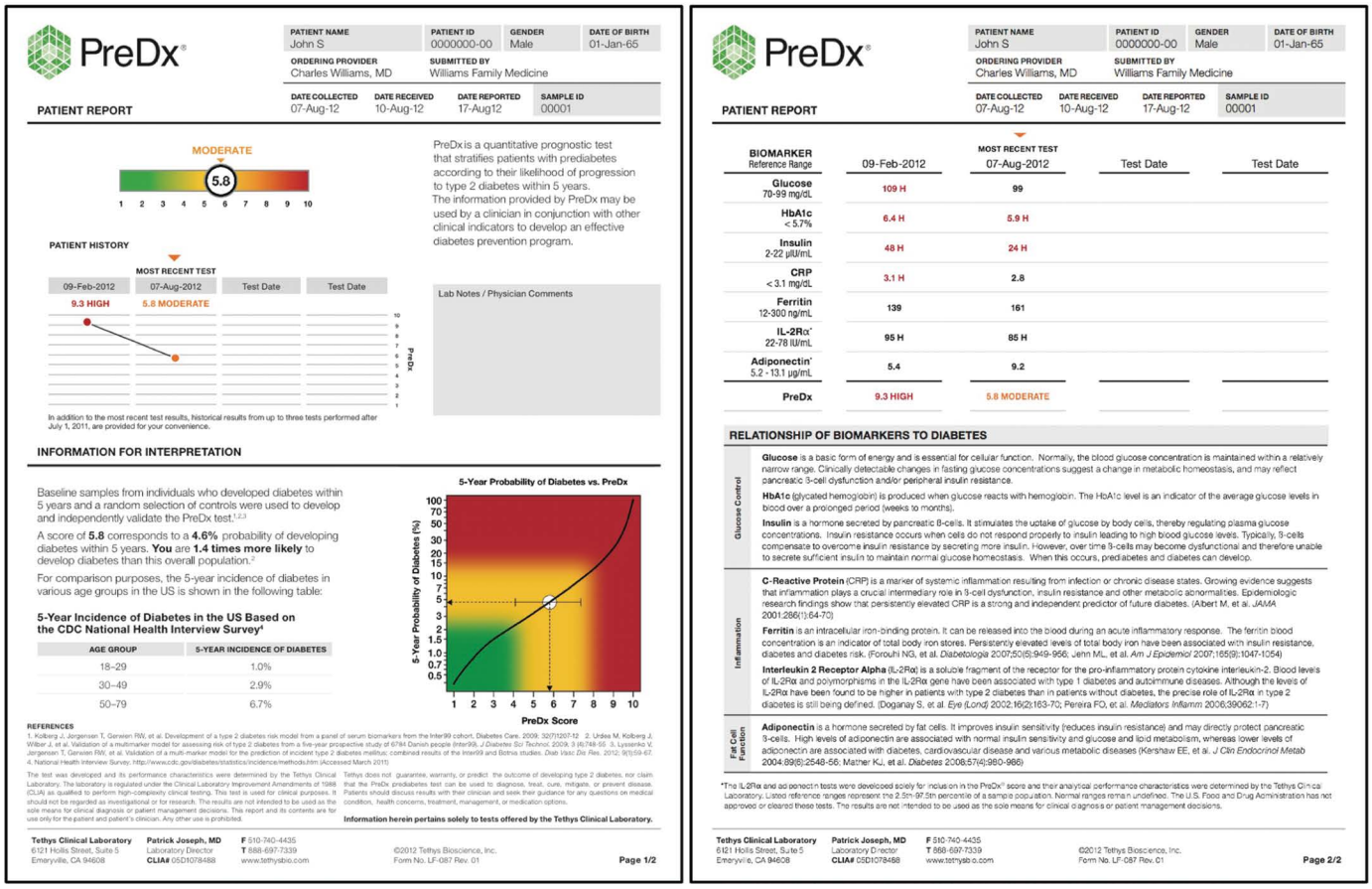

Figure 1. Sample of the PreDx test report form. The test report provides the PreDx score, as well as the corresponding absolute and relative 5-year likelihood of progression to type 2 diabetes. The individual analytes that are used to calculate the PreDx score and their reference ranges are also provided.

the authors concluded that the cost-effectiveness of diabetes prevention may be improved by identification of high-risk individuals using the PreDx test.

Clinical Experience

The clinical utility of the PreDx test is twofold: *1*) to stratify patients with prediabetes according to their 5-year likelihood of developing type 2 diabetes and *2*) to monitor and quantify the impact of lifestyle and/or pharmacological interventions. A key advantage of the PreDx test is its potential to motivate patients to make necessary lifestyle modifications to reduce their risk.

Many clinicians have reported that use of the PreDx test has motivated their highest-risk patients to make significant lifestyle changes that could delay or prevent the progression to type 2 diabetes.[22] Albeit anecdotal, these clinician-reported changes in patient motivation are supported by a recent study by Markowitz et al.[32] that looked at how genetic testing for diabetes risk affects motivation. Most study participants reported that "higher" risk results would prompt them to modify their health behaviors.

Other studies have shown that presenting A1C results to patients in graphic formats is linked to improved glycemic control.[33,34] These studies suggest that providing patients with an objective measure of risk can be an effective motivator for making lifestyle changes.

There is also growing evidence that use of the PreDx test positively affects clinician behaviors, prompting more intensive management of high-risk patients. A retrospective study[35] using comprehensive electronic medical records from a health care system treating ~ 3.2 million patients found that those who received the PreDx test were more likely to have follow-up monitoring of biometric risk factors by a physician than patients who did not receive the test. In addition, patients with high PreDx scores were more intensively treated for risk factor control than those with lower PreDx scores or no test. Moreover, there was significant improvement in risk factors for patients who received the PreDx test.

Using the PreDx test in our own practices, we have observed similar findings with many of our patients. The following case studies are representative of our experiences.

Case 1: J.N.

J.N. is a 62-year-old white man who is, 6'1" tall and has a family history of coronary artery disease (CAD) and hypertension but no history of type 2 diabetes. In 2001, he was surgically treated for CAD and is currently taking medication for dyslipidemia and hypertension. J.N. is a nonsmoker and drinks alcohol occasionally.

Previous efforts to encourage J.N. to make lifestyle changes to reduce his cardiovascular risk have been unsuccessful. He continues to eat an unhealthy diet (high in calories and saturated fat) and remains sedentary with no formal exercise program.

J.N. was seen in the clinic for an annual physical exam in November 2010 (Table 3). Although his FPG was only slightly elevated, the PreDx score indicated that J.N. was at very high risk for developing type 2 diabetes within the next 5 years (PreDx score 8.5, 5-year diabetes risk of 16.5%).

We adjusted his lipid and blood pressure medication doses based on his elevated LDL cholesterol and blood pressure, counseled J.N. on the need for lifestyle changes, and referred him to a formal diabetes prevention program at a local hospital. Although J.N. elected not to participate in a formal program, he initiated a diet and exercise routine consisting of cycling ~ 10 miles daily and eating a reduced-calorie diet that was high in fiber and low in saturated fat.

At his next annual exam (March 2012), his blood pressure, fasting glucose, and lipid levels were improved, and his PreDx score was significantly lower (PreDx score 4.5). This reduced his 5-year diabetes risk from a baseline of 16.5% to 2.8%—less than half of the 5-year risk of the general population within his age-group (6.7%).[4]

Table 3. Physical Assessment and Laboratory Values, Case 1

Physical/Laboratory Findings	November 2010	March 2012
Weight (lb)	208	200
BMI (kg/m^2)	28	28
Blood pressure (mmHg)	148/92	110/76
A1C (%)	5.4	5.1
FPG (mg/dl)	103	95
Total cholesterol (mg/dl)	152	109
LDL cholesterol (mg/dl)	91	46
HDL cholesterol (mg/dl)	40	41
Triglycerides (mg/dl)	103	78
PreDx diabetes risk score	**8.5**	**4.5**
Absolute 5-year diabetes likelihood (%)	**16.5**	**2.8**

Table 4. Physical Assessment and Laboratory Values, Case 2

Physical/Laboratory Findings	March 2011	September 2011	March 2012
Weight (lb)	263	193	198
BMI (kg/m^2)	37	27	27
Blood pressure (mmHg)	142/82	110/76	124/76
A1C (%)	5.3	5.1	5.1
FPG (mg/dl)	105	98	101
Total cholesterol (mg/dl)	256	153	—
LDL cholesterol (mg/dl)	188	63	—
HDL cholesterol (mg/dl)	45	62	—
Triglycerides (mg/dl)	115	63	—
PreDx diabetes risk score	**9.2**	**7.0**	**8.0**
Absolute 5-year diabetes likelihood (%)	**28.6**	**7.5**	**12.2**

Case 2: J.W.

J.W. is a 71-year-old white man who is 5'10" tall and has a history of hypertension, hyperlipidemia, obesity, and IFG dating back to 2008. He is a nonsmoker and has a family history of heart disease and diabetes.

When seen in March 2011, J.W. weighed 263 lb (BMI 37 kg/m^2) and had elevated blood pressure, lipid, and fasting glucose levels (Table 4). His PreDx score was 9.2, giving him an absolute 5-year risk for diabetes of 28.6%.

J.W. was counseled on the need to modify his diet, exercise regularly, and lose weight. When he returned for follow-up in September 2011, he had lost 70 lb, reduced his BMI to

27 kg/m^2, and significantly improved his blood pressure and lipid status. Although his PreDx score had decreased to 7.0, he was still at relatively high risk for developing diabetes despite the significant weight loss.

At his next follow-up visit in March 2012, J.W. had gained 5 lb and his FPG had risen to 101 mg/dl. His PreDx score had increased to 8.0, giving him a 12.2% 5-year diabetes risk. At that visit, we started J.W. on metformin (500 mg/day). Four months later, he had lost 1 lb, his FPG was < 100 mg/dl, and his PreDx score had dropped to 4.3, reducing his 5-year diabetes risk to 2.6%—less than half of the risk of the general population within his age-group (6.7%).[4]

Case 3: D.W.

D.W. is a 58-year-old white man who is 6'1" tall and has a history of hypertension, hyperlipidemia, obesity, arterial fibrillation, and IFG dating back to 2010. He is a nonsmoker and has a family history of CAD.

When seen in January 2012, D.W. weighed 281 lb (BMI 38 kg/m^2) and had normal blood pressure and elevated lipid and fasting glucose levels (Table 5). Despite his elevated FPG of 110 mg/dl, which placed him in the prediabetes glucoregulatory category, his PreDx score was 6.3. This gave him a 5-year diabetes risk of 5.6%.

Although D.W. was strongly counseled on the need to reduce his weight through diet modification and exercise to address his cardiovascular risk, we determined that prescribing a diabetes medication to help prevent diabetes was unwarranted at this time. We will continue to closely follow D.W. to help support his lifestyle modification efforts, and we will use fasting glucose and, if necessary, a follow-up PreDx test to monitor his glucoregulatory status and any changes in his diabetes risk.

Table 5. Physical Assessment and Laboratory Values, Case 3

Physical/Laboratory Findings	January 2012
Weight (lb)	281
BMI (kg/m^2)	38
Blood pressure (mmHg)	120/74
FPG (mg/dl)	110
A1C (%)	6.0
Total cholesterol (mg/dl)	181
LDL cholesterol (mg/dl)	118
HDL cholesterol (mg/dl)	40
Triglycerides (mg/dl)	174
PreDx diabetes risk score	**6.3**
Absolute 5-year diabetes likelihood (%)	**5.6**

Clinical Applications

The three patient cases presented in this article illustrate how the PreDx test can both motivate patients to make necessary lifestyle changes and guide treatment decisions regarding referral to formal diabetes prevention programs and/or pharmacological interventions. In the first case, the PreDx test prompted the patient to initiate intensive dietary modification and a regular exercise program to reduce his diabetes risk. As demonstrated in the second case, the PreDx test not only helped motivate the patient to lose a significant amount of weight but, on follow-up, it provided an indication that lifestyle changes were not effective enough and that pharmacological treatment with metformin was needed. The third patient case provides an example of how the PreDx test can help us more efficiently use resources. Reliance on the FPG value alone may have prompted us to initially prescribe a diabetes medication that could have potentially affected the patient's employment status and health care coverage and could have important side effects. Instead, we focused our attention on lifestyle intervention efforts and his other cardiovascular risk factors.

It is important to note that, although the three cases presented above illustrate the use of the PreDx test in white men, a recent analysis using blood samples from the Insulin Resistance and Atherosclerosis Study (a study in a multiethnic U.S. cohort) demonstrated that PreDx test performance characteristics were similar in whites, Hispanics, and African Americans and did not differ based on sex.[36] Many insurers currently provide reimbursement for the test; the reimbursement rate varies by payer.

To help clinicians effectively use the PreDx test in their practices, we have constructed a straightforward, four-step process to identify and implement diabetes prevention efforts in patients with prediabetes.

1. Screen for diabetes.

Use the screening criteria presented in Table 1 to identify and screen all patients who may be at risk for diabetes or prediabetes. Patients meeting the criteria in Table 1 should have their glucoregulatory status assessed using FPG, A1C, or OGTT. Although each method has advantages and disadvantages, all are adequate for assessing the presence of diabetes or prediabetes as defined by the ADA.[6] Table 2 presents the glycemic thresholds for diabetes and prediabetes.

2. In patients with prediabetes, stratify the likelihood of near-term progression to diabetes.

Use the PreDx test to assess the patient's 5-year likelihood of progressing from prediabetes to type 2 diabetes. As discussed above, the

PreDx test classifies patients as low, moderate, or high risk and provides an estimate of the 5-year likelihood of progressing to type 2 diabetes. Because all patients with prediabetes are at risk for macrovascular and potentially microvascular disease regardless of the PreDx score, clinicians must appropriately manage blood pressure, lipids, and body weight through lifestyle and/or pharmacological interventions.

Patients with normal glucose regulation or prediabetes should be re-screened for diabetes with one of the above-mentioned tests (Step 1) annually, or sooner if they develop symptoms of diabetes.

3. Initiate appropriate interventions. In patients with prediabetes, based on the PreDx test in conjunction with other clinical information, appropriate lifestyle and/or pharmacological interventions should be instituted. We know that lifestyle interventions such as weight loss and regular physical activity can prevent or delay the development of type 2 diabetes.[2] However, changing health habits is a difficult task for most patients. All patients with prediabetes, irrespective of their PreDx score, should receive counseling related to increased diabetes risk and the importance of good nutrition and physical activity for diabetes prevention and general health.

As deemed appropriate and based on the clinical picture and PreDx score, we recommend that patients be referred to a formal diabetes prevention program in their community where they can receive counseling and support from qualified health care providers. If a community program is not available or if the patient is unwilling or unable to participate in such a program, clinicians can provide lifestyle counseling and support during clinic visits. The National Diabetes Education Program (NDEP), in partnership with the National Institutes of Health, offers clinicians a comprehensive guide (G.A.M.E. P.L.A.N.) for diabetes prevention strategies and patient counseling. The guide can be downloaded free of charge from the NDEP Web site (http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=71). The National Diabetes Prevention Program also provides information and resources to clinicians and patients. These resources can be obtained from the Centers for Disease Control and Prevention at its Web site (http://www.cdc.gov/diabetes/prevention).

In addition to lifestyle changes, pharmacological interventions with metformin, thiazolidinediones, and α-glucosidase inhibitors have also been shown to be effective in slowing or preventing the progression to type 2 diabetes.[2–4] There are no medications approved by the FDA for treatment of prediabetes. However, if the risk:benefit profile for individual patients is deemed to be favorable, these medications may be considered for use in combination with lifestyle interventions or when behavioral interventions have failed.[6]

4. Monitor effectiveness of intervention. After initiating the above interventions, clinicians may then use the PreDx test quarterly or biannually to monitor treatment effectiveness, make any necessary adjustments to patients' treatment plan, and provide feedback to patients to sustain and enhance motivation and engagement in their diabetes prevention efforts.

Conclusion

The diabetic epidemic shows no signs of slowing. With an estimated 79 million American adults currently considered to be at risk for developing type 2 diabetes,[1] providing the necessary clinical and financial resources to deliver intensive preventive care to all of these individuals will be a difficult (if not impossible) task. Although it is clear that diabetes prevention should remain a high priority for patients, clinicians, and payers, it is also crucial that new technologies such as the PreDx test be used to accurately diagnose individuals who have the highest likelihood of developing diabetes in the near term to enhance the clinical efficacy of prevention efforts and ensure the viability of the national health care system.

ACKNOWLEDGMENTS

Funding for the development of this article was provided by Tethys Bioscience, Inc., of Emeryville, Calif., which developed the PreDx test.

REFERENCES

[1]Centers for Disease Control and Prevention: National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, Ga., U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011

[2]Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

[3]DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, Clement SC, Henry RR, Hodis HN, Kitabchi AE, Mack WJ, Mudaliar S, Ratner RE, Williams K, Stentz FB, Musi N, Reaven PD: Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 364:1104–1115, 2011

[4]Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet* 368:1096–1105, 2006

[5]Geiss LS, James C, Gregg EW, Albright A, Williamson DF, Cowie CC: Diabetes risk reduction behaviors among U.S. adults with prediabetes. *Am J Prev Med* 38:403–409, 2010

[6]American Diabetes Association: Standards of medical care in diabetes—2012. *Diabetes Care* 35:S11–S63, 2012

[7]Nichols GA, Hillier TA, Brown JB: Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes Care* 30:228–233, 2007

[8]Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA: Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 156:1070–1077, 2002

[9]Urdea M, Kolberg J, Wilber J, Gerwien R, Moler E, Rowe M, Jorgensen P, Hansen T, Pedersen O, Jorgensen T, Borch-Johnsen K: Validation of a multimarker model for assessing risk of type 2 diabetes from a five-year prospective study of 6784 Danish people (Inter99). *J Diabetes Sci Technol* 3:748–755, 2009

[10]Kolberg JA, Jorgensen T, Gerwien RW, Hamren S, McKenna MP, Moler E, Rowe MW, Urdea MS, Xu XM, Hansen T, Pedersen O, Borch-Johnsen K: Development of a type 2 diabetes risk model from a panel of serum biomarkers from the Inter99 cohort. *Diabetes Care* 32:1207–1212, 2009

[11]Lyssenko V, Jorgensen T, Gerwien RW, Hansen T, Rowe MW, McKenna MP, Kolberg J, Pedersen O, Borch-Johnsen K, Groop L: Validation of a multi-marker model for the prediction of incident type 2 diabetes mellitus: combined results of the Inter99 and Botnia studies. *Diab Vasc Dis Res* 9:59–67, 2012

[12]Shafizadeh TB, Moler EJ, Kolberg JA, Nguyen UT, Hansen T, Jorgensen T, Pedersen O, Borch-Johnsen K: Comparison of accuracy of diabetes risk score and components of the metabolic syndrome in assessing risk of incident type 2 diabetes in Inter99 cohort. *PLoS One* 6:e22863, 2011

[13]Geberhiwot T, Haddon A, Labib M: HbA1c predicts the likelihood of having impaired glucose tolerance in high-risk patients with normal fasting plasma glucose. *Ann Clin Biochem* 42:193–195, 2005

[14]Selvin E, Crainiceanu CM, Brancati FL, Coresh J: Short-term variability in measures of glycemia and implications for the classification of diabetes. *Arch Intern Med* 167:1545–1551, 2007

[15]Stern MP, Fatehi P, Williams K, Haffner SM: Predicting future cardiovascular disease. *Diabetes Care* 25:1851–1856, 2002

[16]Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW: Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population. *Diabetes Care* 29:1263–1268, 2006

[17]Fajans SS, Herman WH, Oral EA: Insufficient sensitivity of hemoglobin A1C determination in diagnosis or screening of early diabetic states. *Metabolism* 60:86–91, 2011

[18]James C, Bullard KM, Rolka DB, Rolka DB, Geiss LS, Williams DE, Cowie CC, Albright A, Gregg EW: Implications of alternative definitions of prediabetes for prevalence in U.S. adults. *Diabetes Care* 34:387–391, 2011

[19]Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS: Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. *Diabetes Care* 33:2184–2189, 2010

[20]Malkani S, Mordes JP: Implications of using hemoglobin A1C for diagnosing diabetes mellitus. *Am J Med* 124:395–401, 2011

[21]Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC: Harmonizing the metabolic syndrome. *Circulation* 120:1640–1645, 2009

[22]Kolberg JA, Gerwien RW, Watkins SM, Wuestehube LJ, Urdea M: Biomarkers in type 2 diabetes: improving risk stratification with the PreDx (R) Diabetes Risk Score. *Expert Rev Mol Diagn* 11:775–792, 2011

[23]Pan X-R, Li G-W, Hu Y-H, Wang J-X, Yang W-Y, An Z-X, Hu Z-X, Juan-L, Xiao J-Z, Cao H-B, Liu P-A, Jiang X-G, Jiang Y-Y, Wang J-P, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997

[24]Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001

[25]McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, Kerr EA: The quality of health care delivered to adults in the United States. *N Engl J Med* 348:2635–2645, 2003

[26]Blendon RJ, Schoen C, DesRoches CM, Osborn R, Zapert K, Raleigh E: Confronting competing demands to improve quality: a five-country hospital survey. *Health Aff (Millwood)* 23:119–135, 2004

[27]Yarnell K, Ostbye T, Krause K, Pollak K, Gradison M, Michener L: Family physicians as team leaders: "Time to share the care." *Prev Chronic Dis* 6:A59, 2009

[28]DPP Research Group: The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 61:1075–1081, 2006

[29]Bristol-Myers Squibb: Glucophage (metformin hydrochloride) package insert. Bristol-Myers Squibb Company, New York, 2009

[30]Tuomilehto J, Lindstrom J, White M, Penn L, Walker M, Mathers JC, den Boer ATH, Blaak EE, Gerwien RW, Kolberg JA, Rowe MW: Changes in a diabetes risk score due to intensive lifestyle intervention in the European Diabetes Prevention Study (EDIPS). Diabetes 60 (Suppl. 1):A366, 2011

[31]Sullivan SD, Garrison LP Jr, Rinde H, Kolberg J, Moler EJ: Cost-effectiveness of risk stratification for preventing type 2 diabetes using a multi-marker diabetes risk score. *J Med Econ* 14:609–616, 2011

[32]Markowitz SM, Park ER, Delahanty LM, O'Brien KE, Grant RW: Perceived impact of diabetes genetic risk testing among patients at high phenotypic risk for type 2 diabetes. *Diabetes Care* 34:568–573, 2011

[33]Chapin RB, Williams DC, Adair RF: Diabetes control improved when inner-city patients received graphic feedback about glycosylated hemoglobin levels. *J Gen Intern Med* 18:120–124, 2003

[34]Levetan CS, Dawn KR, Robbins DC, Ratner RE: Impact of computer-generated personalized goals on HbA(1c). *Diabetes Care* 25:2–8, 2002

[35]Conrad SE: A comparative study of the use of the PreDx® Diabetes Risk Score (DRS) in primary care: how are medical management and patient outcomes affected? Presented at the Fourth International Congress on Prediabetes and the Metabolic Syndrome, 6–9 April 2011, Madrid, Spain

[36]Rowe M, Bergman RN, Wagenknecht LE, Kolberg JA: Performance of a multi-marker diabetes risk score in the Insulin Resistance Atherosclerosis Study (IRAS), a multi-ethnic US cohort. *Diabetes Metab Res Rev.* 28:519–526, 2012

Paul A. Rich, MD, is a physician at Comprehensive Physician Associates, LLC, in Youngstown, Ohio. Charles F. Shaefer, MD, FACP, is a physician at University Physicians, Primary Care, in Augusta, Ga. Christopher G. Parkin, MS, is president of CGParkin Communications, Inc., in Boulder City, Nev. Steven V. Edelman, MD, is a professor of medicine at the University of Southern California, San Diego.

Note of disclosure: *The authors have received consulting fees from Tethys, Bioscience, Inc., which developed the PreDx test.*