

Diabetes in Urban African-Americans. XIX. Prediction of the Need for Pharmacological Therapy

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OBJECTIVE — To develop a prediction rule that will identify patients who will require pharmacological therapy within 6 months of first presentation to a diabetes clinic.

RESEARCH DESIGN AND METHODS — Among the patients who came to the Grady Diabetes Clinic between 1991 and 1997, we randomized 557 frequent attenders to a development group and 520 frequent attenders to a validation group. Using multiple logistical regression, we derived a prediction rule in the development group to project whether patients would require pharmacological intervention to achieve HbA_{1c} levels <7% after 6 months. The utility of the prediction rule was then confirmed in the validation group and tested prospectively on an additional group of 93 patients who presented from 1997 to 1998. Performance of the prediction rule was assessed using receiver operating characteristic (ROC) curves.

RESULTS — The rule ($-4.469 + 1.932 \times \text{sulfonylurea Rx} + 1.334 \times \text{insulin Rx} + 0.196 \times \text{duration} + 0.468 \times \text{fasting glucose}$, where "Rx" indicates a prescription) predicted the need for pharmacological intervention in the development group ($P < 0.0001$). Use of insulin or sulfonylurea therapy at presentation, duration of diabetes, and fasting glucose levels were significant predictors of the future need for pharmacological management. The prediction rule also performed well in the validation group (positive predictive value 90%, correlation between predicted and observed need for medical management 0.99). ROC curves confirmed the value of the prediction rule (area under the curves was 0.91 for the development group, 0.85 for the validation group, and 0.81 for the prospective group).

CONCLUSIONS — Early identification of individuals who will require pharmacological intervention to achieve national standards for glycemic control can be achieved with high probability, thus allowing for more efficient management of diabetes.

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To minimize the development and progression of diabetes complications, providers must achieve therapeutic goals as rapidly as possible. Patients with type 2 diabetes often exhibit complications at initial presentation (1–4) that result in considerable morbidity and a substantial financial burden (5,6). Data from the

Kumamoto Study suggest that a divergence in the incidence of microvascular complications between intensively and conventionally treated patients with type 2 diabetes occurs as early as 6 months after intensive therapy is begun (7). Therefore, appropriate therapy should be started quickly to optimize inadequate glycemic control (7).

Accordingly, early and accurate prediction of patients who will do well with diet alone or who will require pharmacological intervention may facilitate necessary therapeutic decisions and help reduce the morbidity that is directly attributable to diabetes.

The precedent for clinical prediction models is well established. Successful algorithms have been developed to predict outcomes such as in-hospital mortality associated with coronary bypass surgery (8), survival of patients with colorectal carcinoma (9), and the mortality of patients with sepsis (10). However, we are unaware of models that predict the need for pharmacological therapy to achieve good glucose control in type 2 diabetes. Such a model would be particularly useful for populations such as that at the Grady Health System Diabetes Clinic (GDC) (Atlanta, GA) where ~50% of obese patients who present taking insulin can be managed with diet alone after 12 months of care (11).

The development of a stable prediction algorithm requires a large and unbiased population with substantial records of personal and clinical characteristics. We developed the Grady Diabetes Patient Tracking System in 1991 to manage data collection on all patients new to the GDC since 15 April 1991; we now have records from more than 50,000 visits for more than 8,700 patients. For this study, we selected patient characteristics and laboratory results from our database that would be readily available to diabetes caregivers in most settings. We then developed a rule to identify patients who will require pharmacological therapy to achieve tight glycemic control after 6 months of treatment.

RESEARCH DESIGN AND METHODS

Setting

The study was conducted at the GDC. This outpatient facility provides care for ~950 new and ~5,000 returning patients each year. The population served is urban and economically disadvantaged (11), and the functional health literacy of many patients is

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Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; GDC, Grady Diabetes Clinic; OR, odds ratio; PPV, positive predictive value; ROC, receiver operating characteristic; Rx, prescription.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Baseline characteristics

	Development group	Validation group	Prospective group
<i>n</i>	557	520	93
Age (years)	57.9 ± 0.5	56.7 ± 0.5	52.6 ± 1.2
Duration of diabetes (years)	7.2 ± 0.4	6.5 ± 0.3	6.1 ± 0.9
Fasting plasma glucose (mmol/l)	10.7 ± 0.2	10.6 ± 0.2	9.9 ± 0.5
HbA _{1c} (%)	8.9 ± 0.1	8.8 ± 0.1	8.6 ± 0.3
Female/male	66/34	68/32	68/32
African-American	87	88	86
Taking sulfonylureas	37	37	52
Taking insulin	35	37	35

Data are *n*, means ± SEM, or %. Comparisons (development group vs. validation group) are by *t* test for continuous and χ^2 test for categorical variables. *P* > 0.05 for all cases.

inadequate to marginal (12). Diagnosis of type 2 diabetes is based on elevated blood glucose levels per the American Diabetes Association (ADA) standards in effect at the time and standard clinical criteria (11). At each visit, patients are examined initially by a nurse provider who continues or modifies management and subsequently by an endocrinologist who reviews and/or amends the care plan. Dietitians provide nutrition education. In accordance with ADA guidelines (13), our goal is to achieve HbA_{1c} levels <7.0%. If diet and exercise fail to achieve adequate glycemic control during the first 2 months after initial GDC presentation, then pharmacological therapy is added or intensified at subsequent visits. Clinical and laboratory data are routinely collected and stored prospectively in the Grady Diabetes Patient Tracking System and were used to develop the prediction equation.

Study design

We identified patients who made an initial visit to the GDC between 15 April 1991 and 20 April 1998 who had type 2 diabetes of known duration (by patient recall) of >2 months. Patients with initial visits before 1 January 1997 and who returned for at least 6 of the 7 scheduled visits during the first 6 months of clinic enrollment were then randomly divided into a development group (*n* = 557) and a validation group (*n* = 520) using the terminal digit of the medical record number.

Our outcome (need for pharmacological therapy) was defined as the inability to achieve HbA_{1c} levels <7% without pharmacological intervention. The prediction rule for this outcome was derived using the development group. The performance of this rule was then confirmed using the separate validation group. We subsequently

tested the rule prospectively using 93 patients who came to the GDC for a first visit between 1 January 1997 and 20 April 1998 regardless of the number of missed follow-up appointments. To evaluate the performance for patients with newly diagnosed diabetes, the rule was also tested on patients with a duration of diabetes <2 months (initial visit before 1 January 1997).

Statistics

Baseline characteristics were compared using *t* tests for continuous variables (age, duration, glucose, and HbA_{1c}) and χ^2 tests for nominal variables. For logistical regression, we tested independent variables that would be readily available to most practitioners.

Using the logistical regression equation, point estimates of the probability of need for pharmacological intervention were calculated for each patient. Using these point estimates, we created receiver operating characteristic (ROC) curves to assess the performance of the prediction rule. The area under the curve (AUC) was calculated using the nonparametric method. Performance of the prediction rule was also evaluated by correlating observed and predicted need for pharmacological therapy. StatView Version 5.0 (SAS Institute, Cary, NC) and SPSS Version 9.0 (Chicago) software were used for statistical analyses.

RESULTS — A total of 1,077 patients between 15 April 1991 and 31 December 1996 met the criteria for analysis; 557 subjects were randomized to the development group, and 520 subjects were randomized to the validation group. Baseline characteristics are outlined in Table 1. The mean age of the population was 57 years, two-thirds were female, almost 90% were African-

American, mean duration of diabetes was 6.9 years, and initial HbA_{1c} levels averaged 8.8%. No significant differences were evident between randomization groups at baseline (all *P* > 0.05).

Univariate analysis revealed that duration of diabetes, presence of sulfonylurea or insulin therapy at baseline, fasting plasma glucose, HbA_{1c}, total cholesterol, and C-peptide were all significantly associated with the need for pharmacological therapy after 6 months; however, none of these variables demonstrated adequate predictive power when studied individually. Other tested variables that were not significant included age, sex, race, BMI, blood pressure, serum creatinine, and urine microalbumin.

In the development group, 399 patients had sufficient data for multiple regression analysis. In the validation group, 379 patients had sufficient follow-up data available after 6 months to test the prediction rule. Baseline characteristics were similar between patients with and without sufficient data available in both the development group and in the validation group (all *P* > 0.05). In the multivariate model, only sulfonylurea and insulin therapy, duration of diabetes, fasting plasma glucose, and HbA_{1c} remained significant. Because fasting plasma glucose and HbA_{1c} levels were highly correlated and because fasting plasma glucose measurements are more immediately available, HbA_{1c} level was removed from the final model. Using the approach of Nagelkerke (14) to determine the contribution to *R*² (for failure of nonpharmacological management), the full model provided an *R*² of 0.33, whereas a reduced model lacking pharmacological therapy at presentation showed an *R*² of 0.28. Thus, duration of diabetes and glucose at presentation are dominant contributors to the model. This multiple regression equation significantly predicted the need for pharmacological intervention after 6 months in the development group (likelihood ratio test, *P* < 0.0001).

The point probability of each patient's chance of requiring pharmacological therapy by 6 months can be calculated using the logistical regression equation

$$\exp(-4.469 + 1.932 \times \text{sulfonylurea Rx} + 1.334 \times \text{insulin Rx} + 0.196 \times \text{duration} + 0.468 \times \text{fasting glucose}) / [1 + \exp(-4.469 + 1.932 \times \text{sulfonylurea} + 1.334 \times \text{insulin} + 0.196 \times \text{duration} + 0.468 \times \text{fasting glucose})]$$

where “exp” designates e^x and “Rx” designates a prescription. A point probability of 0.80 achieves a 90% positive predictive value (PPV) for the requirement of pharmacological intervention in the validation group. In a simplification of the logistical regression equation [$1.932 \times \text{sulfonylurea Rx} + 1.334 \times \text{insulin Rx} + 0.196 \times \text{duration (years)} + 0.468 \times \text{fasting glucose (mmol/l)}$], a value of ≥ 5.86 yields a 90% PPV. Sensitivity, specificity, and PPV for each potential cutoff level (using the point probabilities calculated with the full logistical regression equation) are plotted in Fig. 1A. A total of 75% of patients in the validation group were in need of pharmacological intervention after 6 months of care. The cutoff of 0.80 (or 5.86 using the simplified formula) successfully captured 80% of these cases.

After adjustment for other variables (Table 2), patients taking sulfonylurea therapy at presentation to the clinic had 6.5-fold increased odds ($P < 0.0001$) of requiring drug treatment after 6 months, and subjects taking insulin therapy at presentation had 3.7-fold increased odds ($P = 0.001$). The need for pharmacological treatment was progressively related to the duration of diabetes with an almost 7-fold greater odds ($P < 0.0001$) for a duration >5 years compared with a duration <1 year. Fasting plasma glucose was also progressively related to an increased risk of the need for pharmacological therapy. When fasting plasma glucose was >12.5 mmol/l, a substantial elevation in odds ratio (OR) occurred (OR = 51.0, $P < 0.0001$).

The prediction rule from the development group was then tested on the validation group. The observed need for pharmacological intervention was compared with the predicted need for pharmacological intervention by quartiles of risk. The correlation of observed to expected need for drug treatment was 0.99 (data not shown).

We also used ROC analysis to assess the performance of the prediction rule in the validation group (Fig. 1B). ROC curves plot sensitivity versus (1 - specificity) for each potential cutoff level of a diagnostic rule. The diagnostic rule in this case was the multivariate logistical regression equation, and the outcome was the observed need (or absence of need) for pharmacological treatment to achieve an HbA_{1c} level $<7\%$ after 6 months. The nonparametric AUC was similar for both groups (0.91 [95% CI 0.88–0.94] for the development group and 0.85 [0.81–0.89] for the validation group),

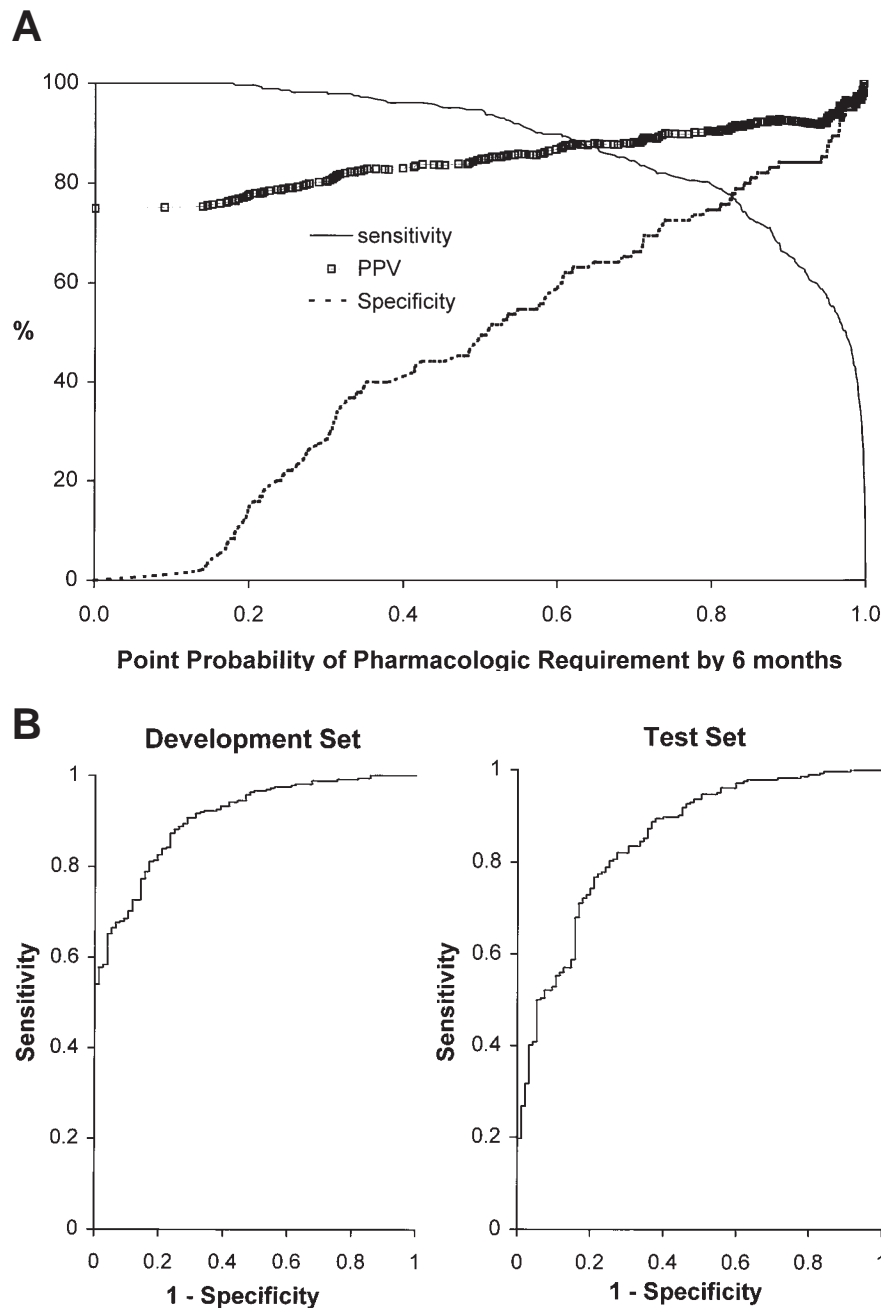


Figure 1—A: Plot of sensitivity, specificity, and PPV versus logistical regression criteria in the prediction of failure of dietary therapy after 6 months in the validation group. B: ROC curves for the development group (AUC = 0.91 [0.88–0.94], n = 399) and the validation group (AUC = 0.85 [0.81–0.89], n = 379).

which indicates that the rule is a valid predictive instrument.

The performance of the prediction rule was also assessed in other populations. A total of 965 patients with a type 2 diabetes duration >2 months were seen for an initial visit at the GDC between 1 January 1997 and 20 April 1998. Of these, 93 subjects had sufficient data after 6 months of follow-up to permit prospective testing of the prediction rule. Baseline characteristics were

similar between patients with and without available follow-up data (all $P > 0.05$). In this population, ROC analysis revealed an AUC of 0.81 (0.71–0.91). During a similar analysis of 272 patients with a duration of diabetes <2 months, the rule did not perform as well (AUC 0.65 [0.59–0.72]).

CONCLUSIONS — Stepped-care strategies are frequently used to guide therapy in patients with type 2 diabetes (11).

Table 2—Association between clinical variables and failure to achieve strict glycemic control after 6 months using diet alone

Variable	Multivariate analysis	P*
Taking sulfonylureas		<0.0001
No	1.0	
Yes	6.5 (3.0–14.1)	
Taking insulin		<0.001
No	1.0	
Yes	3.7 (1.7–8.1)	
Duration of diabetes (years)		<0.0001
<1	1.0	
1–5	3.2 (1.3–7.9)	
>5	6.7 (3.0–15.3)	
Fasting glucose (mmol/l)		<0.0001
<6.1	1.0	
6.1–6.9	1.5 (0.5–4.6)	
7.0–9.7	2.6 (1.0–6.4)	
9.8–12.5	17.8 (5.0–63.4)	
>12.5	51.0 (9.8–266.0)	

Data are ORs (95% CIs). *P value for likelihood ratio test.

The aim of this approach is to methodically derive an appropriate treatment for every patient regardless of treatment at presentation. A rigorous trial of lifestyle interven-

tions is often attempted first because many patients can be managed with diet alone (11,15). If lifestyle modifications are not successful in lowering glucose levels to tar-

get goals, then pharmacological therapy is usually initiated. More sophisticated protocols for the selection of pharmacological agents attempt to increase the efficiency of stepped-care methods by individualizing therapy; for example, slim patients may be targeted for sulfonylurea therapy, and overweight patients may be targeted for metformin therapy (16). These methods should work well for large groups of patients but may delay the attainment of appropriate pharmacological regimens for individual patients, thus prolonging the period of hyperglycemia.

A further enhancement for stepped-care protocols would be the early prediction of eventual pharmacological requirements based on individual patient characteristics as suggested by Mazze et al. (17). We have developed a highly reliable clinical rule that predicts the need for pharmacological intervention after 6 months of therapy in the GDC. The rule uses readily available patient data and yields a PPV of 90%. We have validated the rule on a concurrent random sample of patients not included in its derivation and prospectively on an additional group of

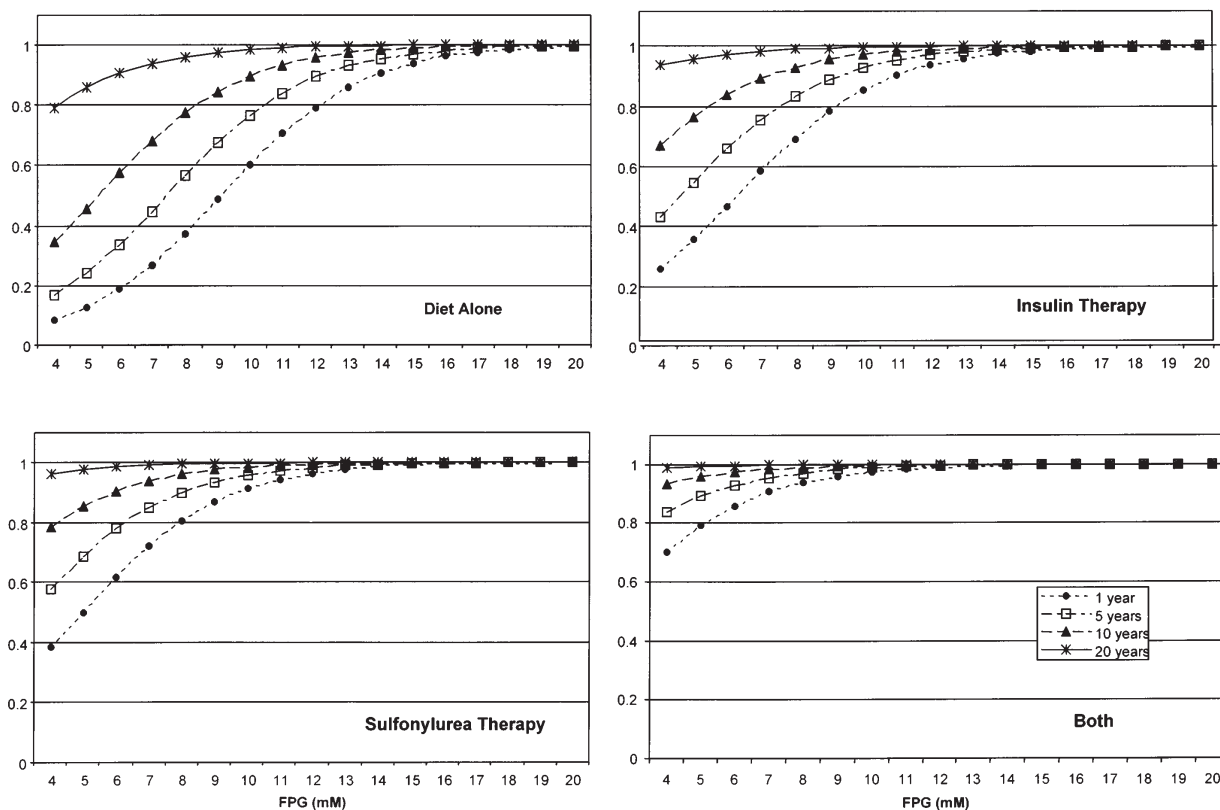


Figure 2—Curves using the variables from the prediction rule that illustrate how the probability of the need for pharmacological therapy is influenced by duration of diabetes, glucose levels, and use of medication at presentation. FPG, fasting plasma glucose.

patients. ROC analysis demonstrated a very high AUC, which is indicative of substantial accuracy (18).

Despite the promulgation of national guidelines, glycemic control in patients with diabetes is often substandard (13,19–21). Even in studies implementing intensive therapy, HbA_{1c} often deteriorates after an initial period of time (7,23). Delayed initiation of pharmacological therapy and insufficient intensification are probable contributors to suboptimal control (24). The purpose of our prediction rule is to facilitate identification of patients who will require medical intervention to reach target glucose levels. Once identified, these individuals can begin taking pharmacological agents promptly while concurrently receiving instruction on appropriate dietary and other lifestyle changes. This strategy should reduce time with poor metabolic control, which may help diminish the complications associated with diabetes.

Close inspection of our prediction rule suggests that clinicians may consider convenient cutoff values as signs of the need for pharmacological therapy. For example, a fasting plasma glucose level of 12.5 mmol/l (225 mg/dl) yields a point probability of at least 0.80 for the need for pharmacological therapy after 6 months regardless of duration of diabetes or current sulfonylurea or insulin treatment. Without current sulfonylurea or insulin treatment and with a fasting plasma glucose level as low as 6.0 mmol/l (108 mg/dl), a duration of diabetes of just >15 years results in a point probability of 0.80. Surprisingly, current sulfonylurea therapy is more predictive of the future need for pharmacological intervention than current insulin therapy. With a fasting plasma glucose level of 6.0 mmol/l and a duration of diabetes of 2 months, current therapy with a sulfonylurea yields a point probability of 0.58, whereas current therapy with insulin yields a point probability of 0.43 (current therapy with both sulfonylurea and insulin yields a point probability of 0.84). We speculate that many patients with easily manageable diabetes may be placed on insulin during times of acute illness when glucose levels are greatly elevated. After the acute episode resolves, such patients may subsequently do well with lifestyle modifications alone. In contrast, patients who present taking sulfonylureas may already have exhibited chronic hyperglycemia that was refractory to nonpharmacological management.

The variables in our prediction rule can also be used to develop curves that illustrate how the probability of need for pharmacological therapy is influenced by the duration of diabetes, fasting glucose level at presentation, and medications on presentation as shown in Fig. 2. Apparently, patients with a longer duration of diabetes and substantial glucose elevations have a high likelihood of requiring pharmacological therapy that is exacerbated by presenting while taking sulfonylurea therapy but less so by presenting while taking insulin therapy.

The major potential limitation of our study is generalizability. Although our prediction rule has been well validated among our patient population with a duration of diabetes >2 months, it is not applicable to patients with a new diagnosis of diabetes. Glucose toxicity (25,26) in patients with newly diagnosed diabetes may possibly preclude management via lifestyle modification. Initial use of medication may allow glucose toxicity to resolve and permit subsequent discontinuation of pharmacological therapy (11,15). Therefore, accurate prediction of the long-term need for pharmacological treatment in such patients using a formula relying on glucose levels and therapy at presentation will be extremely difficult. Furthermore, the predictive equation may require some modification for other populations. Although a recent study suggests that socioeconomic status is not related to glycemic control (20), the GDC population is urban and predominantly African-American and has a high prevalence of poverty and limited reading skills; GDC patients may present later in their natural history than other populations, but including such variables in our model was not possible.

This clinical prediction rule or others like it should be validated in other patient populations. Algorithms should also be developed that predict not only the need for pharmacological intervention but also the most appropriate glucose-lowering agent for a given patient. Such efforts should speed the attainment of glycemic goals, which should reduce the considerable morbidity and expense associated with diabetes.

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