

# Identifying the Target Population for Primary Prevention: The Trade-Offs

**C**ompelling evidence now exists that type 2 diabetes can be prevented or delayed in subjects with impaired glucose tolerance (IGT) (2-h oral glucose tolerance test [OGTT] 140–199 mg/dl) (1–4), a group at great risk for subsequent diabetes and cardiovascular disease (5,6). This evidence has held consistently across different populations, in different countries, among men and women, and in all age and racial and ethnic groups. Based on these studies, national health organizations, including those in the U.S. and Finland, are now calling for action (7,8). The American Diabetes Association (ADA) has recommended to consider clinic-based (opportunistic) screening for prediabetes (impaired fasting glucose [IFG] 110–125 mg/dl or IGT) among persons aged >45 years and among younger persons with other diabetes risk factors; they strongly recommend opportunistic screening in persons aged >45 years with BMI  $\geq 25$  kg/m<sup>2</sup> (7). Approximately one-third of individuals with either IFG or IGT and two-thirds of individuals with both will develop extant diabetes within 6 years (5). However, at present we know little about validated strategies to detect prediabetes in the “real world.” Using fasting, random, and postprandial glucose measurements or A1C levels are options. Anecdotally, performing glucose challenges is cumbersome, difficult, more costly, time consuming, and less acceptable to both patients and health care providers than fasting glucose or A1C measurements. Thus, our first clinical and public health challenge for primary prevention is clear: how are we going to find people with prediabetes?

The study of Saydah et al. (9) in this issue of *Diabetes Care* begins to shed light on this important question. They examined detection strategies aimed at minimizing the use of OGTTs and identifying persons with IGT who would have been eligible for the U.S. Diabetes Prevention Program (DPP) by using BMI in combination with fasting plasma glucose (FPG) and A1C measurements. Population-

based data (from the Third National Health and Nutritional Examination Survey [NHANES III]) for individuals 40- to 74-years-old found that 11% of this group met DPP eligibility criteria (BMI  $\geq 24$  kg/m<sup>2</sup> and 2-h OGTT 140–199 mg/dl, and FPG 96–125 mg/dl). Using cut points of BMI  $\geq 24$  kg/m<sup>2</sup> and FPG  $\geq 105$  mg/dl would result in recommending OGTTs for 37% of the general population and the detection of 56% of the total IGT population (missing 44%); using the same BMI cut point and an A1C  $\geq 5.5\%$  cut point would result in recommending OGTTs in 38% of the population and the detection of 60% (missing 40%). Enriching the population based on age, race, and family history of diabetes did not significantly reduce the proportion that would be recommended for OGTT or enhance the detection rate. Subanalyses also found that requiring BMI  $\geq 24$  kg/m<sup>2</sup> and either an FPG  $\geq 105$  mg/dl or an A1C  $\geq 5.5\%$  can detect 83% of cases, but the proportion of the population who would be recommended for an OGTT would probably increase sharply. In general, lower glucose or A1C cut points can detect more cases but will require more OGTTs. Saydah et al. also recommended an annual FPG test so that missed cases can be detected in the following year. Thus, trade-offs using different strategies can offer various advantages.

Although this study helps address the problem of detecting prediabetes, some issues remain unclear. First, as the authors note, the NHANES III data do not have OGTT information on all DPP age-groups, specifically those aged 25–39 years and >74 years. Thus, finding all DPP-eligible persons was not possible. Second, we do not know how these findings help apply the current ADA recommendations (7), which call for detecting all prediabetes in the population attending clinics who are aged >45 years—not simply those with IGT. Targeting all those with prediabetes is justified by the level of risk for diabetes, the potential for benefiting from the primary prevention inter-

ventions, and the potential for a successful intervention if subjects are aware of their risk status (10).

At least two other studies have examined prediabetes detection strategies. One was conducted among a clinic-based population, whereas the other was a population-based study that included detailed clinical measurements (11,12). Rolka et al. (11) studied a clinic-based population using risk assessment questionnaires and random capillary glucose (RCG) measurements to detect dysglycemia (IGT, IFG, or undiagnosed diabetes). They found an RCG measurement alone performed better than the risk assessment questionnaires alone to detect prediabetes. In the population-based study by Stern et al. (12), the ability to predict diabetes for a 7.5-year period using “routinely available” clinical information (i.e., age, sex, ethnicity, fasting glucose, systolic blood pressure, HDL cholesterol, BMI, and family history of diabetes) was assessed. This model was a better predictor than a 2-h OGTT measure alone, although it would miss current unrecognized diabetes (which would require a 2-h OGTT).

Many other ongoing studies that are examining the ability of various strategies to predict diabetes may be forthcoming and may shed more insight. The optimal method should become more apparent over the next few years as additional information becomes available. At present, there are at least two reasons to consider a fuller assessment of glycemic status (i.e., considering measurement of both FBG and postprandial tests). First, primary prevention interventions requires long-term commitment of substantial health care resources that will likely far exceed the resources required for any case identification strategy (13). Thus, for now, we should be sure that most persons (in order to gain the benefit from extant science) actually have prediabetes before they are referred and treated. This can be accomplished using both fasting and postprandial tests. Second, without full

glycemic testing, we cannot be certain whether unrecognized diabetes is present because it may occur with either a normal fasting glucose and diagnostic 2-h glucose or a normal 2-h OGTT glucose and a diagnostic fasting glucose. If diabetes is present, nutritional and activity recommendations may be similar for prediabetes and diabetes, but treatment goals and the choice of medication for glycemia, hypertension, and hyperlipidemia are different, as is the need to screen for existing complications.

To take advantage of the benefits of primary prevention, our first step should be to find sound prediabetes detection strategies. We also need to know more about the performance, costs, feasibility, acceptability, and cost effectiveness of the various strategies. In addition, further thinking may be needed to refine our definition of prediabetes and diabetes. While thinking about these, we must strike a balance between “easier” detection strategies with lower certainty of correctly identifying most and only prediabetes and diabetes, and more “difficult” strategies that provide greater certainty but are more complex and costly. Although the risk model by Stern et al. reports clinical factors that perform well as predictors, Saydah et al. and others have found the standard diabetes risk factors of little help. The population-based Hoorn Study (7) found the fasting and 2-h glucose levels to be the most important predictors of future diabetes.

While there may be several advantages to using fasting glucose and A1C measurements, assuming that we can minimize the requirement for some type of postprandial glucose measurement may be premature. Other “friendlier” strategies, such as a self-administered standardized meal, similar to that used during the Da Qing IGT and Diabetes

Study in China (3), need closer examination and may provide an alternative to usual glucose tolerance testing. We have taken some of the initial steps to identify the target population but more steps need to follow.

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