Risk of progression to IDDM has been assessed extensively in first-degree relatives of IDDM patients, and highly specific prediction is possible within a small subset of this population. Because ~90% of future cases will come from those who have no close relative with IDDM, prediction and intervention within the general population will become the main priority for the future. This review presents a decision tree analysis of risk of progression to IDDM, highlights the different prognosis of markers when applied to those with and without a family history of the disease, and proposes a strategy for disease prediction in the latter. Large collaborative studies in well-characterized populations will allow new predictive markers and models to be evaluated, and strategies of intervention to be tested with maximum efficiency and minimal delay. Diabetes 42:213-20, 1993
body levels and insulin secretion in response to intravenous glucose. The aim of much of this activity is to identify a point of no return at which the potential risks of intervention might be justified. This strategy, therefore, strives to attain a specificity of prediction approaching 100%—with the unstated but inevitable consequence of loss of sensitivity. Because the relation of specificity to sensitivity is reciprocal, the more certain we become that individuals included in a predictive model will develop diabetes, the greater the proportion of those at risk we thereby exclude from the possible benefits of intervention. To reach these people—the great majority—requires an approach that will allow us to structure and evaluate lower degrees of probability.

How do we structure uncertainty? Clinical judgment is often almost reflexive but can be formalized and improved by decision analysis (2,3). The probability of a given outcome can be set out in a series of steps known as a decision tree, which provides a means of integrating the knowledge we use when handling a complex and evolving body of information. The probability of a given outcome can be refined at each successive step, and the utility of further diagnostic procedures evaluated in the light of information already available. Bayes’ rule, described in the next paragraph, is intrinsic to this approach.

"The common reasoning error of neglecting the base rate (3)" is most often encountered, within a medical context, in clinical evaluation of diagnostic tests. Simply stated, the predictive power of a test is related to the pre-existing level of risk in the individuals to whom it is applied. If this risk is high, the test will have a high yield of true positives, few false positives, and a high positive predictive power. Conversely, if risk is low, true positives fall, and the false-positive rate will rise, with a corresponding reduction in predictive power. Mathematical formulation was first given to these principles by Thomas Bayes, an eighteenth century nonconformist minister who published on divine benevolence and the theory of probability. This concept is inherent in the decision tree approach in which positive selection with sequential criteria results in an effective stepwise increment of the baseline risk.

**Absolute risk.** Many factors influence the absolute risk of developing IDDM. This changes with age, rises to a peak around puberty, and recedes gradually through adult life (4). Dramatic geographical differences have been observed, such that a child born in Finland has 10 times the risk of developing diabetes as a child born in Northern Greece (5). Changes occur within a given population over time; the incidence in Finland rose by an average of 2.4% each year between 1965 and 1984 (6), and childhood diabetes is now some 2–3 times more common in much of Europe than it was in the 1960s and 1980s (7). These considerations greatly modify the subsequent analysis; a test such as ICAs would be expected to have a higher predictive value in Finland than in Greece or in children rather than in adults.

**Familial risk.** This represents the first branch in the decision tree. The lifetime cumulative incidence in siblings of a child with IDDM in Europid populations is quoted at 5–8% (8,9) against a background cumulative incidence of 0.1–0.5%. In our own family studies, a sibling is 15–20 times more likely to develop diabetes before 20 yr of age than children from a background population in the same area with a sibling risk of 6% (P.J.B., E.B., E.A.M.G., unpublished observations) and a background risk of 0.3% (10). Parents and children of an individual with IDDM have been estimated to have 50–66% the risk of siblings (8). An important consideration is that the proportion of new cases of childhood diabetes with an affected first-degree relative averages 10%, with little apparent variation between high prevalence and low prevalence populations.

Although relatively few cases arise in family members, most information on risk markers of IDDM has been derived from studies within families, and we will consider this branch of the decision tree first (Fig. 1). We have chosen to illustrate the risks over a 5-yr period of follow-up because this has been widely used in prospective studies and is feasible for trials of intervention. Siblings <20 yr of age have an average risk of developing IDDM within 5 yr of 1.5%.

**Risk of ICA in relatives.** Despite the technical difficulties encountered in ICA measurement (11) and uncertainty as to the target antigen(s), all current models of diabetes prediction are still based on this marker. ICAs are detectable in 70–80% of new cases of childhood IDDM (12) and in 5–8% of first-degree relatives, provided a sensitive assay is used. Most future cases of IDDM are concentrated in this ICA⁺ subgroup, within which risk is directly proportional to ICA titer. Thus, 5% of first-degree relatives with ICA 4–19 JDF U and 35% of those with ICA ≥20 JDF U will require insulin within 5 yr; 60–70% will likely be on insulin within a decade (13,14), even though progression to diabetes does not appear inevitable in the remainder (15). Thus, this single marker has the power to identify a group of relatives who are more likely than not to develop diabetes within 10 yr. ICA measurement, therefore, provides an excellent stepping stone towards more specific prediction.

**FIG. 1. The risk of diabetes within 5 yr in a sibling of an IDDM patient; 6% of siblings will develop IDDM before age 20, giving a 1.5% average risk of IDDM within 5 yr of 1.5%. The risks associated with detectable ICA ≥4 JDF U and ICA ≥20 JDF U are derived from life-table analysis in the Bart’s-Windsor family study (13).**

![Diagram](image-url)
Two other autoantibodies of major importance have been identified (22): IAA (23) and autoantibodies to the islet 64,000 M, antigen, subsequently identified as the enzyme GAD (24). IAAs appear to have little prognostic significance in the absence of ICAs, provided a sensitive ICA assay is used, but the combination, although present in ~50% of those who develop IDDM, is highly predictive (25,26). In the Boston-Sacramento family study, family members with IAA plus ICA ≥40 JDF U had a 77% risk of diabetes within 5 yr, compared with 42% for those with ICA ≥40 JDF U alone. Because IAAs are inversely related to age (27), some doubt exists as to the extent to which these variables are independent.

Antibodies to the 64,000 M, islet antigen and to GAD are found in ~80% of relatives studied before diagnosis (22,28,29). On the other hand, high levels of GAD antibodies also are found in the absence of diabetes in stiff-man syndrome, a rare neurological disorder (30), and GAD may be the autoantigen of β-cell–selective ICAs, which, as we have seen, carry a lower risk of progression to IDDM. Their prognostic significance might increase as different GAD antibody specificities are identified. Distinct specificities of the 64,000 M, antibody have been demonstrated (31). Antibodies to a 64,000-M, trypsin fragment are found in most IDDM patients but also are present in 15% of monozygotic twins who remain discordant for IDDM after prolonged follow-up and in all ICA+ polyendocrine patients who did not develop IDDM. In contrast, antibodies to 37,000/40,000-M, trypsin fragments, distinct from GAD, are found in the majority of IDDM patients and correlate well with whole islet ICA. These are found in only 2% of discordant twins and are absent in ICA+ polyendocrine patients who have not developed diabetes (32,33). Currently, however, no clear view has emerged as to the prognostic utility of these various antibodies.

代谢试验。β细胞功能测试是逻辑上的，因为它是对目标器官在IDDM中的伤害性的一次测量。FPIR在静脉内葡萄糖浓度下降前的胰岛素浓度过低是高预测性的，因为它在第二百分位控制人群中的高预测性。FPIR的失常在IDDM患者中是高预测性的，在第一百分位水平以上，其预测性在IDDM患者中是高预测性的。比较结果已经表明，被预测为高风险的那些患者在一定程度上具有几率下降的风险。
before insulin was started. Predicting insulin dependence according to patterns of insulin secretion without regard to the coexistence of diabetes would be somewhat illogical. Therefore, the ADA Ad Hoc Committee has recommended that biochemical evidence of diabetes (defined by the OGTT in asymptomatic individuals) should be the end point used in intervention trials rather than the clinical decision to use insulin (18). Even this approach is limited by poor reproducibility of the 2-h glucose value in the OGTT, so that, paradoxically, we still lack a well-defined reproducible end point for the early diagnosis of borderline diabetes.

**The dual parameter model.** Elevated titers of IAA and loss of the FPIR are each strongly predictive of rapid progression in high-titer ICA+ relatives. Preliminary reports indicate that a model based on combined analysis gives highly specific prediction in end-stage diabetics, with progression within 3–4 yr in ~90% of those identified, although prediction beyond 3 yr is less certain (38). This dual parameter model, described in outline as early as 1988 but not as yet published in full, has, in the interim, exerted enormous influence on attitudes to diabetes prediction and prevention. It has, for example, been used to evaluate pilot testing of nicotinamide and insulin in high-risk individuals (39,40) and has been used as the basis for planning large-scale intervention studies. A model such as this must evolve through three stages. In the first stage, a retrospective correlation is made in a sample of individuals who have already progressed to diabetes; this is known as the practice set. In the second stage, the predictive formula is applied to an independent data set (the test set). If further refinement is needed at this stage to improve the fit, the new data should be considered a modified practice set and validated against a new test set. Finally, in the third stage, independent validation by other centers would be sought before the model is generally accepted.

Viewed in this perspective, the dual parameter model appears promising, but the process of evaluation is clearly far from complete. Its great attraction is that it appears to define what amounts to a point of no return, but this should not be assumed until it is more convincingly demonstrated. We have certainly seen persistence and even recovery from very low insulin secretory responses without progression to diabetes, and we have experienced both false-negative and false-positive results in our efforts to apply the model to our own population (P.J.B., E.B., E.A.M.G., unpublished observations). Larger scale evaluation of this approach is clearly a matter of some urgency.

**WHAT PROPORTION OF THE AT-RISK POPULATION CAN WE PREDICT?**

If screening is limited to family members of IDDM patients, the scope of prediction is immediately reduced to ~10% of the at-risk population (Fig. 3). Prospective study shows that 10–30% of these will not have detectable levels of ICAs, and that another 30% will have moderately low levels (<40 JDF U) (13,14). We can therefore anticipate that no more than 40–50% of future cases will have ICA >40 JDF U at screening, the level at which the dual parameter model can be applied. This model predicts early progression only in those with high IAA levels and/or impaired insulin secretion, representing perhaps 15% of the family population at risk. Highly specific prediction from a single screening point is therefore only possible in <20% of family members or 2% of all future cases. Repetitive testing could probably identify the majority of future cases derived from relatives with high-titer ICA, but it seems clear that even highly effective intervention directed to this subgroup would have little impact on IDDM as a public-health problem. To achieve this, risk reduction and risk assessment must be extended to nonfamilial IDDM.

**Prediction in individuals with no family history of IDDM.** Of IDDM patients, 90% have no family history of diabetes and come from a population with a very low base rate of disease. Bayes' theorem dictates that markers applied in such a situation will have low predictive value and will generate a large proportion of false positives. How do these considerations influence predictive testing for IDDM within the general population?

**Risk of ICA in the general population.** We compared the prevalence of ICA and the risk of diabetes in 2925 schoolchildren 9–13 yr of age and 272 age-matched nondiabetic siblings recruited for our family study and living in the same region. ICAs were detected (with a threshold of 4 JDF U) in 2.8% of schoolchildren and 6.6% of siblings. Our incidence data showed that 0.2% of the schoolchildren would be expected to develop diabetes within 10 yr compared with 2.8% of the siblings (estimated from life-table analysis). Thus, siblings were 2 times as likely to have a given titer of ICA than schoolchildren, but they were 14 times as likely to develop diabetes. The predictive value of ICA in the general population would fall, therefore, to about one-seventh of that in siblings (41). This indirect estimate has subsequently found support from prospective data collected from siblings and schoolchildren in Finland (42) and, indeed, accords well with the theoretical estimate derived from Bayes' rule. This correction factor implies that progression to diabetes within 5 yr would occur in 2–3% of schoolchildren.
Assuming that the sensitivity and specificity of ICA are expected PPV of ICA 2-4 JDF U for developing IDDM can be applied. The PPV of a test applied to a population of given disease prevalence can be given by the following formula (44):

$$PPV = \frac{(sensitivity \times prevalence)}{(sensitivity \times prevalence) + [(1-specificity) \times (1-prevalence)]}$$

Assuming that the sensitivity and specificity of ICA are similar in the general population and family members, the expected PPV of ICA ≥ 4 JDF U for developing IDDM can be estimated by using the sensitivity (88%) and specificity (96%) observed for the same assay in the Bart's-Windsor family study. In schoolchildren, this gives an expected PPV of 2% within 5 yr. If, however, ICA testing were confined to those already identified as genetically susceptible by DQ typing (again applying the Finnish oligonucleotide screen), the expected PPV would rise to 35%. If subjects with this susceptible DQ combination and ICA ≥ 4 JDF U were followed for 10 yr, 60% would be expected to develop IDDM; a level of prediction equivalent to that achieved by ICA ≥ 20 JDF U in family members. This approach obviously needs testing, bearing in mind that the genetic marker can be applied only within the population in which it was developed. Moreover, any genetic screening method will be useful only if it can achieve a level of discrimination comparable with that reported in the Finnish study. Finally, note that tests that enhance the predictive power of ICA in family members could be applied in similar fashion to ICA+ genetically susceptible individuals and have the potential to reach equally high levels of specificity, albeit with corresponding loss of sensitivity.

**DISCUSSION**

The approach to diabetes prediction outlined in this decision tree analysis (Fig. 5) has many advantages. It provides a simple and easily visualized framework within which it is possible to summarize and link a vast and evolving mass of data. The framework is flexible, easy to use, can be elaborated to finer detail if required, and the analysis involved could readily be held on computer. The approach forces the user to be explicit, and it is readily apparent that certain steps in our illustrative use of the model are well documented, whereas others rest on scanty data or speculation. Research efforts can be directed to these weak points, and initial judgments can be discarded or updated on the basis of later and more complete information.

Discussion of diabetes prediction tends to focus on the possibility of new and improved predictive markers in the hope that some future magic marker, with 100% specificity and 100% sensitivity, will be identified. Sequential analysis of probability suggests that it is highly unlikely that any such marker will emerge. Further, it emphasizes that the prognostic significance of any marker varies in populations at differing levels of risk and shows that sequential analysis can overcome some of these limitations, at least in part. It demonstrates that adding in further tests has a limited yield once high specificity has been achieved by the preceding steps in the analysis, so that, for example, generic testing has limited use in relatives with high titers of ICA. On the other hand,
genetic testing is likely to prove essential to diabetes prediction within the general population, and the necessary level of discrimination can be defined already.

Lack of standardization of assays and clinical procedures has been a recurrent theme in the quest for diabetes prediction. The need for standardization of assays led to the establishment of the Immunology of Diabetes Workshops, which have been instrumental in setting standards and assessing comparability. Another problem is that these assays have often been evaluated in inadequate population samples. ICARUS arose from the conviction that research into the pathogenesis of IDDM was being held back because the many clinical and population studies currently underway individually lack the power to evaluate new genetic or immune markers rapidly and definitively or lack the power to provide the basis for intervention trials designed to delay onset of the disease. The basic concept of the register has been to treat ICA* in a nondiabetic individual as a rare disease, to establish standard methods of investigation and follow-up, and to set up a shared database and bank of serum, served by international reference laboratories. This resource will provide the basis for larger scale collaborative studies designed to provide rapid and convincing answers to some of the unanswered questions identified in this review.

Two parallel and complementary strategies emerge from the analysis (Figs. 6 and 7). In the shorter term, highly specific prediction is essential if we are to evaluate novel strategies of intervention. With this approach, the smallest possible number of nonprogressors will be exposed unnecessarily to therapy, and hypotheses can be tested within a relatively short time in small samples of high-risk individuals. First-degree relatives are the logical source and are more likely to be motivated to take part. Specific prediction increases the potential benefit of therapy, implying that a higher margin of risk, for example, that involved in conventional immunosuppression, might be contemplated. Even if highly effective, however, such therapy would have limited relevance to the longer term aim of reducing the future incidence of IDDM.

The second strategy could be applied to a much larger segment of the at-risk population. The future course of attempted diabetes prevention will depend on our ability to identify risk within the total population. The strategy will necessarily entail loss of specificity, meaning that therapy would inevitably need to be offered to groups containing some individuals who would not in any case have developed the disease. This might seem abhorrent at first sight, especially when children are among those at risk.

Risk estimation and risk reduction are nonetheless routine elements of clinical practice. To take an example from another disease, middle-aged individuals with moderate hypertension are routinely offered antihypertensive therapy, even though the only confirmed benefit of this in one large trial was to reduce the risk of stroke over the next 10 yr from 2.6% in the placebo group to 1.4% in the treated group (45). We live in a society in which it is considered not only reasonable but necessary to treat this level of risk. In contrast to the level of risk described for hypertension, relatives with ICA >20 JDF U have a risk of diabetes >60% over 10 yr, and, as we have seen, equivalent levels of risk could potentially be identified in the general population.

Viewed in this light, it may seem less unreasonable to offer treatment to the whole group at risk, provided — and this is the key point — this therapy is relatively safe. In this context, a highly effective therapy with a relatively high rate of toxic side effects would offer a lower ratio of risk to benefit than a safer but less efficacious intervention. This must be a prime consideration in the development of novel forms of therapy, and it is logical that agents that appear relatively safe, such as insulin and nicotinamide, should have priority when clinical trials are undertaken.

Screening is itself a form of intervention. The outcome may be highly welcome to the people screened, as when the mother of a diabetic child can be reassured that her other children do not have detectable levels of ICA. But anxiety can be generated where none existed previously, as when the parents of a healthy child are informed that ICAs have been detected in the course of a research study. As confidence in screening procedures improves, they are likely to be used more widely and less critically.
Negative consequences of screening include alerting the individual to a risk for which no effective remedy exists, unnecessary anxiety because of false-positive tests, or inappropriate reassurance because of false-negative tests. Adequate counselling and support should form an integral part of any screening program, and a simplified decision tree analysis could prove a useful way of helping individuals to reach their own decision concerning participation. Finally, consider the potential socioeconomic consequences of a positive screening test. The label that is attached to an individual, perhaps incorrectly, could harm his or her prospects for employment and health insurance. Such consequences will accumul-late in parallel with our ability to predict and intervene in IDDM.

CONCLUSIONS
Complexity and uncertainty are intrinsic to risk assessment in individuals predisposed to IDDM, particularly as we strive to extend the scope of prediction into the wider population. The overview presented here suggests that, at present, no simple solutions are available. Instead, a sustained research effort is likely to be needed. A major collaborative research campaign linking the efforts of basic scientists with large-scale population studies offers a logical approach. It would allow scientific developments in genetics, immunology, or immunotherapy to be evaluated in a clinical setting, and, where appropriate, to be applied to clinical problems with maximum efficiency and minimum delay. The challenge is great, but so is the reward.

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