Proposed Guidelines on Screening for Risk of Type 1 Diabetes

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These guidelines represent the recommendations of the Immunology of Diabetes Society (IDS) on the assessment of risk of type 1 diabetes in unaffected first-degree relatives of patients with the disease, and are based on the consensus reached at a symposium held at the fourth meeting of the IDS (Fiuggi, Italy, November 1999).

Assessment of risk of type 1 diabetes in relatives was initially based on detection of circulating islet cell antibodies (ICAs) supplemented by measurement of insulin autoantibodies (IAAs), and evaluation of β-cell function by determination of the first-phase insulin response (FPIR) in the intravenous glucose tolerance test. Other islet autoantigens, including GAD and the protein tyrosine phosphatase IA-2/ICA512, have subsequently been identified, and the role of autoantibodies to these antigens in assessment of risk of type 1 diabetes in first-degree relatives has been investigated in a number of large prospective studies. In addition, the genetic susceptibility to type 1 diabetes, particularly that conferred by genes in the HLA class II region, has been more precisely defined, and alleles conferring both susceptibility for and protection from the disease have been identified. This offers the possibility of combining immune, metabolic, and genetic markers in strategies to identify family members at risk, with the hope that it will eventually be possible to intervene in such individuals to delay the clinical onset of type 1 diabetes either before or after the initiation of the autoimmune processes that result in β-cell destruction. While a number of intervention trials are ongoing, no agent has yet to be shown as effective in the prevention of type 1 diabetes. Therefore, the major indication for testing is to identify individuals at risk for inclusion in intervention trials or prospective studies of the natural history of autoimmune diabetes.

RECOMMENDATIONS — Screening for immune or genetic markers of risk of type 1 diabetes should usually be undertaken only in the context of defined research studies.

Testing for antibodies to GAD and/or IA-2 or for GAD antibodies and/or IAA using sensitive radiobinding assays can identify >85% of cases of newly diagnosed or future type 1 diabetes with 98% specificity. It is therefore recommended that, as a minimum, primary testing to identify relatives at increased risk should include measurement of levels of antibodies to GAD with either IAAs or antibodies to IA-2. The appearance of IAAs may precede that of antibodies to GAD and/or IA-2, and IAAs may be the only antibodies detected at diagnosis in very young children. Thus, it is recommended that determination of IAAs be included in primary testing of children aged <10 years to maximize sensitivity. The requirements of prospective studies of natural history of the disease in infancy are different from those of risk assessment, and it is desirable to include all autoantibody markers in the primary test.

Risk of type 1 diabetes is strongly associated with the number of antibodies found to have raised levels, and only individuals with elevated levels of two or more markers should be considered as being at high risk. Individuals found to have elevated levels of one or more of the antibodies included in the primary test should therefore be further evaluated by measurement of other markers to quantify risk more precisely. Strategies for full evaluation of risk should include determination of at least three of the four best-established markers, IAAs, ICAs, and antibodies to GAD and IA-2.

Results of antibody testing in any laboratory should be interpreted in light of the sensitivity and specificity of the assays in newly diagnosed type 1 diabetes. Participation in workshop or proficiency programs that allow laboratories to determine these parameters is strongly recommended.

Genetic testing is of limited value in family members in whom autoantibody levels are known. However, HLA class II typing may be useful in identifying infants for prospective follow-up for the appearance of islet autoantibodies or for recruitment into trials of interventions aimed at prevention of the initiation of autoimmunity.

Metabolic testing with evaluation of the FPIR in an intravenous glucose tolerance test can be used to identify the subgroup of individuals with elevated levels of multiple antibodies who are at the greatest risk of progression to diabetes in the short term. Individuals with multiple islet antibodies in whom FPIR is preserved are, however, at high risk for delayed development of diabetes, and clinical onset may occur up to at least 20 years after first antibody detection.

Findings from studies in first-degree relatives should not be assumed to apply to other populations in which assessment of risk of type 1 diabetes might be considered (e.g., the general population or patients with gestational or type 2 diabetes). Preliminary results suggest that detection of multiple antibodies in individuals from the general population is associated with increased risk, but the number of individuals studied prospectively is currently insufficient to allow quantification of risk.

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