is consistent with a diagnosis of this disease (1).

The American Diabetes Association (ADA), the Juvenile Diabetes Research Foundation, and the Endocrine Society published a joint statement in 2015 that describes distinct stages of T1D in which the measurement of islet autoantibodies plays a major role (2) (See Figure 1). In Stage 1 of T1D, a person is euglycemic with no symptoms but positive for multiple islet autoantibodies. Stage 2 of T1D occurs when a person with multiple autoantibodies begins to have metabolic abnormalities (dysglycemia) but remains clinically asymptomatic. In Stage 3 of T1D, a patient has classic diabetes symptoms in the presence of dysglycemia and is therefore diagnosed with T1D based on standard clinical diagnostic criteria.

The most recent Standards of Medical Care in Diabetes, published annually by the ADA, supports the use of islet autoantibodies to make an early diagnosis of T1D (1). Clinically, an early diagnosis based on multiple autoantibodies may help reduce the rate of diabetic ketoacidosis and the associated morbidity and mortality that can occur at onset of T1D. According to ADA, diagnosing early stages of T1D is a necessary framework for research and regulatory decisions related to T1D.

However, despite the clinical utility of iAb measurement in diagnosing T1D, approximately 10% of patients with the disease do not have measurable iAb at onset. These patients are classified diagnostically as having type 1b diabetes and likely have an immune response to self-antigens that have yet to be identified. Of all T1D patients, approximately 50%–80% are GADA-positive at the time of diagnosis, 30%–70% are IA-2A-positive, 50%–70% are ZnT8-positive, and 50%–90% are IAA-positive (3). IAA are more prevalent in younger children.

Of note, IAA must be measured within 2 weeks of beginning treatment with insulin: After that point, antibodies may be produced in response to exogenously administered insulin, rendering their presence unhelpful in confirming a diagnosis of T1D. As noted above, the autoimmune markers of T1D are islet cell autoantibodies (ICA, GADA, IA-2A, ZnT8A) and autoantibodies to insulin (IAA), and T1D is defined by the presence of one or more of these autoimmune markers (1). Therefore, we recommend measuring all four iAb (GADA, IA-2A, ZnT8A, IAA) when possible to accurately diagnose the disease and maximize sensitivity for detecting autoimmune diabetes.

Beyond confirming their diagnosis of T1D, clinicians often order iAb testing to help differentiate T1D from type 2 diabetes (T2D), as well as to detect rarer forms of diabetes such as maturity onset diabetes of the young (MODY). Clinicians also must rely on iAb when clinical and metabolic markers such as age, pubertal status, sex, body mass index, HbA1c, and family history do not readily help with the differential diagnosis.

One of these rarer forms of diabetes is latent autoimmune diabetes in adults (LADA), also known as type 1.5 diabetes. In newly diagnosed cases of T2D in adults, approximately 10% of patients are positive for a single iAb, predominately GADA. These patients, who also progress slowly to needing insulin, often receive a LADA diagnosis. Given the phenotypic variability of LADA-diagnosed patients in combination with the presence of iAb, LADA most likely is not a distinct entity but rather a slowly progressive form of autoimmune T1D.

By the same token, close to 30% of adolescents with newly diagnosed T2D will show evidence of autoimmunity when tested for iAb, with GADA or IA-2A being most common. These young patients also likely have a slowly progressive form of autoimmune T1D or have been misdiagnosed based on clinical features such as obesity—an increasingly prevalent condition. iAb typically are not detectible in cases of diabetes caused by defects in beta-cell function (e.g., MODY), genetic defects in insulin action, drug- or chemical-induced beta-cell damage, diseases of the exocrine pancreas (e.g., cystic fibrosis-related diabetes), or gestational diabetes.

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**Figure 1: Islet Autoantibodies Predict Risk of Progression to Type 1 Diabetes**

This model of the natural history of type 1 diabetes (T1D) is modified from George Eisenbarth’s original model from 1986. T1D occurs in people at high genetic risk after an unidentified event initiates a cell-mediated autoimmune attack and loss of functional beta-cell mass. Stage 1 of T1D is defined by the presence of pancreatic autoimmunity with two or more islet autoantibodies. Stage 2 begins with the presence of abnormal glucose metabolism. Stage 3 occurs with the onset of clinical T1D symptoms such as polyuria, polydipsia, and weight loss.