



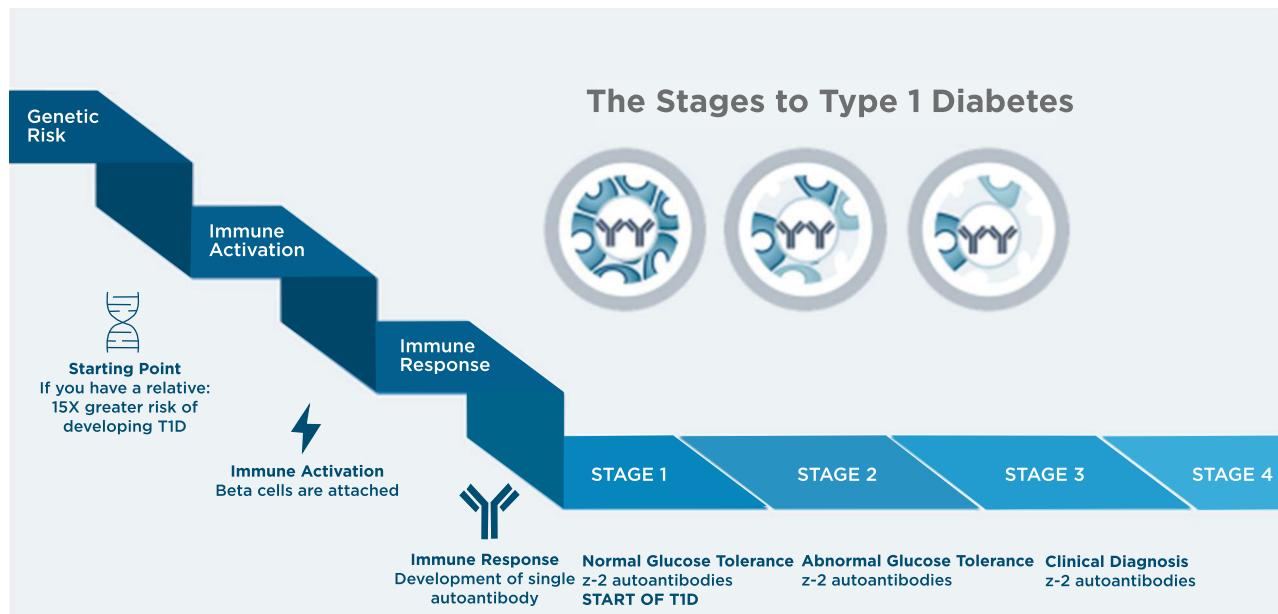
# Diabetes Mellitus

# Diabetes Mellitus type 1 autoantibody Panel

## Introduction:

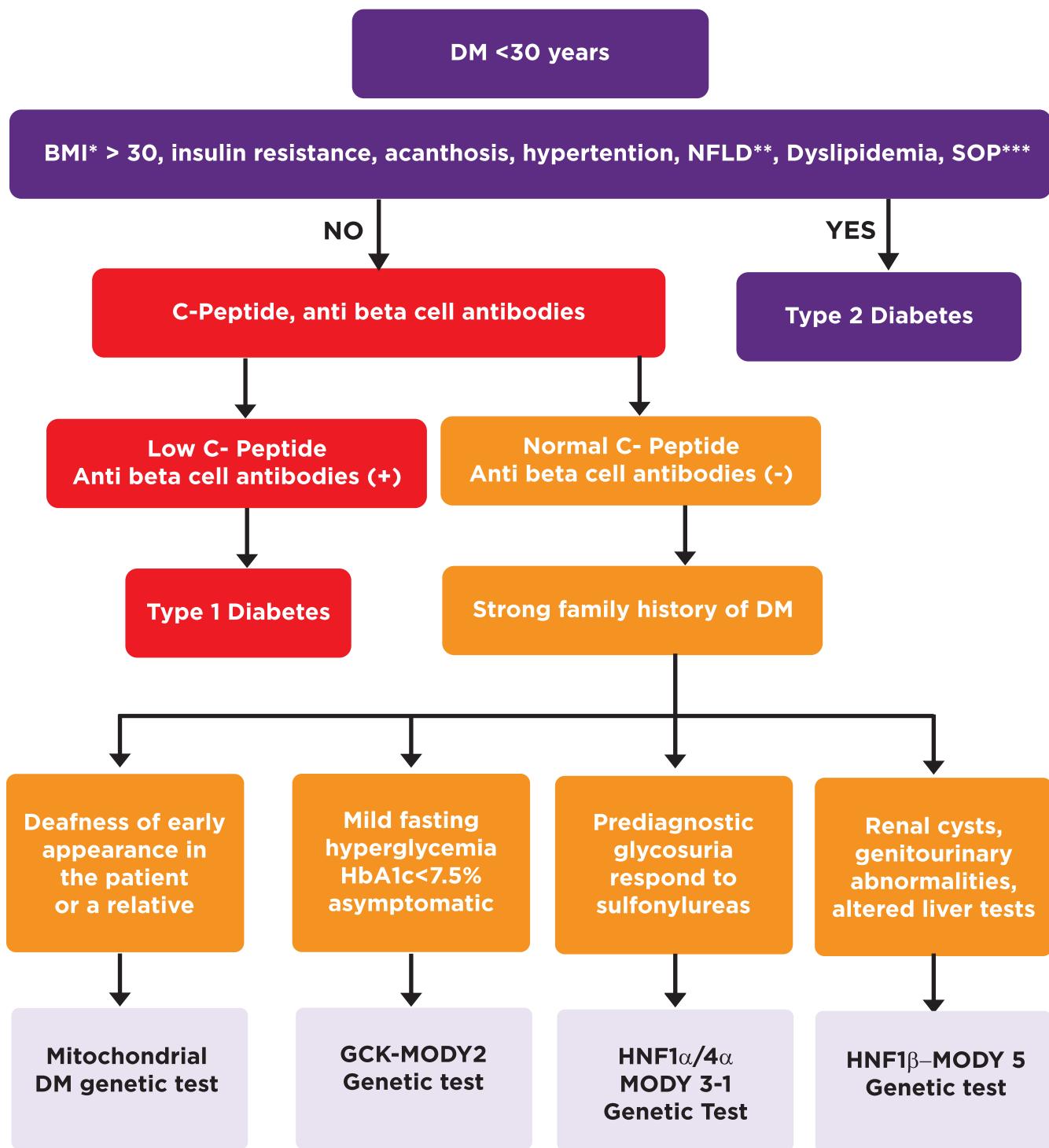
- ▶ The term diabetes mellitus describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.
- ▶ Inadequate insulin secretion and/or diminished tissue responses to insulin in the complex pathways of hormone action result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and/or action may coexist in the same patient.
- ▶ While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed later in further detail): type 1 diabetes, which is characterized primarily by deficiency of insulin secretion; or type 2 diabetes, which results from a combination of resistance to insulin action, as well as an inadequate compensatory insulin secretory response for the degree of insulin resistance.
- ▶ While type 1 diabetes remains the most common form of diabetes in young people in many populations, especially those of European background, type 2 diabetes has become an increasingly important public health concern globally among children in high risk ethnic populations as well as in those with severe obesity.
- ▶ The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both treatment and education. Diagnostic tools, which may assist in confirming the diabetes type if the diagnosis is unclear, include:
- ▶ Diabetes-associated autoantibodies: glutamic acid decarboxylase 65 autoantibodies (GAD); Tyrosine phosphatase-like insulinoma antigen 2 (IA2); insulin autoantibodies (IAA); and  $\beta$ -cell-specific zinc transporter 8 autoantibodies (ZnT8). The presence of one or more of these antibodies confirms the diagnosis of type 1 diabetes.

## Type 1 Diabetes Disease Progression



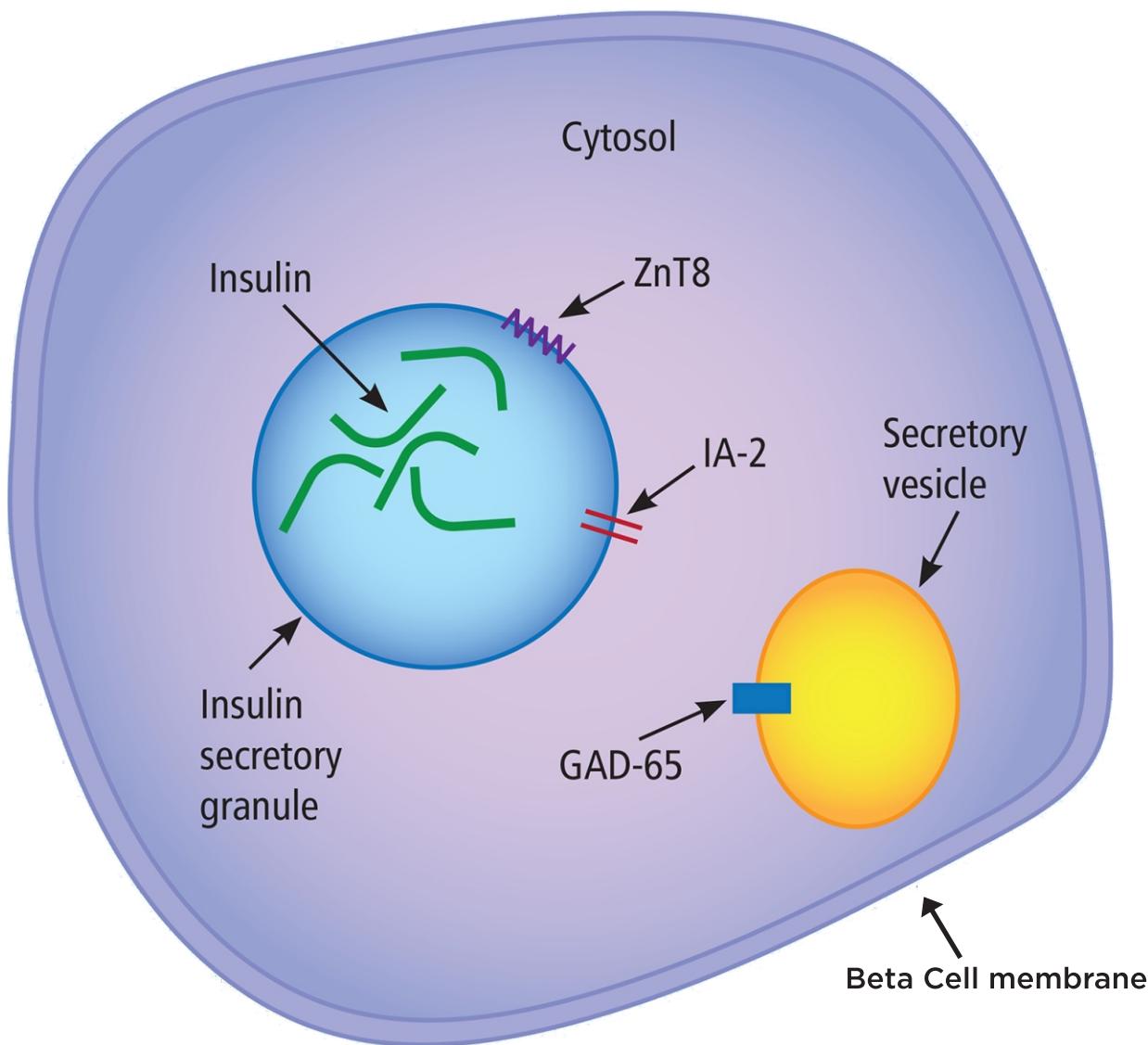
**FIGURE 1** The stages of type 1 diabetes (T1D) (Diabetes TrialNet.org). A proportion of individuals who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. The development of two or more islet antibodies (stage 1) ultimately progresses to dysglycemia (stage 2) and then to symptomatic T1D (stage 3).

# Diagnosis flow chart for Diabetes Mellitus



\*BMI- Body mass index ( $\text{kg}/\text{m}^2$ ), \*\*NFLD= Non- alcoholic fatty liver disease,  
\*\*\*POS=polycystic ovary syndrome

## Autoantibodies present in DM-1



### Anti- glutamic acid decarboxylase antibodies (GADA)

- ▶ The beta-cell destruction that leads to insulin deficiency in Type 1 diabetes is associated with circulating antibodies to insulin (IAA), islet cell cytoplasmic antigens (ICA), glutamic acid decarboxylase antibodies (GADA), and protein tyrosine phosphatase-like protein (IA-2ab).
- ▶ GADA are present in most patients with autoimmune diabetes at or before diagnosis and related to insulin secretion abnormalities and to the onset of Type 1 diabetes.
- ▶ Reported to be present in <5% to more than 20% of adults diagnosed as presumably having Type 2 diabetes, GADA are also markers of a slowly evolving form of autoimmune diabetes, frequently called latent auto-immune diabetes in adults (LADA).
- ▶ Most studies to date have evaluated individuals at or after diagnosis of diabetes, and little attention has been directed to the question of whether the presence of GADA predicts the development of diabetes in middle-aged adults.

## Islet cell antibody (ICA)

- ▶ ICA constitute an important marker for the identification of individuals at risk to develop type 1 diabetes among predisposed individuals and the indirect immunofluorescence test on sections of frozen human pancreas has become the routine approach to detect ICA.
- ▶ Even though it is a well standardized method, the sparsity of human pancreas and the fact that it is a complex technique make it difficult for deduction of ICA in screening in population programs or in cloning of auto-reactive T and B cells.

## Anti-insulin antibody (IAA) & Insulinoma-antigen 2 antibodies (IA-2A)

- ▶ Type 1 diabetes (T1D) is an organ-specific autoimmune disease caused by the autoimmune response against pancreatic cells.
- ▶ T1D is often complicated with other autoimmune diseases, and anti-islet autoantibodies precede the clinical onset of disease.
- ▶ Anti-islet autoantibodies are predictive and diagnostic markers for T1D. Islet autoantibodies recognize insulin (IAA), glutamic acid decarboxylase (GADA), protein phosphatase-like IA-2 (IA-2A), and ZnT8 (ZnT8A), all antigens that are found on secretory granules within pancreatic beta cells.

## Zinc transporter 8 antibody (Zn8TA)

- ▶ Zinc is essential for the proper storage, secretion, and the action of insulin and is transported from cytoplasm to insulin secretory granules in the pancreatic  $\beta$ -cells by SLC30A zinc transporters (ZnT).
- ▶ ZnT8 is specifically expressed in the pancreatic  $\beta$ -cells and has been identified as a novel target autoantigen in patients with type 1 diabetes. Humoral auto reactivity to ZnT8 is unique in terms of a key determinant, which is not reported on other islet autoantigens such as insulin, glutamic acid decarboxylase or IA-2.
- ▶ Zinc transporter 8 (ZnT8) was identified as a novel autoantigen based on a bioinformatics analysis for discovery of  $\beta$ -cell-specific proteins associated with the regulatory pathway of secretion. The amino acid encoded by a common polymorphism in human ZnT8 at aa325 (rs13266634C>T, R325W) is a key determinant of humoral auto reactivity to ZnT8.



## Diabetes mellitus type 1 antibody panel

### This test includes

Fasting insulin

C-peptide level

GAD 65 Ab

Insulin autoantibody

Islet cell antibody

IA-2 antibody

Zinc transporter 8 (ZnT8) antibody

**Sample type:** Serum

**Specimen Volume:** 4 mL

**Transportation Instructions:** Refrigerated

**TAT:** 1 day

# PARTNERS IN HEALTH



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