Diagnosis of Type 1 Diabetes

Differential Diagnosis of Type 1 and Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Usual clinical course	Insulin-dependent	Initially non-insulin-dependent
Usual age of onset	<20 years (but ~50% over 20 years)	>40 years but increasingly earlier
Body weight	Often lean but ~50% overweight or obese	Usually obese
Onset	Often acute	Subtle, slow
Ketosis prone	Yes	No
Family history	≤15% with 1st-degree relative	Common
Frequency of HLA-DR3, DR4, DQB1*0201, *0302	Increased	Not increased
Islet autoantibodies (GADA, ICA, IA-2A, IAA, ZNT8A)	Present	Absent

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8.

*Needs to be refined for nonwhite population groups.

Rewers M. *Diabetes Metab J*. 2012;36:90-97.

Classifying Diabetes

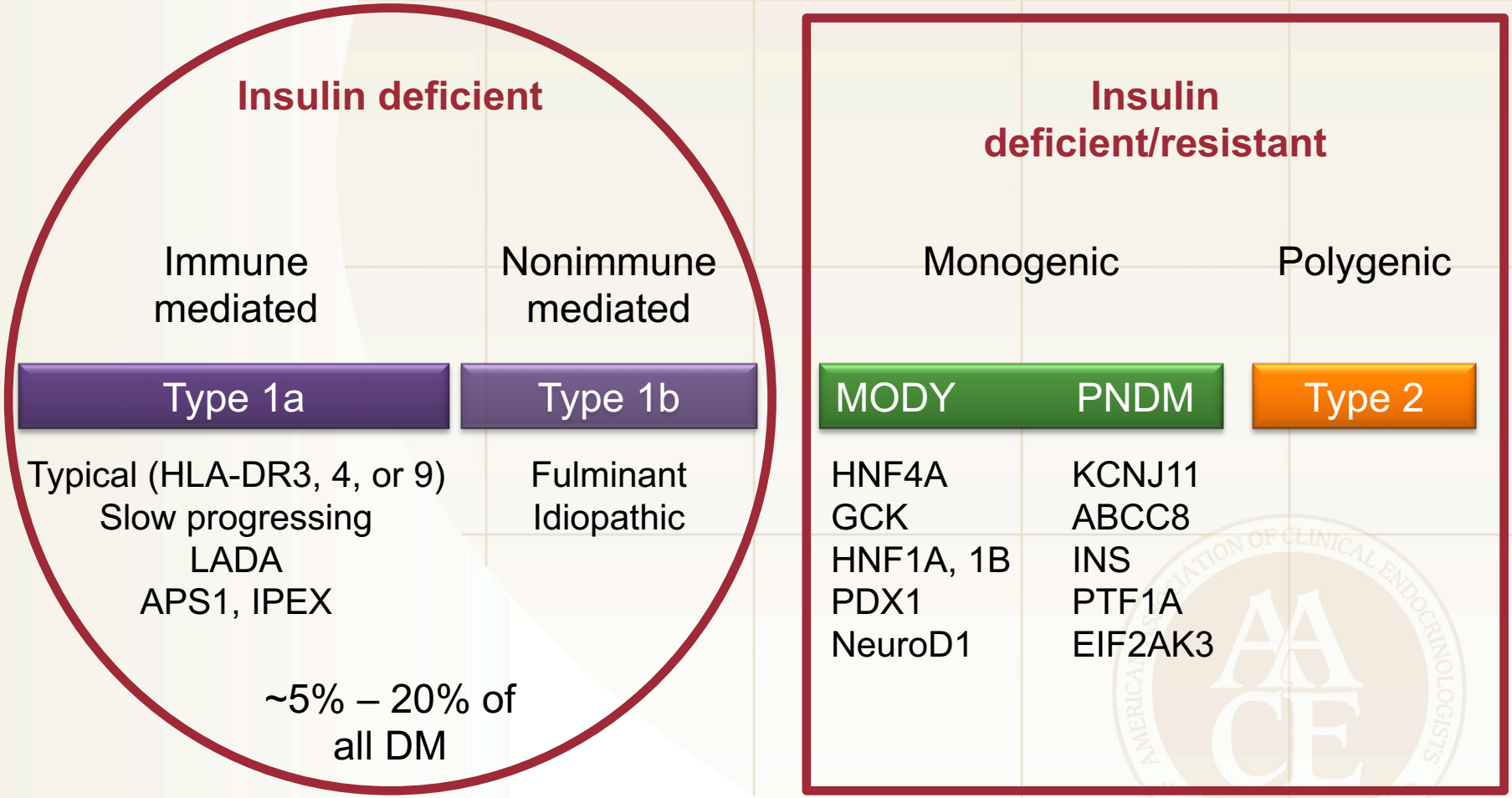
<table>
<tr><td rowspan="2">High-risk HLA* DR3/4, DQ1B1*0302, DR4/4, DR4/8, DR3/3 (10% of T1D population)</td><td rowspan="2">IAA+
GADA+
IA-2A+
or
ZnT8A+</td><td colspan="2">Autoantibody negative at onset</td></tr>
<tr><td colspan="2">C-peptide (ng/mL)</td></tr>
<tr><td>HLA+</td><td colspan="3" rowspan="2">T1aD = 80%</td></tr>
<tr><td>HLA-</td><td>T1bD
5%</td><td>T2D
10%</td></tr>
</table>

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, the tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8; T1aD, type 1 (immune-mediated) diabetes; T1bD, type 1 (idiopathic) diabetes; T2D, type 2 diabetes.

*Needs to be refined for nonwhite population groups.

Rewers M. *Diabetes Metab J.* 2012;36:90-97.

Etiologic Classification of Diabetes



APS1, autoimmune polyendocrine syndromes 1; HLA, human leukocyte antigen; IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome; LADA, latent autoimmune diabetes of adults; MODY, maturity-onset diabetes of the young; PNDM, permanent neonatal diabetes mellitus.

Rewers M. *Diabetes Metab J.* 2012;36:90-97.

Genetic Defects of β-Cell Function

- Chromosome 12, HNF-1α (MODY3)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 20, HNF-4α (MODY1)
- Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
- Chromosome 17, HNF-1β (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Mitochondrial DNA

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Immune-Mediated Diabetes (T1a Diabetes)

β-Cell Destruction

- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

Immune Markers

- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Genetic Markers

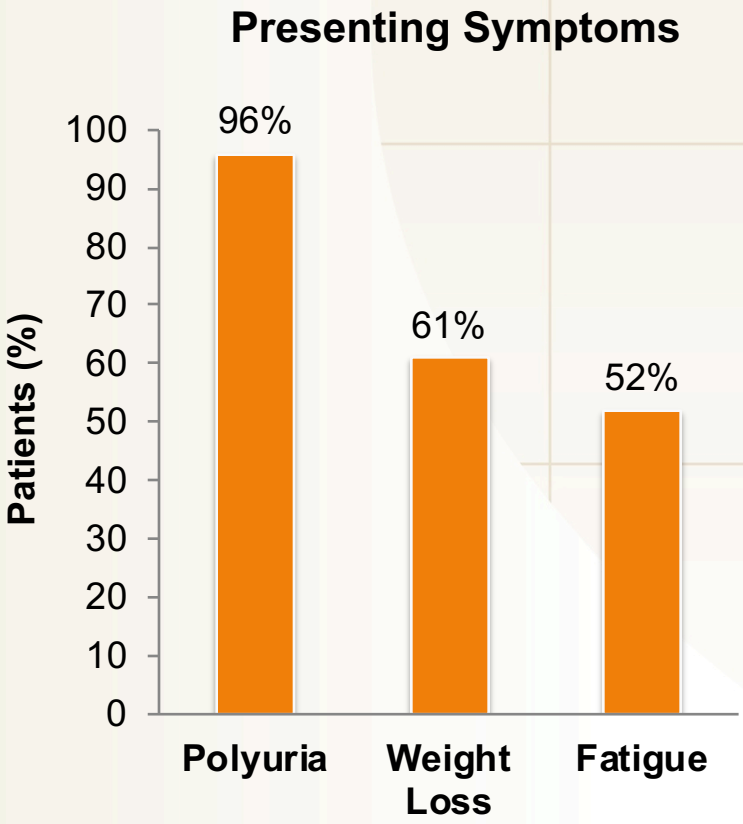
- Strong HLA associations, with linkage to the DQA and DQB genes
- Influenced by the DRB genes
- HLA-DR/DQ alleles can be either predisposing or protective

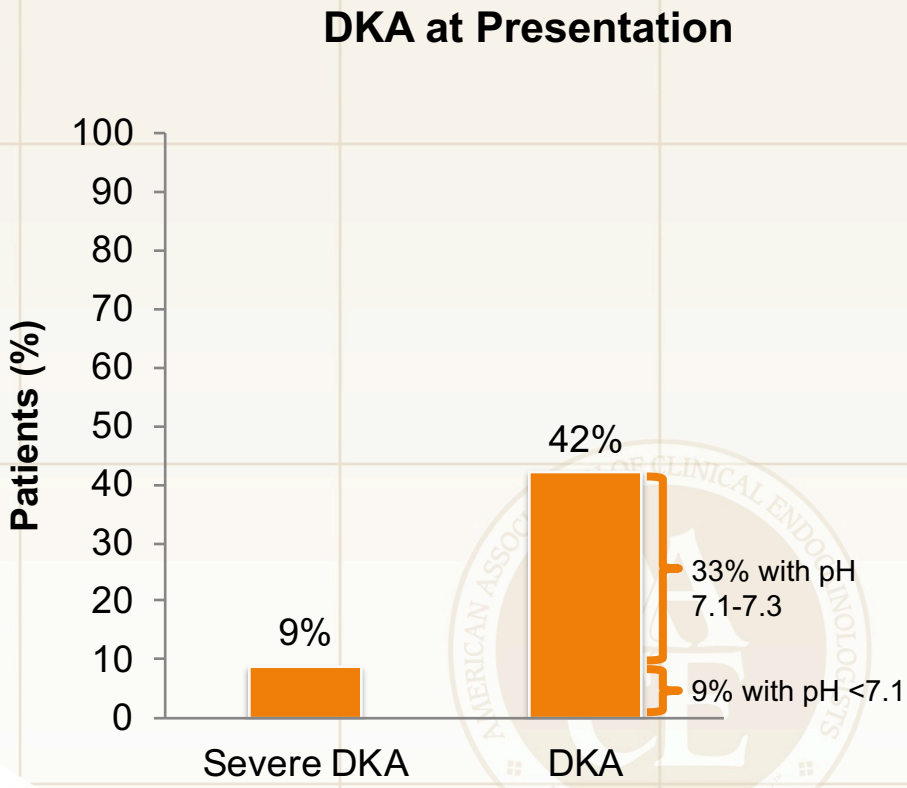
HLA, human leukocyte antigen.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Symptoms and Severity of T1D at Presentation

EURODIAB (N=1260)

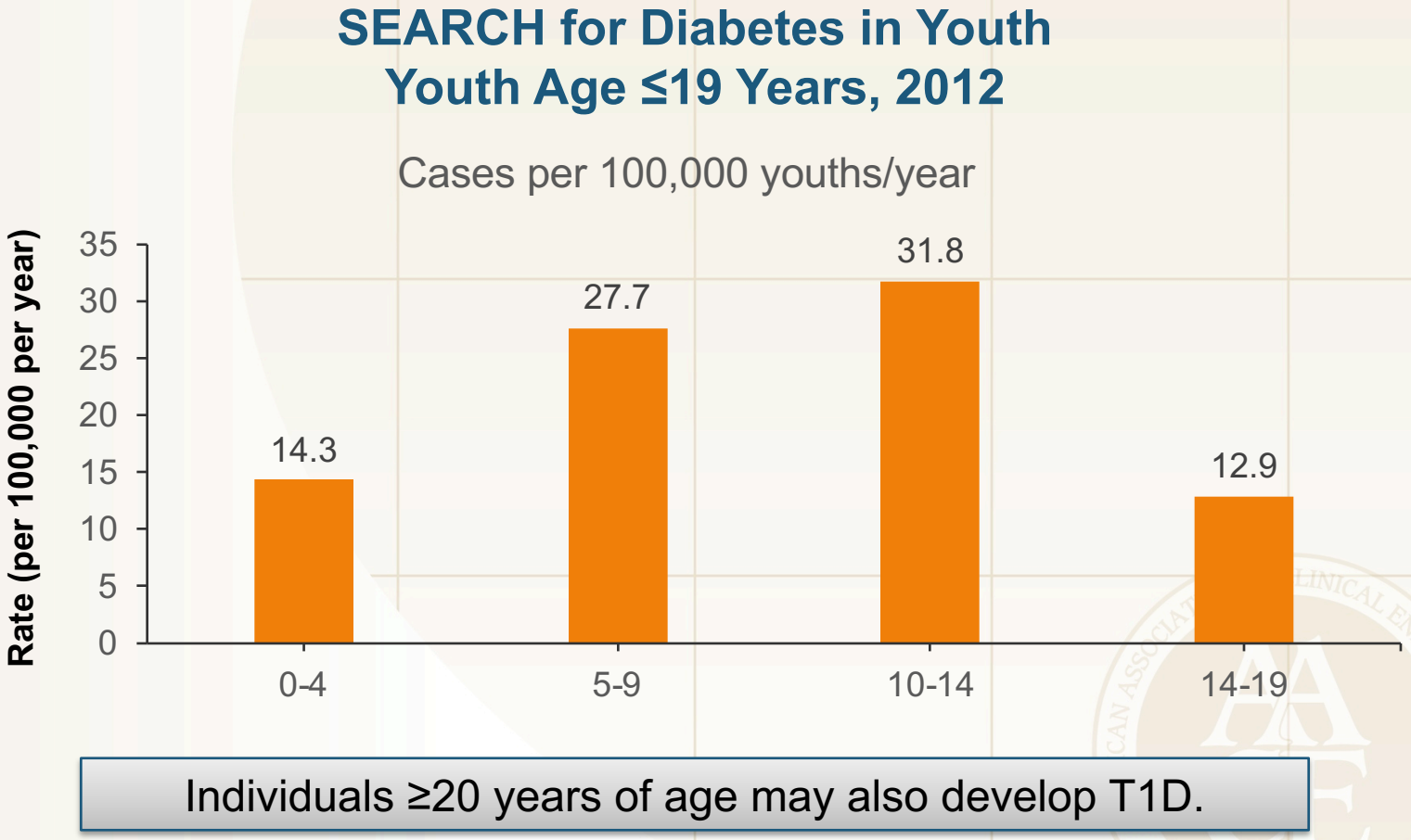




DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

Levy-Marchal C, et al. *Diabetologia*. 2001;44 (Suppl 3):B75-B80.

T1D Age at Diagnosis Among Youth



Individuals ≥20 years of age may also develop T1D.

Mayer-Davis EJ, et al. *N Engl J Med*. 2017;376:1419-1429.

Immunological Changes and Incidence of Type 1 Diabetes

- Rising incidence of T1D is associated with altered immunophenotype at diagnosis
- Prevalence of IA-2A and ZnT8A has increased significantly
- IAA and GADA prevalence and levels have not changed
- Suggests T1D is now characterized by a more intense humoral autoimmune response

IAA, autoantibodies to insulin; GADA, GAD; IA-2A, islet antigen-2; T1D, type 1 diabetes; ZnT8A, zinc transporter 8.

Long AE, et al. *Diabetes*. 2012;61:683-686.

Ketoacidosis in T1D

- First manifestation of T1D in many patients, especially children and adolescents
- May be precipitated by infection or environmental triggers
  - Rapid change from modest fasting hyperglycemia to severe hyperglycemia
- In some patients (especially adults), residual β-cell function may prevent ketoacidosis for many years
  - Once patients become insulin dependent (with low or undetectable plasma C-peptide), they are at risk for ketoacidosis

T1D, type 1 diabetes.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

T1D and Obesity

- Although T1D patients are rarely obese when they present, the presence of obesity is not incompatible with T1D

T1D, type 1 diabetes.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

T1D: Clinical Course

- Typically characterized by the acute onset of the classic symptoms of diabetes
  - Polyuria, polydipsia, weight loss
- Course of autoimmune diabetes characterized by ongoing β-cell destruction
- Exogenous insulin required for survival
  - T1D should be identified as soon as possible to avoid high morbidity due to a delay in insulin treatment

T1D, type 1 diabetes.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

T1D and Susceptibility to Other Autoimmune Diseases

- Addison's disease
- Autoimmune hepatitis
- Celiac sprue
- Graves' disease
- Hashimoto's thyroiditis
- Myasthenia gravis
- Pernicious anemia
- Vitiligo

T1D, type 1 diabetes.

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Idiopathic Diabetes (Type 1b Diabetes)

- No known etiology
- Strongly inherited
  - No immunological evidence for β-cell autoimmunity and no HLA association
  - More common with African or Asian ancestry
- Patient presentation
  - May have permanent insulinopenia
  - Prone to ketoacidosis, with varying degrees of insulin deficiency between episodes

ADA. *Diabetes Care.* 2014;37 (suppl 1):S81-S90.

Fulminant T1D

- Presentation
  - Extremely high glucose levels with diabetic ketoacidosis
  - On average only 4 days of hyperglycemia
  - Normal or near-normal A1C
- Often preceded by common cold–like and gastrointestinal symptoms
- Sometimes associated with pregnancy
- Pancreatic enzymes often elevated

T1D, type 1 diabetes.

Hanafusa T, Imagawa A. *Nat Clin Pract Endocrinol Metab*. 2007;3:36-45.