

# Diabetes-Associated Autoantibodies

## Indications for Ordering

- If pursuing antibody testing to determine autoimmune diabetes mellitus (DM), perform at least 2 antibody tests
  - In most cases, use glutamic acid decarboxylase antibody (GAD) in combination with another insulin antibody test listed below
- Most useful to establish autoimmune etiology in previously diagnosed type 1 DM
- Do not use to differentiate type 1 from type 2 DM, for most cases

## Test Description

### Glutamic Acid Decarboxylase Antibody

- Semiquantitative enzyme-linked immunosorbent assay (ELISA)

### Glutamic Acid Decarboxylase Antibody (GAD65) and Insulin Antibodies with Reflex to IA-2 Antibody

- Quantitative radioimmunoassay/quantitative ELISA

### IA-2 Antibody (IA-2)

- Semiquantitative radioimmunoassay

### Insulin Antibody (IAA)

- Semiquantitative radioimmunoassay

### Zinc Transporter 8 Antibody (ZnT8)

- Semiquantitative ELISA

### Islet Cell Cytoplasmic Antibody, IgG (ICA)

- Semiquantitative indirect fluorescent antibody

## Tests to Consider

### Primary tests

#### Insulin antibody tests

- [Glutamic Acid Decarboxylase Antibody 2001771](#)
  - Use in combination with another insulin antibody test to determine autoimmune DM
- [Glutamic Acid Decarboxylase Antibody \(GAD65\) and Insulin Antibodies with Reflex to IA-2 Antibody 2002862](#)
  - Panel test most useful to establish autoimmune etiology in previously diagnosed type 1 DM
  - If either GAD or IAA is negative, then IA-2 will be added
- [IA-2 Antibody 0050202](#)

- [Insulin Antibody 0099228](#)

- Use to determine presence of antibodies to exogenous insulin analogues
- Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur

- [Zinc Transporter 8 Antibody 2006196](#)

- [Islet Cell Cytoplasmic Antibody, IgG 0050138](#)

### Related tests

Diagnose and monitor DM and prediabetes

- [Hemoglobin A1c 0070426](#)

- [Glucose Tolerance Test 0020542](#)

- [Glucose, Plasma or Serum 0020024](#)

## Disease Overview

### Type 1 DM

#### Prevalence

- Most common metabolic disease of childhood
  - 1/400-600 children and adolescents
- ~5-10% of all diagnosed cases of diabetes in adults

**Age of onset** – most common in children but can develop in individuals of any age, especially in late 30s or early 40s

#### Symptoms

- Excessive thirst, hunger, and urination
- Fatigue, nausea, blurred vision
- Unexplained weight loss
- Obesity is rare when individual is first diagnosed
- May have other autoimmune disorders

#### Physiology

- Caused by autoimmune-mediated destruction of insulin-producing beta cells of the islets of Langerhans in the pancreas
- Five major autoantibodies of diagnostic interest
  - GAD
  - IA-2
  - IAA
  - ZnT8
  - ICA
- Antibodies may be present in individuals years before the onset of clinical symptoms
- Presence of these antibodies in individuals with diabetes confirms an autoimmune etiology

## Test Interpretation

### Sensitivity/specificity

Moderate sensitivity, high specificity in newly diagnosed type 1 DM

- Presence of antibodies may decrease with prolonged disease
- Insulin antibody testing loses specificity once patient has been on exogenous insulin for >2 weeks

### Results

- Presence of multiple insulin antibodies (GAD, IA-2, IAA, ZnT8, and ICA) is highly suggestive of type 1 DM
- If one autoantibody is found, others should be assayed
  - Risk of type 1 DM increases (>90%) if an individual tests positive for 2 or more autoantibodies
- For further risk stratification, HLA DR/DQ genotyping may be helpful

### Limitations

- Negative test results do not rule out autoimmune diabetes
  - Autoantibody response varies in individuals
- Presence of a single autoantibody in the absence of clinical symptoms has low predictive value (1-2% in healthy individuals)
- Not all individuals with antibodies will develop type 1 DM
- Do not use to monitor or diagnose type 1 DM
- Insulin antibody RIA test does not differentiate between antibodies specific for endogenous and exogenous forms of insulin

### References

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Indications for Insulin Antibody Testing	
<ul style="list-style-type: none"> <li>• <b>Do not order individual antibody tests;</b> order at least 2 antibodies if pursuing testing (Insel, 2015)</li> <li>• For most cases, use GAD in combination with <math>\geq 1</math> of the following – IA-2, IAA, ZnT8, ICA</li> </ul>	
<b>Type 1 DM</b>	<ul style="list-style-type: none"> <li>• Patient should have diagnosed DM                             <ul style="list-style-type: none"> <li>◦ Antibody testing is not useful for the diagnosis of DM</li> <li>◦ Patients should ideally be receiving insulin <math>\leq 2</math> weeks                                     <ul style="list-style-type: none"> <li>▪ Testing not recommended for patients receiving insulin &gt;2 weeks, as insulin antibody formation may occur (false-positive result possible)</li> </ul> </li> </ul> </li> <li>• Most useful in newly diagnosed DM in children &lt;18 years to establish autoimmune etiology (ADA, 2016; AACE, 2015)</li> <li>• May be useful in difficult adult cases when it is unclear if patient has type 1 or 2 DM (Bingley, 2010)</li> </ul>
<b>Type 2 DM</b>	<ul style="list-style-type: none"> <li>• No indication for routine evaluation or management (Insel, 2015)</li> </ul>
<b>Screening</b>	<ul style="list-style-type: none"> <li>• Not recommended for screening family members of patients with type 1 DM (so-called risk prediction) except in research settings (ADA, 2016)</li> </ul>

### Indications for Insulin Antibody Testing

#### Limited Use

Latent autoimmune DM in adults (LADA)

- Differentiate LADA from type 2 DM (Lampasona, 2010; Stenström, 2005; Nambam, 2010)

Genetic testing

- Identify patients with DM for whom a genetic etiology is suspected (eg, monogenic DM, maturity onset diabetes of the young [MODY]) (Bingley, 2010; NIH, 2016)
  - Lack of antibodies suggests these genetic disorders

Gestational diabetes mellitus (GDM)

- Screen women with history of GDM to identify those at high risk for progression to type 1 DM (Nilsson, 2007; de Leiva, 2007; Bingley, 2010)
  - No evidence to suggest test results alter outcomes or improve care when compared to intermittent hemoglobin A1c testing

DM = diabetes mellitus, GAD = glutamic acid decarboxylase antibody, IA-2 = islet antigen-2, IAA = insulin antibody, ICA = islet cell cytoplasmic antibody, ZnT8 = zinc transporter 8 antibody