
***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Islet Cell Autoantibody Testing

Description/Background

Over 90% of diabetes can be attributed to either type 1 or type 2 diabetes; however, there are atypical forms of diabetes that must be considered in the evaluation of the diabetic patient.[1] The focus of this policy is the identification of two atypical forms: latent autoimmune diabetes in adults and idiopathic diabetes.

Islet autoantibodies (iAb) are markers of pancreatic autoimmune disease that recognize antigens found in insulin-producing pancreatic beta cells (islet cells). These antigens are found on the surface of islet cells, within the islet cells or are products of islet cells. Currently, there are five well-characterized iAb: islet cell cytoplasmic autoantibodies (ICA), glutamic acid decarboxylase autoantibodies (GADA or GAD65), insulinoma-associated-2 autoantibodies (IA-2A), zinc transporter 8 autoantibodies (ZnT8A) and insulin autoantibodies (IAA). These are directed against autoantigens: islet cell cytoplasm autoantigens (other than GAD65), glutamic decarboxylase (GAD65), insulinoma-like tyrosine-phosphatase-2 (IA-2), islet beta-cell zinc cation efflux transporter 8 (ZnT8), and insulin, respectively. IA-2 and ZnT8 reside on the surface of secretory granules in beta cells, insulin lies within the secretory granules, and ICA and GAD65 inhabits the cytoplasm of microvesicles.[2]

Latent Autoimmune Diabetes in Adults (LADA)
LADA is an autoimmune disorder that, as in type 1 diabetes, results in destruction of insulin-producing beta cells. However, it presents with a later onset (in the third or fourth decade of life) and with a lower BMI compared to what is typical in type 2 diabetes. Its presentation often results in misdiagnosis as type 2 diabetes. Inappropriate treatment of LADA with type 2 diabetes strategies may lead to insufficient glycemic control. To differentiate LADA from type 1 or type 2 diabetes, the Immunology of Diabetes Society has proposed three criteria: (a) adult age of onset (> 30 years of age); (b) presence of at least one circulating autoantibody (GAD, ICA, IAA or IA-2) and; (c) insulin independence for the first 6 months after the time of diagnosis. Of the various antibodies associated with autoimmune diabetes, GAD autoantibodies are present in most patients with LADA.[1,3]

Idiopathic diabetes

This form of diabetes is also referred to as “atypical diabetes”, “ketosis-prone diabetes” or “Flatbush diabetes” and has no known etiology. It is characterized by the acute onset of severe hyperglycemia with or without ketoacidosis, mimicking type 1 diabetes. During the hyperglycemia episode, patients with ketosis-prone diabetes lose the ability of glucose to stimulate beta cell insulin secretion; however, nonglycemic pharmacologic agents (glucagon and arginine) will stimulate insulin secretion. Following restoration of normal glycemia, the ability of glucose to stimulate insulin secretion returns toward normal and by 8 to 12 weeks has maximally improved. Although most patients are able to stop insulin therapy, there are some specific patient populations who may continue to require insulin treatment: African American, African-Caribbean, or sub-Saharan African populations; Hispanic populations; and Chinese, Indian, and Japanese populations.[1] This classification of diabetes has four categories, based on the presence of autoantibodies and β-cell function. Patients can resemble either type 1 diabetes (lean and poor β-cell function) or type 2 diabetes (BMI ≥ 28 and preserved β-cell function). Classification of ketosis-prone diabetes should be performed following discharge from the hospital by testing C-peptide levels and GAD autoantibodies.[4]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. Tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing.

The following laboratories are certified under the Clinical Laboratory Improvement Amendments, and provide testing for Glutamic Acid Decarboxylase Antibody: ARUP Laboratories, Mayo Medical Laboratories, LabCorp, Quest Diagnostics, etc. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

The U.S. Food and Drug Administration (FDA) in 2005 granted 510(k) premarket approval to the KRONUS (Star, ID) Glutamic Acid Decarboxylase Antibody (GADAb) RIA Assay Kit (K051061). It is indicated as a useful aid in the diagnosis of Type I diabetes (autoimmune mediated diabetes). Product code NWG.

Medical Policy Statement

Islet cell autoantibody testing is considered **established** when used for medical management of an individual with diabetes when criteria is met.

Islet cell autoantibody testing for any other indication, such as predicting the onset of diabetes, is considered experimental/investigational as the clinical utility has not been established.

Inclusionary and Exclusionary Guidelines

Inclusions:

Islet cell autoantibody testing is considered established when it is used to distinguish type 1 diabetes from type 2 diabetes in an individual whose clinical history is ambiguous and there is suspicion of:

- Latent autoimmune diabetes in adults (LADA); OR
- Idiopathic (atypical, ketosis-prone) diabetes

Islet cell autoantibody testing for any indication other than above (such as predicting the onset of diabetes) is considered experimental/investigational as the clinical utility has not been established.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

86337 86341

Other codes (investigational, not medically necessary, etc.):

NA

Note: Codes may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Fagbemi et al (2017) reported on a study in the Republic of Benin, West Africa, of 102 individuals, 51 of whom had type 1 diabetes and 51 of whom had type 2 diabetes. The aim of the study was to assess the prevalence of GAD65 antibodies (GAD65Ab) and investigate the association of GAD65Ab with C-peptide values and with HLA Class II alleles genotyping. GAD65Ab were found to be present in 74.5% of those with type 1 diabetes. The GAD65Ab test sensitivity and specificity were found to be 74.5% and 94.1%, respectively.[5]

Römkens et al (2006) sought to establish the prevalence of GAD antibodies in a diabetic outpatient clinic of a Dutch, non-university teaching hospital. The authors noted that 95% of European patients with type 1 diabetes have GAD65 and/or IA2 antibodies, confirming the autoimmune etiology. The authors also identified that a subgroup of diabetic patients exist that have evidence of autoimmunity but who clinically resemble type 2 diabetes at diagnosis – those with latent autoimmune diabetes in adults (LADA). GAD65 antibodies were evaluated in

244 type 2 diabetic patients who were on oral therapy for at least three months before becoming insulin-dependent. GAD65 antibodies were found in 26 of the patients (11.6%).[6] Demographic characteristics were compared to those who were negative for GAD65 antibodies. Those with GAD65 antibodies had fewer metabolic syndrome features.

Lebastchi and Herold (2012) reported on results from two workshops that used blinded samples to determine is autoantibodies could distinguish patients with type 1 diabetes from healthy control subjects. Sixty-one percent of subjects with type 1 diabetes were positive for 2 or more autoantibodies versus 0% of the control subjects. In evaluation of the sensitivity, specificity, and reproducibility of immunologic markers in type 1 diabetes, the specificity for any single autoantibody ranged from 92%–99% in one workshop, or 85% in the other workshop. However, the sensitivity of autoantibody measurements was as low as 59%–67% when a single autoantibody was measured. When any one of two autoantibodies (i.e., GADA and/or IA-2A) was present, the sensitivity improved.[7]

The Danish Diabetes Academy Workshop (2014), in their discussion of immunological features of type 1 diabetes, stated that “GADA is by far the most common autoantibody in adult-onset diabetes (90% of positive cases) …”[8]

Guidelines from the Royal Australian College of General Practitioners (RACGP) (2020), recommend that for suspicion of type 1 diabetes to consider non-urgent confirmatory tests for glutamic acid decarboxylase (GAD) and/or insulinoma antigen-2 (IA-2) antibodies. They note “These will be present in 90% of patients with type 1 diabetes. When measuring antibodies, higher rates of false negative results occur early in the development of type 1 diabetes. However, false negative results decrease when two different antibody tests are measured.”

The guidelines further state that “latent autoimmune diabetes of adults (LADA – also called ‘type 1.5’ diabetes) is diabetes with β-islet cell antibodies that occurs more commonly in adulthood. LADA often presents similarly to type 2 diabetes, but it involves a more rapid course of β-cell destruction, a poorer metabolic response to non-insulin therapy and a more rapid progression to requiring insulin to control hyperglycemia due to β-cell failure.”[9]

Measurement of GAD65 antibodies has been proposed for evaluating the risk of developing type 1 diabetes in persons at high risk. However, the value of this testing is unproven, as there are no interventions that have been demonstrated to be effective in preventing the onset of type 1 diabetes. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (Prebtani et al 2018) discuss two trials of interventions to prevent or delay the onset of type 1 diabetes. The guidelines conclude that “As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.”[10]

Supplemental Information

The American Diabetes Association, Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2020

Type 2 Diabetes:

> The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior gestational diabetes mellitus (GDM), in those with hypertension or dyslipidemia, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives, more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood. In adults without traditional risk factors for type 2 diabetes and/or younger age, consider antibody testing (eg, GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes.[11]

The American Association of Clinical Endocrinologists and American College of Endocrinology
Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan 2015[12], state:

> Recommendation 6
> T1D is usually characterized by absolute insulin deficiency and should be confirmed by the presence of autoantibodies to glutamic acid decarboxylase, pancreatic islet β cells (tyrosine phosphatase IA-2), zinc transporter (ZnT8), and/or insulin (Grade A; BEL 1). [Recommendation grade Strong; Evidence grade Strong]

Government Regulations
National/Local:

There is no NCD or LCD regarding islet cell autoantibody testing for diabetes.

Local:

There is no LCD on this topic.

CMS Clinical Laboratory Fee Schedule 2024 lists a fee for billing codes 86337 and 86341. A listed fee is not a guarantee of payment.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

NA

References

1. Feingold KR. Atypical forms of diabetes. (Updated 2019 Mar 19). Endotext (Internet). South Dartmouth (MA). https://www.ncbi.nlm.nih.gov/books/NBK279128/ Accessed 9/13/24.
2. Simmons KM et al. Islet autoantibody testing: current utility, future prospects in predicting and diagnosing type 1 diabetes. American Association for Clinical Chemistry, Clinical Laboratory News Jul 1, 2017 https://www.aacc.org/cln/articles/2017/july/islet-autoantibody-testing-predicting-and-diagnosing-type-1-diabetes Accessed 9/13/24.
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12. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. AACE / ACE Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan – 2015. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015 - PubMed (nih.gov)Accessed 9/13/24

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/13/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/18/03	3/18/03	3/4/03	Joint policy established
5/1/07	2/10/07	2/10/07	Routine maintenance
7/1/09	4/21/09	5/14/09	Routine maintenance; references updated
9/1/12	6/12/12	6/19/12	Routine maintenance; references updated. Policy reformatted on new template
3/1/14	12/10/13	1/6/14	Routine maintenance
5/1/15	2/17/15	2/27/15	Routine maintenance Policy recommended for retirement
11/1/18	12/15/20		Policy unretired. New title: Islet Cell Autoantibody Testing; new status of MXD.
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		Routine maintenance Vendor: NA (No Avalon Policy)
3/1/23	12/20/22		Routine maintenance (jf) Vendor: NA (No Avalon Policy)
3/1/24	12/19/23		Routine maintenance (jf) Vendor: NA
3/1/25	12/17/24		Routine maintenance (jf) Vendor: NA • MPS and inclusions edited o Removal of a patient, added an individual

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ISLET CELL AUTOANTIBODY TESTING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered
BCNA (Medicare Advantage)	See Government Regulations Section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.