



Type 1 diabetes screening handbook

A comprehensive guide to early identification of T1D

INDICATION

TZIELD is a CD3-directed monoclonal antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

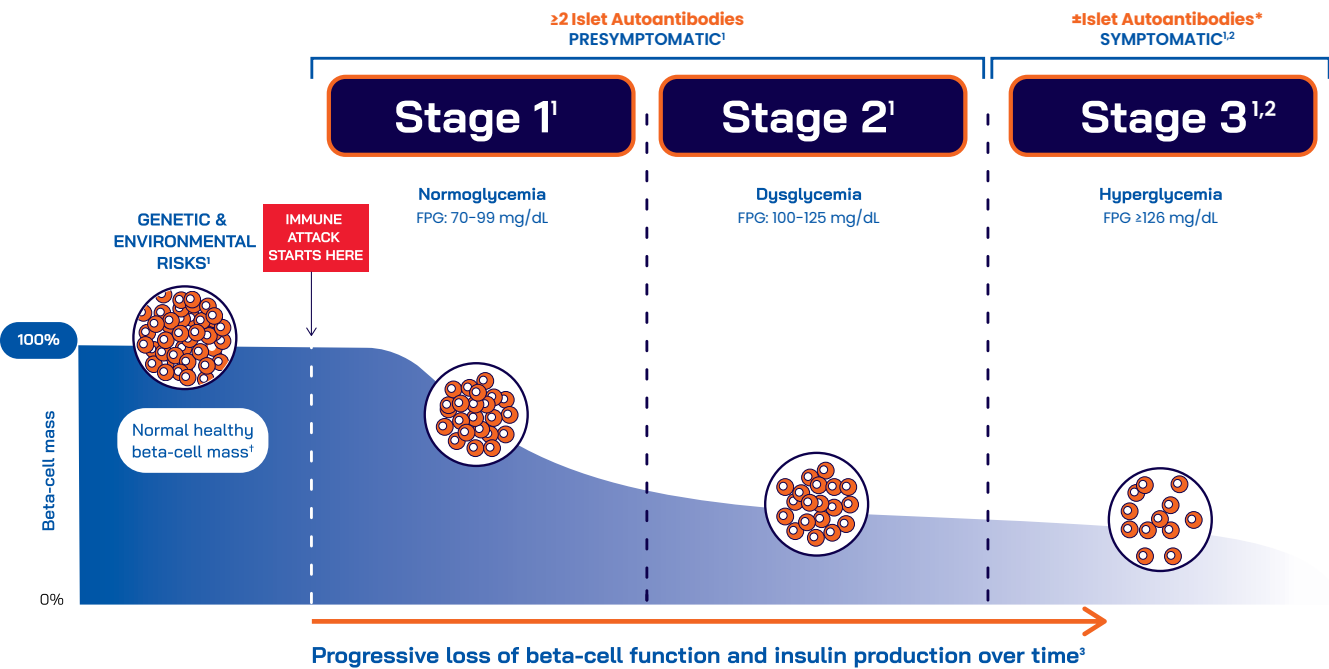
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Cytokine Release Syndrome (CRS):** CRS occurred in TZIELD-treated patients during the treatment period and through 28 days after the last drug administration. Prior to TZIELD treatment, premedicate with antipyretics, antihistamines and/or antiemetics, and treat similarly if symptoms occur during treatment. If severe CRS develops, consider pausing dosing for 1 day to 2 days and administering the remaining doses to complete the full 14-day course on consecutive days; or discontinue treatment. Monitor liver enzymes during treatment. Discontinue TZIELD treatment in patients who develop elevated alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.

Autoimmune T1D progression is not a matter of if, but when¹

T1D occurs in 3 distinct and detectable stages determined by the presence of islet AAbs and glycemic status¹



When positive for ≥2 islet AAbs, the lifetime risk for progression to Stage 3 T1D approaches 100%.¹

¹AAbs may become absent at this stage.
²For illustrative purposes only.
AAb=autoantibody; T1D=type 1 diabetes.

Presence of ≥2 AAbs in addition to glycemic status determines a patient’s Stage of autoimmune T1D

Key characteristics of each stage include:

	Stage 1 ^{1,2,4}	Stage 2 ^{1,2,4}	Stage 3 ^{1,2,4}
Autoimmunity	⚠️ ≥2 autoantibodies	⚠️ ≥2 autoantibodies	⚠️ ± autoantibodies*
Symptoms	✅ No symptoms	✅ No symptoms	⚠️ Symptomatic [†]
Glycemic Status	✅ Normoglycemia ³	⚠️ Dysglycemia ³	⚠️ Hyperglycemia ³
• Fasting Plasma Glucose ⁴	70–99 mg/dL	100–125 mg/dL	≥126 mg/dL
• HbA1c ⁴	<5.7%	5.7%–6.4% or ≥10% increase in HbA1c	≥6.5%
• Oral Glucose Tolerance Test ⁴	<140 mg/dL	140–199 mg/dL	≥200 mg/dL

*AAbs may become absent at this stage.
[†]Classic hyperglycemic symptoms include polyuria, polydipsia, and unexplained weight loss.
AAbs=autoantibodies; ADA=American Diabetes Association; JDRF=Juvenile Diabetes Research Foundation.



Certain groups may be at increased risk for autoimmune T1D

The American Diabetes Association (ADA) recommends screening for 4 islet AAbs^{2*}



Experts recommend screening for the following groups:



Relatives of patients with T1D⁵

First-degree family members have a **~15x greater risk** of T1D versus the general public



Those with personal/family history of certain autoimmune diseases, including⁶

- Hashimoto's disease
- Graves' disease
- Celiac disease



Those with abnormal glucose levels^{2,7}

Over **40% of adults >30 years of age with T1D are initially diagnosed with T2D** and the risk of error increases with age

Proactive screening helps determine whether abnormal glucose levels are related to an autoimmune attack (type 1) or insulin resistance (type 2)



- Glutamic acid decarboxylase 65 AAb (**GADA**)
- Insulinoma-associated antigen 2 AAb (**IA-2A**)
- Insulin AAb (**IAA**)
- Zinc transporter-8 AAb (**ZnT8A**)

Screening identifies those at risk of T1D and gives them the potential to^{3,8,9}:

- Reduce the risk of DKA at T1D diagnosis
- Prepare for disease management
- Seek presymptomatic intervention

T2D=type 2 diabetes.

*Islet cell AAb (ICA) is also available for testing, but is not recommended as it is an imprecise biological assay.⁷





Guidance on initial screening ¹⁰	
Children	Adults
Screen during recommended well-child visits to improve feasibility, starting as early as age 1. Screen at: ✓ 1-2 years of age ✓ 11-13 years of age	Screen during recommended yearly visits to help improve feasibility.

If negative for AAbs ¹⁰	
Children	Adults
<ul style="list-style-type: none">Rescreen patients with increased risk in 1 yearFor all other patients, rescreen around 6 years and 9-11 years	<ul style="list-style-type: none">Rescreen patients with increased risk in 1 year

If positive for 1 AAb ¹⁰	
Children	Adults
<ul style="list-style-type: none">Conduct confirmatory tests and consider collaborating with specialistsIf <3 years: rescreen every 6 months for 3 years, then annually for 3 more years<ul style="list-style-type: none">If no additional AAbs, stop AAb screeningIf ≥3 years: rescreen annually for 3 years<ul style="list-style-type: none">If no additional AAbs, stop AAb screening	<ul style="list-style-type: none">Conduct confirmatory testsFor patients with increased risk: to monitor for risk of progression, screen annuallyFor all other patients: repeat screen every 3 years

If positive for ≥2 AAbs, collaborate and/or refer to a specialist based on stage¹¹

Patients positive for 1 AAb*†	
Children	Adults
<ul style="list-style-type: none">After first positive screen: RBG and HbA1c with AAb screening for 2 years	<ul style="list-style-type: none">Consider annual monitoring if the patient has a first-degree relative with T1D or elevated T1D genetic risk, dysglycemia, or history of stress hyperglycemiaIf no risk factors, perform metabolic monitoring every 3 years

Patients with Stage 1 T1D*†	
Children	Adults
<ul style="list-style-type: none">Repeat HbA1c with RBG or 10-14 day CGM:<ul style="list-style-type: none">If <3 years of age: every 3 monthsIf 3-9 years of age: every 6 monthsIf >9 years of age: annuallyTo diagnose progression to Stage 2 or Stage 3: use OGTT or a 2-hour blood glucose test	<ul style="list-style-type: none">Provide SMBG meters/strips to check glucose with illness or symptomsRepeat HbA1c annually<ul style="list-style-type: none">Adjust frequency according to individual riskIf HbA1c changes by ≥10%, perform OGTT to stageIf normoglycemic for 5 years, reduce monitoring to every 2 years

Patients with Stage 2 T1D*†	
Children	Adults
<ul style="list-style-type: none">Provide SMBG meters/stripsMonitor metabolic status every 3 months	<ul style="list-style-type: none">Monitor metabolic status every 6 months using HbA1c and one of the following: blinded CGM, higher frequency SMBG, or 2-hour plasma glucose following OGTT<ul style="list-style-type: none">If HbA1c changes by ≥10%, perform OGTT to stageConsider C-peptide assessment to ensure proper classification

*Please refer to the full Breakthrough T1D consensus guidance for recommendations on psychosocial assessment and support for screened patients.
†The full Breakthrough T1D consensus guidance includes 6 possible metabolic monitoring methods: CGM, C-peptide, HbA1c, OGTT, random blood glucose, and SMBG.⁴ CGM=continuous glucose monitoring; RBG=random blood glucose; SMBG=self-monitoring blood glucose.



Screening options in your community for those at risk of autoimmune T1D



	TEST	WHERE	ELIGIBILITY	ADA Recommended ²				
				GADA	IAA	IA-2A	ZnT8A	ICA
Commercial Labs ^{2,3}	Blood draw	<ul style="list-style-type: none">At commercial lab (eg, Labcorp, Quest Diagnostics) or HCP's officeResults shared with patient and provider	<ul style="list-style-type: none">Any individual with a valid script from a licensed HCPCost based on insurance coverageMost insurance plans cover some or all of the patient cost	✓	✓	✓	✓	✓
Type 1 Diabetes Screening Central Screenfortype1.com	Blood draw or finger stick	<ul style="list-style-type: none">In lab or kit sent to patient from Screening Central telemed practitioner, if appropriateVia telehealth appointment	<ul style="list-style-type: none">Costs are variable based on service	✓	✓	✓	✓	
Varies depending on method of screening								
Online Ordering ^{12,13}	Dried blood spot	<ul style="list-style-type: none">Testing kits can be sent by vendors, such as Enable Biosciences clinical@enablebiosciences.comResults shared with both patient and provider	<ul style="list-style-type: none">Any individual regardless of family history of T1DMay be processed and covered by insuranceMost insurance plans cover some or all the patient cost	✓	✓	✓		
Autoimmunity Screening for Kids (ASK) ¹⁴⁻¹⁶ AskHealth.org	Blood draw or finger stick	<ul style="list-style-type: none">At Barbara Davis Center for Diabetes in Aurora or other Colorado locationsAt-home screening kits available for familiesResults shared with patient with option for provider	<ul style="list-style-type: none">Any individual (age 1 or older) with or without a family history of T1DNo out-of-pocket costs	✓	✓	✓	✓	
TrialNet ^{3*†} TrialNet.org/participate	Blood draw or finger stick	<ul style="list-style-type: none">At TrialNet location, event, or health fairPatient may also administer a kit at home or bring it to Labcorp or Quest DiagnosticsOnly patient is notified with results	<ul style="list-style-type: none">Only for those individuals with a family history of T1D with certain age restrictions[‡] or those who already tested positive through another programNo out-of-pocket costs	✓	✓	✓	✓	✓
AAb testing available after ≥1 AAbs are found [‡]								

This may not be an exhaustive list of available screening options. The appropriateness of any AAb screening test and the validity of the test results are up to the requesting physician to determine

[‡]In screening, a simple blood test is done to screen for the presence of diabetes-related biochemical autoantibodies (GADA and mIAA). Additional autoantibodies ICA, IA-2A, and ZnT8A will also be measured in individuals positive for mIAA. ICA, IA-2A, and ZnT8A will be measured in individuals positive for GADA.

[†]TrialNet has an age limit of 2.5-45 years for first-degree relatives and 2.5-20 years for second-degree relatives.

*TrialNet will initially test for 2 autoantibodies. If 1 or more autoantibodies are found with the first test, additional testing may be done to screen for other autoantibodies as indicated by the ≥ symbols.



Sample codes for testing*

This is a list of autoimmune T1D codes available as of October 2024; appropriate codes can vary by patient, setting of care, and payer.

Determination, verification, and use of correct coding are the sole responsibility of the provider submitting the claim for the item or service. Sanofi does not make any representation or guarantees concerning reimbursement or coverage for any service or item.

CPT® codes for T1D-related pancreatic islet AAb immunoassays ^{17,18}	
Description	Code
Glutamic acid decarboxylase 65 AAb (GADA) [†]	86341
Insulinoma-associated antigen 2 AAb (IA-2A) [†]	
Zinc transporter-8 AAb (ZnT8A) [†]	
Islet cell autoantibody (ICA)	86337
Insulin autoantibody (IAA) [†]	

CPT® codes for measuring dysglycemia ¹⁹	
Description	Code
Glucose tolerance test (GTT), 3 specimens (includes glucose)	82951
Glucose; quantitative, blood (except reagent strip)	82947
Glucose post glucose dose (includes glucose)	82950
Hemoglobin glycosylated (A1C)	83036

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*A specific test code may be required in addition to the CPT code. Please confirm which codes are required for your preferred laboratory.
[†]ADA-recommended pancreatic islet AAbs.

Commercial lab order codes

Quest Diagnostics ²²	
Description	Code
Diabetes Type 1 Autoantibody Panel (GADA, IA-2A, IAA, ZnT8A) [†]	13621
ICA Screen with Reflex to Titer	36741

Labcorp ¹⁸	
Description	Code
Diabetes Autoimmune Profile (includes GADA, IA-2A, IAA, and ZnT8A) [†]	504050
Antipancreatic Islet Cells	160721

The average national out-of-pocket cost for T1D AAb screening is \$14[‡]

Cost for AAb screening varies by health plan, benefit design, and test. Please check with the health plan to confirm costs for patients.

[‡]n=[4114]. Analysis has been conducted using LAAD Medical and Remittance data from [November 2022 to December 2023]. Includes commercial claims with one of the following current procedural technology (CPT) codes: 86341 and/or 86337. Note: The analysis does not differentiate between the number of autoantibodies tested within each claim.

References: **1.** Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care.* 2015;38(10):1964-1974. **2.** American Diabetes Association Professional Practice Committee. Diagnosis and classification of diabetes: standards of care in diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S20-S42. **3.** Scheiner G, Weiner S, Kruger D, Pettus J. Screening for type 1 diabetes: Role of the diabetes care and education specialist. *ADCS Pract.* 2022;10(5):20-25. **4.** American Diabetes Association. Blood glucose & A1C diagnosis. Accessed July 17, 2024. <https://diabetes.org/about-diabetes/diagnosis> **5.** Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD Clinical Practice Consensus Guidelines Actor 2018 portrayal: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19(suppl 27):20-27. **6.** Popoviciu MS, Kaka N, Sethi Y, et al. Type 1 diabetes mellitus and autoimmune diseases: a critical review of the association and the application of personalized medicine. *J Pers Med.* 2023;13(3):422. **7.** Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of Type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2021;64(12):2609-2652. **8.** Elding Larsson H, Vehik K, Bell R, et al. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. *Diabetes Care.* 2011;34(11):2347-2352. **9.** Barker JM, Goehrig SH, Barriga K, et al. DAISY study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care.* 2004;27(6):1399-1404. **10.** Simmons KMW, Frohnert BI, O'Donnell HK, et al. Historical insights and current perspectives on the diagnosis and management of presymptomatic type 1 diabetes. *Diabetes Technol Ther.* 2023;25(11):790-799. **11.** Phillip M, Achenbach P, Addala A, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. *Diabetes Care.* 2024;47(8):1276-1298. **12.** Enable Biosciences. The role of autoantibodies in type 1 diabetes. Published January 2023. Accessed December 15, 2023. <https://blog.enablebiosciences.com/2023/01/19/the-role-of-autoantibodies-in-type-1-diabetes/> **13.** Enable Biosciences. Type 1 Testing. Accessed December 15, 2023. <https://type1testing.enablebiosciences.com/order-form-2> **14.** McQueen RB, Geno Rasmussen C, Waugh K, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care.* 2020;43(7):1496-1503. **15.** ASK. ASK study screening form. Accessed December 15, 2023. <https://redcap.ucdenver.edu/surveys/?s=YLWCN8MT9R> **16.** ASK. Screening locations. Accessed December 15, 2023. <https://www.askhealth.org/locations> **17.** Breakthrough T1D Formerly JDRF. Breakthrough T1D Early Detection. Accessed September 20, 2024. <https://www.breakthrought1d.org/early-detection/#:-:text=Insulin> **18.** Labcorp. Test menu. Accessed July 29, 2024. <https://specialtytesting.labcorp.com/test-menu/search> **19.** National Institute of Diabetes and Digestive and Kidney Diseases. Reimbursement & coding for prediabetes screening. <https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/diabetes/game-plan-preventing-type-2-diabetes/reimbursement-coding> **20.** ICD10Data.com The Web's Free 2024 ICD-10-CM/PCS Medical Coding Reference. Accessed September 20, 2024. <https://www.icd10data.com/> **21.** Association of Clinical Documentation Integrity Specialists. News: FY 2025 ICD-10-CM code updates, guidelines released. Accessed September 20, 2024. <https://acdis.org/articles/news-fy-2025-icd-10-cm-code-updates-guidelines-released> **22.** Quest Diagnostics. Test directory. Accessed July 29, 2024. <https://testdirectory.questdiagnostics.com/test/home> **23.** TZIELD Prescribing Information. Provention Bio, Inc; 2023.





IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

- **Serious Infections:** Use of TZIELD is not recommended in patients with active serious infection or chronic infection other than localized skin infections. Monitor patients for signs and symptoms of infection during and after TZIELD administration. If serious infection develops, treat appropriately, and discontinue TZIELD.
- **Lymphopenia:** Lymphopenia occurred in most TZIELD-treated patients. For most patients, lymphocyte levels began to recover after the fifth day of treatment and returned to pretreatment values within two weeks after treatment completion and without dose interruption. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia develops (<500 cells per mcL lasting 1 week or longer), discontinue TZIELD.
- **Hypersensitivity Reactions:** Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in TZIELD-treated patients. If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly.
- **Vaccinations:** The safety of immunization with live-attenuated (live) vaccines with

TZIELD-treated patients has not been studied. TZIELD may interfere with immune response to vaccination and decrease vaccine efficacy. Administer all age-appropriate vaccinations prior to starting TZIELD.

- Administer live vaccines at least 8 weeks prior to treatment. Live vaccines are not recommended during treatment, or up to 52 weeks after treatment.
- Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. Inactivated vaccines are not recommended during treatment or 6 weeks after completion of treatment.

ADVERSE REACTIONS

Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia, and headache.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm.
- **Lactation:** A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration.

Please read the accompanying Prescribing Information, including patient selection criteria, and Medication Guide above.

