



Next Steps for Patients and Families After Screening for T1D Autoantibodies

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Supported by an educational
grant from Provention Bio.

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INTRODUCTION

Type 1 diabetes (T1D) autoantibody testing has long been available for relatives of individuals with T1D through TrialNet, a research-based screening and clinical trial program.¹ Now, the general public has ready access to education about T1D autoantibody screening through JDRF's T1Detect program, which also includes in-home, T1D autoantibody testing.² The goal of this program is to facilitate the early diagnosis of T1D, given that about 93% of individuals diagnosed with T1D do not have a family history of the disease.^{2,3} Because people using this in-home autoantibody test are strongly encouraged to follow up with their healthcare providers immediately upon receiving their results, this brief publication provides preliminary guidance on monitoring patients who test positive for T1D autoantibodies, in addition to resources for patients and families and information on clinical trials investigating therapies to slow or delay the progression to T1D. Individuals without a family history of T1D who test positive for T1D autoantibodies can then be referred to TrialNet for follow-up screening and information about participating in their clinical studies.

For more information about the rationale and process for in-home, T1D autoantibody screening programs, please refer to the first brief publication in this series, [Talking to Patients and Families About T1D Risk and Screening Tests](#).

T1D AND AUTOIMMUNITY

T1D is characterized by several pathophysiologic changes that occur before the development of symptomatic disease. The 3 stages of T1D have been classified as follows^{4,5}:

- **Stage 1:** 2 or more autoantibodies, presymptomatic with normal glucose tolerance
- **Stage 2:** 2 or more autoantibodies, presymptomatic with abnormal glucose tolerance
- **Stage 3:** Islet autoimmunity with symptomatic T1D, hyperglycemia, and insulin dependence

The T1Detect screening test evaluates samples for 3 autoantibodies: insulin (IAA), GAD65, and IA-2A.² The TrialNet test initially evaluates samples for GAD65 and IAA; samples that test positive for either of these autoantibodies are then subsequently tested for IA-2A, ZnT8, and islet cell autoantibody (ICA).¹

EXPLAINING RESULTS TO PATIENTS AND FAMILIES

Extensive evidence demonstrates that the number of detected autoantibodies correlates with T1D risk. In children with 2 or more autoantibodies, the risk of developing T1D is approximately 25% within 3 years and 70% within 10 years, translating to an annualized rate of 9% to 11% per year.^{6,7} Among individuals who test positive for a single autoantibody, approximately 14.5% progress to T1D within 10 years.⁶ Risk factors for faster progression to T1D include the presence of multiple autoantibodies and autoantibody seroconversion in children younger than 3 years of age.⁶

Individuals who use in-home, T1D autoantibody screening through T1Detect are strongly encouraged to share their results with their healthcare professionals.² For those who test negative for autoantibodies, healthcare professionals can help patients determine whether future screening is recommended. For those who test positive for one or more autoantibodies, healthcare professionals can discuss T1D risk as well as recommendations for additional testing, monitoring, and enrollment in clinical trials. JDRF also provides resources and support to those who screen positive, including written information about T1D and connection with clinical trials, at www.jdrf.org/t1d-resources.

FOLLOW-UP AND MONITORING AFTER T1D AUTOANTIBODY RISK SCREENING

After an individual undergoes autoantibody screening, next steps depend on the presence and number of autoantibodies (Table 1). Evidence-based guidance for the follow-up and monitoring of patients after T1D autoantibody screening is currently in development and is not yet available. The suggestions provided here are based on expert opinion, but a lack of consensus still exists among experts. It is suggested that any positive autoantibody screening test be confirmed within 2 to 6 weeks.

TABLE 1. Suggestions for Follow-Up and Monitoring After T1D Autoantibody Risk Screening

Results	Next Steps
Autoantibody negative	<ul style="list-style-type: none"> • Rescreen if symptomatic • Rescreen at age 5 years if younger than 5 years at first screen or at 11 years if aged 5-10 years at first screen
Single autoantibody positive	<p>If single autoantibody positive (normal glycemic control [HbA1c < 5.7%]):</p> <ul style="list-style-type: none"> • Follow up in 6 months to exclude diagnosis and repeat metabolic testing (eg, OGTT, fasting blood glucose, random blood glucose) • If single autoantibody positive for 2 years, then follow up yearly
Multiple autoantibody positive	<p>If stage 1 T1D (multiple autoantibody positive, normal glycemic control [HbA1c < 5.7%]):</p> <ul style="list-style-type: none"> • Follow up in 6 months to exclude diagnosis and repeat metabolic testing (eg, OGTT, fasting blood glucose, random blood glucose) • Advise patient to call immediately if any symptoms present <p>If stage 2 T1D (multiple autoantibody positive, dysglycemia):</p> <ul style="list-style-type: none"> • Early T1D education • Fasting and 2-hour post largest meal blood glucose once weekly, can use continuous glucose monitor or strips • If blood glucose > 200 mg/dL, follow up with pediatric endocrinologist immediately • Follow up in 3 months to exclude diagnosis, repeat antibody and metabolic testing (eg, OGTT, fasting blood glucose, random blood glucose) <p>If stage 3 T1D (multiple autoantibody positive, symptomatic):</p> <ul style="list-style-type: none"> • Assess for polyuria, polydipsia, weight loss, fatigue, DKA • Insulin likely needs to be started that day • Call local pediatric endocrinologist for specific follow-up <p>For all patients, in addition to stage-specific recommendations, rescreen and exclude diagnosis using:</p> <ul style="list-style-type: none"> • Confirmatory autoantibody test • HbA1c, blood glucose, urine ketones • OGTT

Note: Patients who test positive for T1D autoantibodies can be referred to an existing screening program, such as TrialNet or possibly a local program in their area:

- **TrialNet:** www.trialnet.org
- **ASK** (Autoimmunity Screening for Kids), which provides screening for T1D and celiac disease for Colorado children and their parents: www.askhealth.org
- **PrIMeD** (Precision Individualized Medicine for Diabetes), which provides screening of children living in Virginia to identify those at risk of developing T1D: <https://sif.virginia.edu/primed>
- **PLEDGE** (Population Level Estimate of Type 1 Diabetes Risk Genes in Children), which provides screening of children younger than age 6 who are patients at Sanford Health (health system headquartered in South Dakota): <https://research.sanfordhealth.org/fields-of-research/diabetes/pledge>
- **CASCADE** (Combined Antibody Screening for Celiac and Diabetes Evaluation), which provides newborn screening of all children born in Washington: <https://cascadekids.org>

OGTT = oral glucose tolerance test.

Best practice recommendations derived from expert opinion. Evidence-based guidelines for the follow-up and monitoring of patients after T1D autoantibody screening are currently in development.

RESOURCES FOR PATIENTS AND FAMILIES

Individuals who test positive for autoantibodies are often learning about the implications of a T1D diagnosis for the first time. This new information can have significant emotional and psychological effects, including increased anxiety, distress, and depression. The lifestyle changes related to living with T1D can be overwhelming, requiring deliberate intervention from healthcare professionals to ensure that patients and caregivers receive the needed emotional and practical support.⁷⁻⁹

Individuals with positive autoantibody test results should receive prompt education related to early

symptoms of T1D as well as symptoms that can indicate life-threatening diabetic ketoacidosis (DKA). Early symptoms of T1D that should be discussed with patients or caregivers include^{10,11}:

- Polyuria
- Polydipsia
- Recent unexplained weight loss
- Fatigue or weakness
- Dry mouth
- Increased appetite
- Blurred vision
- Nausea, vomiting, or stomach pain
- Changes in gums
- Urinary tract or yeast infections
- Bedwetting

In addition to the above, signs and symptoms of DKA that should prompt patients and caregivers to immediately contact their healthcare professionals or seek emergency care include the following^{12,13}:

- Blood glucose levels > 240 mg/dL
- Flu-like symptoms
- Fruity-smelling breath
- Drowsiness, lethargy, or exhaustion
- Confusion or difficulty concentrating
- Rapid breathing
- Ketones detected via urine or blood testing

Patients and caregivers should be instructed to keep blood glucose and ketone testing supplies available to monitor for hyperglycemia and blood or urine ketone levels.¹²

Patients and families should also be linked to resources that can provide support and information, such as the following:

- For continued monitoring and participation in T1D research, go to TrialNet: www.trialnet.org
- For valuable information and support: www.jdrf.org/t1d-resources
- For personalized support through JDRF's T1D Connections Program or Online Diabetes Support Team: www.jdrf.org/t1d-resources/personal-support
- For mental health professionals who specialize in diabetes-related support to help patients cope with test results and early stage T1D diagnosis: https://professional.diabetes.org/mhp_listing

INVESTIGATIONAL THERAPIES TO SLOW T1D PROGRESSION

Diagnosing T1D before symptom onset provides a unique opportunity for preventive interventions. Several recent and ongoing clinical trials are investigating therapies that target the immune system to delay or prevent T1D, including:

- **Teplizumab**, an Fc receptor-nonbinding anti-CD3 monoclonal antibody. Compared with placebo, a single course of teplizumab delayed T1D diagnosis by almost 3 years ($P = .01$) in patients with 2 or more diabetes-related autoantibodies, stage 2 T1D, and a family history of T1D.^{14,15} Teplizumab has been submitted for United States Food and Drug Administration review for the delay or prevention of T1D in at-risk individuals.¹⁶
- **Abatacept**, a selective costimulation modulator that is approved for use in other autoimmune diseases. It is currently under investigation for the prevention of T1D progression and diagnosis in patients with stage 1 disease.¹⁷
- **Hydroxychloroquine**, an antimalarial with anti-inflammatory effects that is approved for use in other autoimmune diseases. It is currently under investigation for the prevention of T1D progression in those with stage 1 disease.¹⁸

In addition, ongoing trials are exploring strategies to slow disease progression in individuals with newly or recently diagnosed T1D who are not candidates for prevention trials. The phase 3 PROTECT study, for example, is investigating the efficacy of teplizumab in children aged 8 to 17 years who were diagnosed with T1D within the previous 6 weeks.¹⁹ The PROTECT study design is based on a subgroup analysis of previous phase 3 trial results that showed that teplizumab may be effective for reducing insulin use early after diagnosis in younger individuals.²⁰ A separate phase 3 study, CLVer, is investigating the benefit of a hybrid closed-loop insulin pump system and verapamil in patients with recently diagnosed T1D.²¹ Results for both PROTECT and CLVer are expected in 2022.^{19,21} Lastly, the TOPPLE study is currently enrolling adults who have

been diagnosed with T1D within the last 4 years to evaluate the safety of the plasmid vector NNC0361-0041, which is hypothesized to prevent patients' immune systems from attacking their β cells.²²

REFERENCES

ADDITIONAL RESOURCES

- JDRF Find a Clinical Trial: www.jdrf.org/impact/research/clinical-trials
- TrialNet Prevention Studies: www.trialnet.org/our-research/prevention-studies
- TrialNet Newly Diagnosed Studies: www.trialnet.org/our-research/newly-diagnosed-t1d
- ClinicalTrials.gov: <https://clinicaltrials.gov>

1. TrialNet. Pathway to Prevention. Study details. www.trialnet.org/our-research/risk-screening. Accessed May 20, 2021.
2. JDRF. T1Detect. www.jdrf.org/t1d-resources/t1detect. Accessed May 18, 2021.
3. Karges B, Prinz N, Placzek K, et al. A comparison of familial and sporadic type 1 diabetes among young patients. *Diabetes Care*. 2021;44(5):1116-1124.
4. 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.
5. Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD Clinical Practice Consensus Guidelines 2018: stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. 2018;19(suppl 27):20-27.
6. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013;309(23):2473-2479.
7. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA*. 2020;323(4):339-351.
8. Hummel M, Ziegler AG, Roth R. Psychological impact of childhood islet autoantibody testing in families participating in the BABYDIAB study. *Diabet Med*. 2004;21(4):324-328.
9. Rankin D, Harden J, Waugh N, Noyes K, Barnard KD, Lawton J. Parents' information and support needs when their child is diagnosed with type 1 diabetes: a qualitative study. *Health Expect*. 2016;19(3):580-591.
10. Quinn M, Fleischman A, Rosner B, Nigrin DJ, Wolfsdorf JI. Characteristics at diagnosis of type 1 diabetes in children younger than 6 years. *J Pediatr*. 2006;148(3):366-371.
11. Muñoz C, Floreen A, Garey C, et al. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. *Clin Diabetes*. 2019;37(3):276-281.
12. JDRF. Diabetic ketoacidosis (DKA): symptoms and prevention. www.jdrf.org/t1d-resources/about/symptoms/ketoacidosis. Accessed February 21, 2021.
13. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. *Am Fam Physician*. 2013;87(5):337-346.
14. Herold KC, Bundy BN, Long SA, et al; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med*. 2019;381(7):603-613.
15. Sims EK, Bundy BN, Stier K, et al; Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med*. 2021;13(583):eabc8980.
16. Provention Bio, Inc. press release. Provention Bio announces US FDA filing of a biologics license application (BLA) and priority review for teplizumab for the delay or prevention of clinical type 1 diabetes in at-risk individuals. *Cision PRNewswire*. January 4, 2021.
17. TrialNet. Abatacept Prevention Study. www.trialnet.org/our-research/prevention-studies/abatacept. Accessed January 18, 2021.
18. TrialNet. Hydroxychloroquine (HCQ). www.trialnet.org/our-research/prevention-studies/hydroxychloroquine-hcq. Accessed January 18, 2021.
19. Clinicaltrials.gov. Recent-onset type 1 diabetes trial evaluating efficacy and safety of teplizumab (PROTECT). <https://clinicaltrials.gov/ct2/show/NCT03875729>. Updated February 16, 2021. Accessed February 20, 2021.
20. Sherry N, Hagopian W, Ludvigsson J, et al; Protégé Trial Investigators. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011;378(9790):487-497.
21. Clinicaltrials.gov. Hybrid closed loop therapy and verapamil for beta cell preservation in new onset type 1 diabetes (CLVer). <https://clinicaltrials.gov/ct2/show/NCT04233034>. Updated December 9, 2020. Accessed February 21, 2021.
22. TrialNet. Tolerance Using Plasmid (TOPPLE) study: phase 1. www.trialnet.org/our-research/newly-diagnosed-t1d/TOPPLE. Accessed May 4, 2021.