Autoimmunity & Type 1 Diabetes

What every non-specialist provider should recognize before hyperglycemia becomes an emergency



Includes TZIELD (teplizumab) and the emerging CAR-T landscape

Type 1 Diabetes • Autoimmunity → Early Detection → Disease Modification



Rachel Edelen, MD and Thea Beyer, DNP

have no conflicts

The Clinical Shift

Why this matters in general practice

- Type 1 diabetes can be clinically silent while immune-mediated β-cell injury is already underway.
- Recognizing presymptomatic disease can support education, monitoring, and DKA-risk reduction.
- Multiple islet autoantibodies identify a high-risk population for structured follow-up and specialty referral
- Therapy is moving upstream: disease modification is now possible before stage 3 diabetes

Autoimmunity

Central Tolerance

- Occurs during lymphocyte development
- Thymus (T cells) and Bone marrow (B cells)
- Negative selection, receptor editing
- First line of protection against autoimmunity

Peripheral Tolerance

- Occurs after lymphocytes mature
- Secondary lymphoid organs and tissues
- Anergy, Tregs, deletion, checkpoint mechanisms
- Backup protection against autoimmunity

FOUNDATION

Autoimmunity: loss of tolerance

NORMAL IMMUNE TOLERANCE

Central Tolerance

Self-reactive lymphocytes are removed or controlled during development.

Peripheral Tolerance

Regulatory mechanisms restrain autoreactive cells that escape.

loss of tolerance

AUTOIMMUNE RESPONSE

Autoreactive T cells

- Can directly mediate tissue injury.

Autoantibodies

- Useful biomarkers of immune targeting.

Tissue injury

- Organ-specific damage emerges over time.

Lack of Tolerance

Think of type 1 diabetes as a military operation:

- **CD4 T cells** are the generals giving orders.
- **B cells** are the intelligence officers producing autoantibodies (GAD65, IA-2, insulin autoantibodies, ZnT8).
- **CD8 T cells** are the soldiers that actually enter the islets and kill β cells.

FROM IMMUNITY TO INSULIN DEFICIENCY
T1D biology in one picture

ISLET AUTOANTIBODIES = CLINICAL BIOMARKERS



Immune attack → progressive β-cell loss → declining endogenous insulin → dysglycemia → stage 3 diabetes

Clinical pearl: obesity does not exclude T1D, and age alone does not determine diabetes type.

THE 3-STAGE FRAMEWORK

T1D is a continuum—not a single diagnostic moment

IMMUNE ACTIVITY → β-CELL LOSS → METABOLIC DETERIORATION

At risk / pre-stage 1
Risk factors or limited/uncertain antibody evidence

Stage 1
≥2 confirmed islet autoantibodies
Normoglycemia
Asymptomatic

Stage 2
≥2 confirmed autoantibodies
Dysglycemia
Asymptomatic

Stage 3
Diagnostic hyperglycemia
Clinical diabetes

Stage 1 and Stage 2 are presymptomatic T1D—not merely "risk factors."

WHY EARLY IDENTIFICATION MATTERS

Stage 2 is the “act now” window

~60%

progress to stage 3 within 2 years

~75%

progress within 5 years

HIGH

priority for monitoring & referral

Individual risk varies by age, antibody profile, and glycemia.

A practical non-specialist workflow

- **Recognize**: diabetes phenotype, autoimmune clustering, ketosis, or concern for T1D.
- **Test**: islet autoantibodies and glycemia when clinically appropriate.
  - FDAIP (Mayo Test Code) will trigger "our epic" to pull up the diabetes mellitus type 1 evaluation lab(4 autoantibodies)
  - Can also direct the family with Type 1 Diabetes history to use TrialNet
- **Confirm:** repeat/confirm antibody positivity and establish metabolic stage.
- **Refer:** connect with us (or preferred diabetes center) for staging, education, monitoring, and therapy evaluation
- **Protect:** safety-net for symptoms, ketones, hyperglycemia, and DKA.

Type 1 Diabetes • Autoimmunity → Early Detection → Disease Modification

Why Do We Want to Know Early?
TZIELD (teplizumab): moving treatment upstream

CD3

T-cell modulation

CURRENT FDA ROLE (2026)

- **Approved to delay onset and progression to stage 3 T1D in adults and pediatric patients ≥1 year with stage 2 T1D.**
  - Pivotal TN-10: 2, 14 daily IV infusions ; median time to stage 3 diagnosis ~49.5 months vs ~24.9 months compared with placebo.
  - **14 daily IV infusions, 1x per life as of now.**
  - **There are ongoing studies for individuals with stage 2 type 1 who receive teplizumab 1x receiving it a 2nd**
- **June 2026 NEWLY approved for pediatric new DKA/Stage 3 type 1 age 8-17 years 2 infusions** given 6 months apart

It delays progression; it is not insulin and is not a cure.

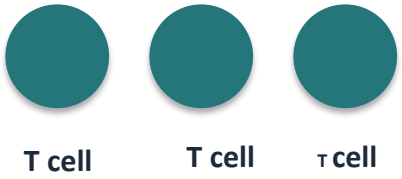
PRACTICE PEARLS

TZIELD: what the non-specialist should know

- Think “specialist evaluation,” not routine infusion: eligibility, baseline assessment, logistics, and monitoring matter.
- Adverse effects include lymphopenia, rash, leukopenia, and headache; infection risk & lab abnormalities require attention.
- The current FDA label includes a boxed warning concerning serious or life-threatening viral(EBV/CMV) reactivation.
- Patients can still progress to stage 3; glucose monitoring and diabetes education remain essential.
- Best referral trigger: confirmed Stage 2 T1D or a patient being evaluated for Stage 2.

EMERGING THERAPY
CAR-T: could immune reprogramming go deeper?

HOW CAR-T WORKS



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ENGINEER

add a chimeric antigen receptor

→

TARGET / TOLERATE

remove pathogenic immune cells or deliver regulation

T1D approaches under study include CAR-T cells and CAR-T regulatory T cells (CAR-Tregs).

CAR-T is investigational for T1D—not standard clinical therapy.

PUTTING THE FIELD IN CONTEXT

TZIELD vs CAR-T: same goal, very different maturity

Clinical status	FDA-approved	Investigational
Where in T1D	Stage 2; plus specific pediatric new-onset use	Clinical trials / research
Approach	CD3-directed immune modulation	Engineered cellular therapy
Goal	Delay progression / preserve function	Potential deeper immune reprogramming
Provider action today	Identify + refer eligible patients	Research centers / trials only

Near-term opportunity: recognize presymptomatic T1D.

Clinical vignette: the patient you do not want to miss

A 13-year-old with a sibling with T1D has:

- normal weight and no symptoms
- A1C 5.8%
- two confirmed islet autoantibodies
- no ketones and normal fasting glucose

What stage?

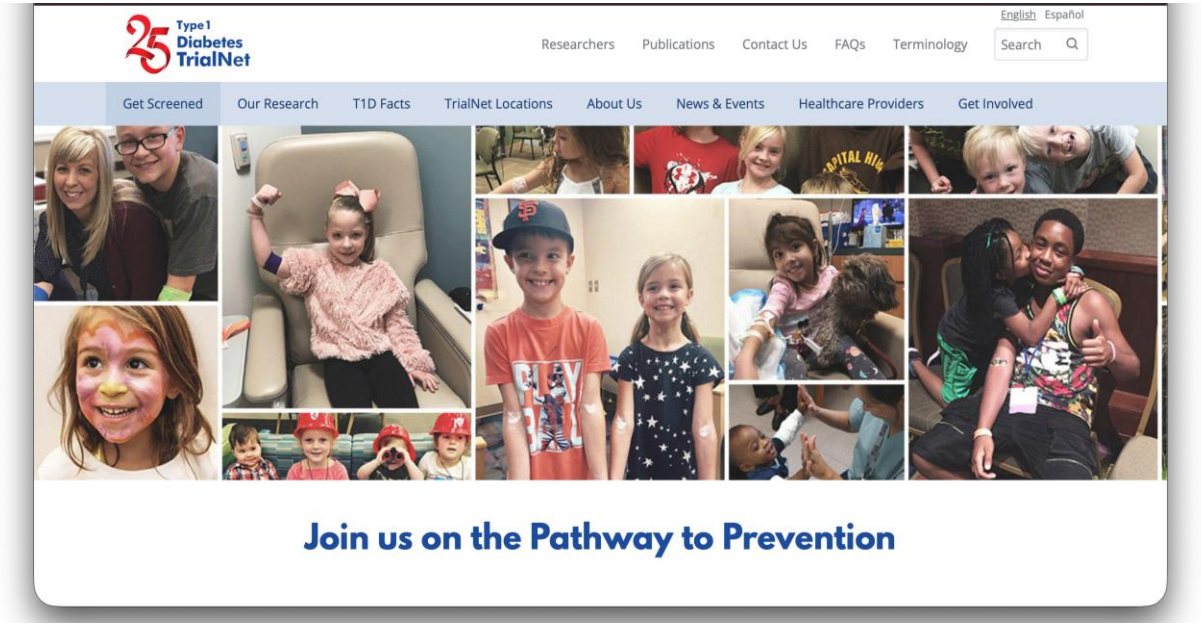
STAGE 1

Presymptomatic autoimmune T1D
→ monitoring + specialty referral

If dysglycemia were present without symptoms → Stage 2, where TZIELD discussion becomes relevant.

To Review: How Can You Screen?

- TrialNet
  - Family History of Type 1 Diabetes
    - **First-Degree Relatives:** Ages 2 to 45 if you have a parent, sibling, or child with T1D.
    - **Second-Degree Relatives:** Ages 2 to 20 if you have a grandparent, aunt, uncle, cousin, niece, nephew, or half-sibling with T1D.
    - **Prior Testing:** Ages 2 to 45 if you have previously tested positive for at least one T1D-related autoantibody outside of TrialNet.
    - **No Diabetes Diagnosis:** You must not have an active diagnosis of diabetes
- Monument Health Epic: DBS-1 Panel or FDAIP
- Outside Facilities can send to Mayo with FDAIP order code



1. Sign Up!

TrialNet risk screening is free for relatives of people with T1D: ages 2–45 with a first-degree relative or ages 2–20 with a second-degree relative. Answer a few quick questions to check your eligibility.

2. Get Screened!

Choose the screening option that's right for you. You can order an in-home test, order a test kit to take to a local lab, or visit one of our many TrialNet locations– all at no cost to you.

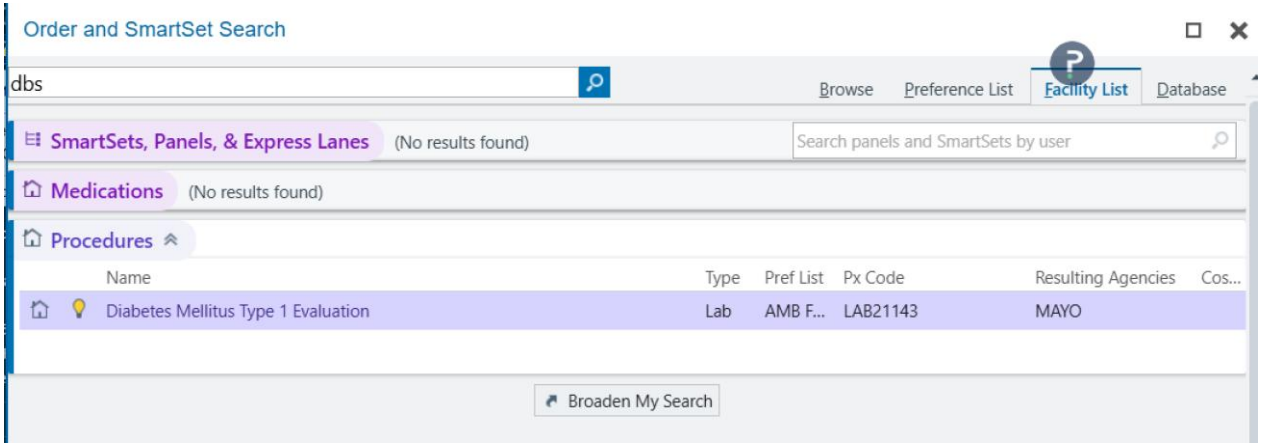
3. Your Results

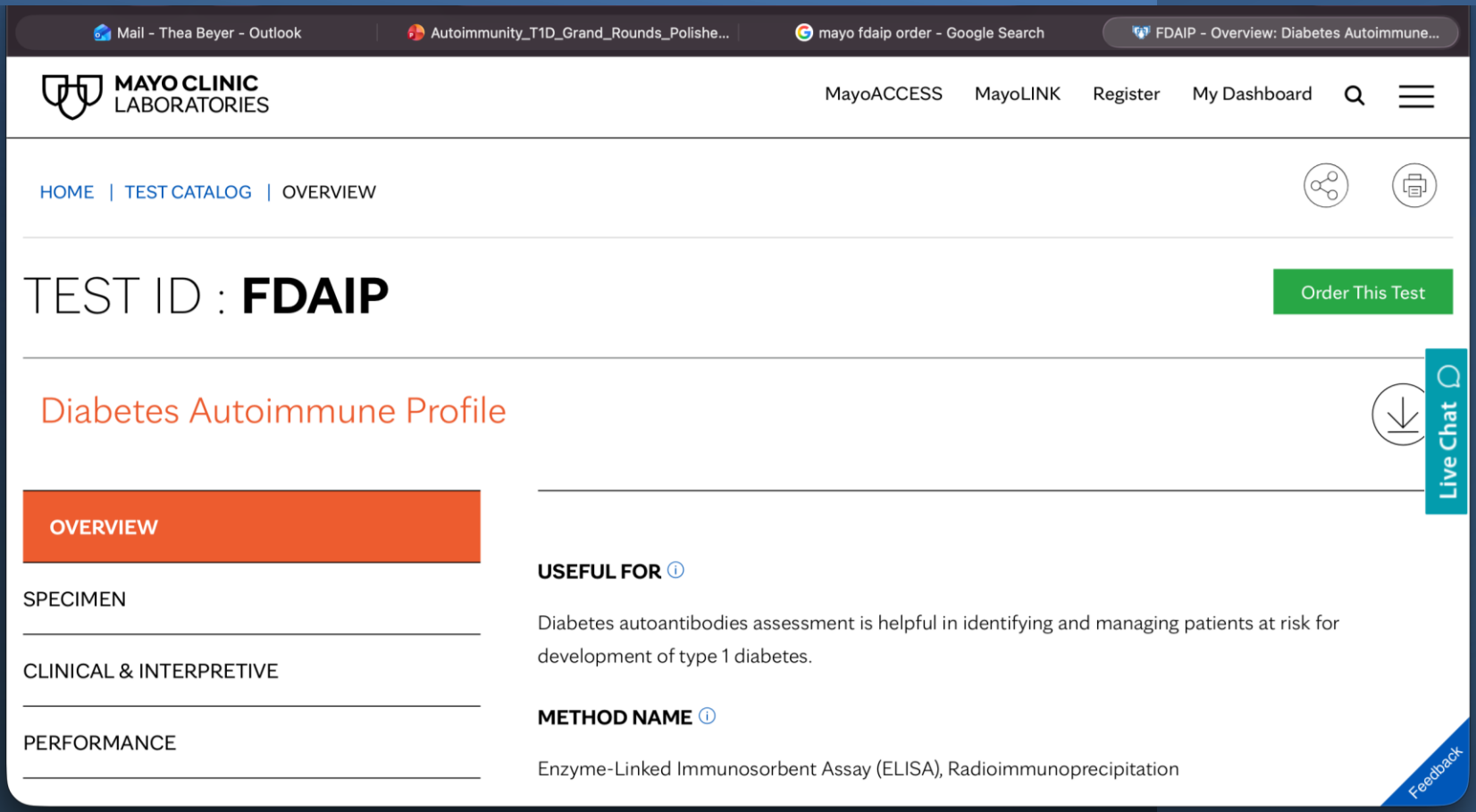
You will receive your screening results in 4-6 weeks. If your results show you are in the early stages of T1D, we will schedule a follow-up visit to see if you are eligible for a prevention study.

Sign Up

OUR EPIC

- **One order**
  - FDAIP panel in epic /DBS1 to mayo
  - favorite
- **Quick text about these being negative**
  - Plan ahead so staff can read off to families
  - Refer if positive or monitor 1 ab but know how often, and the IA2 is like 2 AB but nothing official yet.

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TEST ID : FDAIP
Order This Test
Diabetes Autoimmune Profile
Live Chat
OVERVIEW
SPECIMEN
CLINICAL & INTERPRETIVE
PERFORMANCE
USEFUL FOR
Diabetes autoantibodies assessment is helpful in identifying and managing patients at risk for development of type 1 diabetes.
METHOD NAME
Enzyme-Linked Immunosorbent Assay (ELISA), Radioimmunoprecipitation
Feedback

Practical Approach to Type 1 Diabetes Autoantibody Screening & Monitoring

ISPAD 2024 + ADA 2025

SCREEN

Who?

- First-degree relative
- Genetic risk
- Population screening

Panel: GAD65, IA-2A, ZnT8A, IAA

→

STAGE

0 Ab: Low risk
1 Ab: Confirm & repeat
≥2 Ab: Stage 1/2 T1D

→

MONITOR

Stage 1
HbA1c/CGM q6-12 mo
Stage 2
HbA1c/CGM q3-6 mo
Consider teplizumab

NEGATIVE

Children: ages 2 & 6
Repeat 1-3 yrs if risk

SINGLE Ab+

Confirm persistence
Educate DKA symptoms
Follow q6-12 mo

≥2 Ab+

Early-stage T1D
Endocrinology referral
Structured surveillance

Clinical Pearls: Multiple confirmed autoantibodies = early-stage T1D • Monitoring reduces DKA at diagnosis • CGM supports progression surveillance • Provide education and psychosocial support at every stage

Who to screen? Think Family History- It goes both ways.

People with **type 1 diabetes mellitus have an increased risk of other autoimmune diseases**. The most common are:

- **Autoimmune thyroid disease**
  - Hashimoto thyroiditis and hypothyroidism
  - Less commonly, Graves disease and hyperthyroidism
- **Celiac disease**
- **Other associated conditions include:**
- Autoimmune primary adrenal insufficiency (Addison disease)
- Autoimmune gastritis and pernicious anemia
- **Autoimmune polyglandular syndrome type 2**, which may combine type 1 diabetes, autoimmune adrenal insufficiency, and other autoimmune endocrine disease
- Less commonly: **autoimmune hepatitis, Crohn disease, ulcerative colitis, and juvenile idiopathic arthritis**
- In infants, rare immune-dysregulation syndromes such as **IPEX** may include early-onset type 1 diabetes.
- In children and adolescents, routine screening is recommended for **autoimmune thyroiditis and celiac disease** at type 1 diabetes diagnosis and subsequently at defined intervals; other autoimmune disorders are generally evaluated when suggestive manifestations develop.

Types of endocrine and nonendocrine autoimmune syndromes associated with adrenal insufficiency

Disorder	Prevalence (%)
Polyglandular autoimmune syndrome type 1	
Endocrine	
Hypoparathyroidism	89
Chronic mucocutaneous candidiasis	75
Adrenal insufficiency	60
Primary hypogonadism	45
Hypothyroidism	12
Type 1 diabetes mellitus	1
Hypopituitarism	<1
Diabetes insipidus	<1
Nonendocrine	
Malabsorption syndromes	25
Alopecia totalis or areata	20
Pernicious anemia	16
Chronic active hepatitis	9
Vitiligo	4

Types of endocrine and nonendocrine autoimmune syndromes associated with adrenal insufficiency (cont)

Polyglandular autoimmune syndrome type 2	
Endocrine	
Adrenal insufficiency	100
Autoimmune thyroid disease	70
Type 1 diabetes mellitus	50
Primary hypogonadism	5 to 50
Diabetes insipidus	<1
Nonendocrine	
Vitiligo	4
Alopecia, pernicious anemia, myasthenia gravis, immune thrombocytopenia purpura, Sjögren syndrome, rheumatoid arthritis	≤1

Data from:

1. *Leshin M. Polyglandular autoimmune syndromes. Am J Med Sci 1985; 290:77.*
2. *Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. Medicine (Baltimore) 1981; 60:355.*

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CLOSE

Five take-home messages

01	**T1D starts before glucose rises.**	Autoimmunity and β-cell loss precede symptomatic diabetes.
02	**Autoantibodies are an early warning system.**	Multiple confirmed antibodies identify a high-risk trajectory.
03	**Stage 2 is actionable.**	It is a high-risk presymptomatic disease state.
04	**TZIELD changes the timeline.**	Eligible patients can be evaluated for disease-modifying treatment.
05	**CAR-T is the frontier—not the standard.**	Promising, but currently investigational in T1D.

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FOR THE CURIOUS CLINICIAN

Selected References & Resources

- American Diabetes Association. Standards of Care in Diabetes—2026: Diagnosis & Classification; Prevention or Delay of Diabetes.
- FDA. TZIELD (teplizumab-mzwv) Prescribing Information and 2026 labeling.
- FDA. TZIELD Drug Trials Snapshot / TN-10 study materials.
- Consensus Guidance for Monitoring Individuals With Islet Autoantibody–Positive Pre-Stage 3 Type 1 Diabetes.
- ClinicalTrials.gov. NCT07395050 — autologous CD6-CAR Treg cells in type 1 diabetes.
- ClinicalTrials.gov. NCT07528105 — allogeneic anti-CD7 CAR-T for type 1 diabetes.

Educational deck—verify current FDA labeling, trial status, and local protocols before clinical use.

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