

NEW DIRECTIONS IN TYPE 1 DIABETES: FROM GENETICS TO SCREENING

Botirova Nigina Akram qizi, PhD
Tashkent State Medical University

Abstract

Type 1 Diabetes (T1D) has historically been regarded as a sudden and unpredictable autoimmune condition — often first recognized only after the onset of symptoms like excessive thirst, frequent urination, unexplained weight loss, and, in many cases, a life-threatening episode of diabetic ketoacidosis (DKA). By the time a diagnosis is made, significant and often irreversible damage to the insulin-producing beta cells of the pancreas has already occurred. However, this traditional, reactive approach is rapidly evolving. Advances in genetics, immunology, and early screening technologies are reshaping our understanding of how T1D develops and how it might be prevented. Researchers now recognize that T1D follows a staged progression, starting silently years before clinical symptoms emerge. This paradigm shift—from waiting for symptoms to identifying and tracking disease risk early—has opened promising new pathways for prediction, prevention, and even delay of disease onset.

Keywords: Type 1 diabetes, early detection, risk stratification, immune intervention, genetics, immunology, early screening.

Introduction

Today, we stand at the forefront of a transformative era in Type 1 Diabetes care—one where early detection, risk stratification, and immune intervention may radically reduce the burden of the disease. This article explores the latest breakthroughs in genetic risk profiling, population-based screening, and emerging prevention therapies that are paving the way toward a future where T1D may no longer be a life sentence, but a preventable condition.

Type 1 Diabetes (T1D) is a complex autoimmune disorder with a well-established genetic component. Although it does not follow a simple Mendelian inheritance pattern, research has identified multiple genes that significantly influence an individual's susceptibility to developing the disease.

Among these, the most influential by far is the human leukocyte antigen (HLA) region located on chromosome 6. This region plays a critical role in immune system regulation, particularly in distinguishing self from non-self. Specific HLA class II alleles—most notably HLA-DR3 and HLA-DR4—are strongly associated with an increased risk of T1D [1]. Individuals who inherit both alleles (DR3/DR4 heterozygotes) are at the highest genetic risk, especially during early childhood.

However, the presence of these alleles alone does not guarantee disease development. In fact, many people with high-risk HLA genotypes never develop T1D, suggesting that genetic predisposition is necessary but not sufficient. Environmental triggers and other genetic factors also play important roles.



Beyond the HLA region, over 60 non-HLA genetic loci have been identified through large-scale genome-wide association studies (GWAS). These include:

- INS (insulin gene) – associated with immune tolerance to insulin.
- PTPN22 – involved in immune cell signaling.
- IL2RA – regulates T-cell activity and immune tolerance.
- CTLA4 – modulates immune checkpoints that prevent autoimmunity.

Each of these genes contributes modestly to overall risk, but when considered in combination, they provide a more comprehensive picture of an individual's genetic predisposition.

Importantly, advances in genetic testing have enabled the development of genetic risk scores (GRS) that combine HLA and non-HLA variants to estimate a person's lifetime risk of developing T1D. These tools are increasingly being used in screening programs and research trials to identify individuals who may benefit from closer monitoring or early intervention [2, 3]. In summary, while genetics alone cannot predict exactly who will develop T1D, our growing understanding of the genetic landscape is allowing for earlier identification of at-risk individuals and creating new opportunities for prevention and personalized care.

For decades, the diagnosis of Type 1 Diabetes (T1D) typically came as an acute and often traumatic event — usually after the onset of symptoms such as excessive thirst, frequent urination, fatigue, and unintended weight loss. In many children, diagnosis followed a dangerous episode of diabetic ketoacidosis (DKA), a life-threatening complication that can occur when insulin deficiency goes undetected for too long [4]. However, recent advances in our understanding of T1D have revealed that the disease unfolds gradually through a series of predictable stages, long before clinical symptoms appear. This has led to a paradigm shift in how we approach diagnosis and prevention.

Researchers now classify the natural history of T1D into three distinct stages [6]:

1. Stage 1: The presence of two or more islet autoantibodies (such as GAD65, IA-2, or ZnT8) in the blood, indicating autoimmune activity directed at the pancreas. At this stage, blood glucose levels remain normal, and there are no outward symptoms.
2. Stage 2: Autoimmunity continues, and dysglycemia (abnormal blood glucose levels) begins to develop. Individuals may still be asymptomatic, but laboratory tests show signs of declining beta-cell function.
3. Stage 3: This is the point of clinical diagnosis, when hyperglycemia becomes symptomatic and requires insulin therapy. By this stage, significant beta-cell destruction has already occurred.

This three-stage model has revolutionized how we think about T1D—not as an event, but as a progressive autoimmune process that begins years before diagnosis.

Recognizing the preclinical stages of T1D has opened the door to screening and early detection, particularly in first-degree relatives of individuals with the disease, who are at significantly higher risk. Testing for islet autoantibodies in these individuals can identify those who are in Stage 1 or Stage 2, even if they feel perfectly healthy.

The benefits of early detection are profound:

- Individuals identified in earlier stages can be closely monitored for changes in glucose metabolism, allowing for timely intervention before symptoms or complications emerge.



- Families gain valuable time to learn about T1D, understand insulin therapy, and prepare emotionally and logistically for a potential diagnosis.
- Those identified early may be eligible for prevention or delay trials, such as those testing immunotherapies or other interventions designed to slow immune attack on beta cells.
- Studies have shown that children diagnosed through screening programs are less likely to present with DKA, reducing initial hospitalization rates and improving long-term outcomes.

As screening technologies become more accurate and accessible, the potential for population-wide screening is growing. Several large-scale research initiatives—such as TrialNet, Fr1da in Germany, and ASK (Autoimmunity Screening for Kids) in the U.S.—are exploring the feasibility and impact of screening both high-risk and general pediatric populations.

For decades, screening for type 1 diabetes (T1D) risk was limited mostly to children with a family history. But most new T1D cases — up to 90% — arise in families with *no* prior history. Programs like ASK (Colorado, USA) and Fr1da (Bavaria, Germany) have shown that broad, population-based screening is both feasible and impactful. Children identified through screening are far less likely to present in emergency situations. In Fr1da, DKA at diagnosis dropped to ~2–5%, compared with 20–40% in unscreened populations. Families given an early warning can prepare emotionally, practically, and medically, making the transition smoother when diabetes develops. Limiting screening to relatives excludes the majority of children at risk. Universal, accessible screening better addresses disparities.

The main concern is psychological: parents may feel anxious knowing their child has autoimmunity but not diabetes yet. However, evidence shows that when programs provide confirmatory testing, education, and follow-up, anxiety usually lessens over time, while the benefits of avoiding DKA and emergency diagnoses remain strong.

Current therapies do not *reverse* diabetes; they *preserve* remaining beta cells. That means timing is everything.

Teplizumab (anti-CD3): The first FDA-approved drug to delay T1D, given in Stage 2. A single course can delay diagnosis by about two years.

Anti-IL-21 + GLP-1 therapies: Support beta-cell survival and slow functional decline in recent-onset disease.

Oral insulin and vaccines: Aim to retrain the immune system before too many beta cells are lost, though results so far are mixed.

If treatment is delayed until Stage 3, when most beta cells are already destroyed, these interventions lose much of their effect.

Safety and Uncertainty: Long-term safety of repeated immunotherapy courses is not yet known, requiring ongoing monitoring.

Feasibility: Universal screening requires affordable assays, education pathways, and structured follow-up to avoid “screening without support.”

Early screening for type 1 diabetes is shifting the paradigm: it not only reduces life-threatening DKA but also creates the window for meaningful prevention. Immunotherapies like teplizumab prove that preserving beta cells *before* symptoms emerge is possible. The real challenge is building systems that deliver these benefits equitably and sustainably.



Conclusion

Type 1 diabetes is no longer an unpredictable disease that strikes without warning. Advances in genetics, population-based screening, and immunotherapy are reshaping the field — shifting the focus from emergency management to proactive prevention.

The evidence from programs like ASK and Fr1da shows that early identification reduces dangerous complications like DKA, helps families prepare, and opens a window for therapies that can meaningfully delay disease onset. But science alone isn't enough. To realize the full promise of these breakthroughs, continued investment is needed in three areas: research to refine therapies and understand long-term outcomes. Education to ensure families and healthcare providers can navigate risk information with clarity and confidence. Equitable access so that all children not just those with family history or resources benefit from prevention and early detection.

References

1. Aribi, M., Moulessehou, S., Benabadji, AB. *et al.* HLA DR phenotypic frequencies and genetic risk of Type 1 diabetes in west region of Algeria, Tlemcen. *BMC Genet* 5, 24 (2004). <https://doi.org/10.1186/1471-2156-5-24>
2. Luckett, A.M., Weedon, M.N., Hawkes, G. *et al.* Utility of genetic risk scores in type 1 diabetes. *Diabetologia* 66, 1589–1600 (2023). <https://doi.org/10.1007/s00125-023-05955-y>
3. Seth A. Sharp, Stephen S. Rich, Andrew R. Wood, Samuel E. Jones, Robin N. Beaumont, James W. Harrison, Darius A. Schneider, Jonathan M. Locke, Jess Tyrrell, Michael N. Weedon, William A. Hagopian, Richard A. Oram; Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. *Diabetes Care* 1 February 2019; 42 (2): 200–207. <https://doi.org/10.2337/dc18-1785>
4. Richard A. Insel, Jessica L. Dunne, Mark A. Atkinson, Jane L. Chiang, Dana Dabelea, Peter A. Gottlieb, Carla J. Greenbaum, Kevan C. Herold, Jeffrey P. Krischer, Åke Lernmark, Robert E. Ratner, Marian J. Rewers, Desmond A. Schatz, Jay S. Skyler, Jay M. Sosenko, Anette-G. Ziegler; Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 1 October 2015; 38 (10): 1964–1974. <https://doi.org/10.2337/dc15-1419>
5. ADCES – Three Stage Model for T1D
6. Jacobsen, Laura M et al. Time to reframe the disease staging system for type 1 diabetes. *The Lancet Diabetes & Endocrinology*, Volume 12, Issue 12, 924 - 933

