SUMMARY (Clinical) 4/25/25 ciT1zen science

Type 1 Diabetes Risk Factors, Prediction, and Presymptomatic Detection
ciT1zen science summary

Source: Bonifacio, E., & Ziegler, A.-G. (2025). Type 1 diabetes risk factors, risk prediction and presymptomatic detection: Evidence and guidance for screening. *Diabetes, Obesity and Metabolism*, *Early View*. https://doi.org/10.1111/dom.16354

Summary: This briefing document summarizes the key themes and important ideas from a recent review article on type 1 diabetes (T1D) risk factors, prediction, and presymptomatic detection. The authors provide an overview of the stages of T1D development, emphasizing the importance of identifying individuals in the presymptomatic phase (Stages 1 and 2) due to the emergence of therapies like teplizumab that can delay disease progression. The document highlights genetic and non-genetic risk factors, practical considerations for screening (including the "2 × 2 × 2 principle"), strategies for staging and predicting progression to clinical disease, limitations of current prediction models, and the crucial aspects of counseling, education, and monitoring. The review concludes by outlining future research needs and the challenges associated with widespread implementation of T1D screening.

Main Themes and Important Ideas:

1. Understanding the Presymptomatic Phase of Type 1 Diabetes:
   - T1D progresses through a presymptomatic phase characterized by the presence of islet autoantibodies before clinical symptoms and insulin dependence arise.
   - This phase is classified into three stages:
   - Stage 1: Presence of two or more islet autoantibodies with normoglycemia.
   - Stage 2: Presence of two or more islet autoantibodies with dysglycemia.
   - Stage 3: Hyperglycemia, often with clinical symptoms, typically requiring insulin therapy.
   - The discovery of islet autoantibodies and the prospect of therapies to delay clinical onset have driven research into this phase.
   - The recent approval of teplizumab has increased the focus on diagnosing individuals in Stages 1 and 2.
   - Diagnosing asymptomatic individuals with a low prevalence of the condition (fewer than 1 in 200) presents significant challenges, necessitating refined diagnostic approaches.

2. Key Biomarkers: Islet Autoantibodies:
   - A hallmark of early-stage T1D is the presence of islet autoantibodies targeting pancreatic beta cell antigens.
   - The four main target antigen groups are: Insulin and proinsulin (IAA), glutamic acid decarboxylase 65 (GAD65), insulinoma antigen-2 (IA-2) and IA-2β, and zinc transporter 8 (ZnT8).
   - The presence of two or more islet autoantibodies in childhood is associated with an almost 100% likelihood of developing clinical T1D by adulthood. This finding established the foundation for staging presymptomatic T1D.
   - Different autoantibodies have varying age-related frequencies and HLA associations (see Table 1 in the original source).
   - While early studies focused on two or more autoantibodies, the review acknowledges the ongoing debate about the significance of single islet autoantibodies.
3. Genetic Risk Factors:
   - T1D has a polygenic basis, with a higher prevalence among individuals with affected relatives.
   - The HLA class II region on chromosome 6 is the most prominent genetic contributor, with specific HLA DRB1-DQA1-DQB1 genotypes conferring varying levels of risk (e.g., DR4-DQ8 and DR3-DQ2 haplotypes are high-risk).
   - Allelic variation in the *INS* gene (encoding insulin) also significantly influences T1D risk and modifies HLA-associated risk.
   - Polygenic risk scores (PRS) integrate information from multiple risk loci and can enhance prediction and aid in screening for early-stage T1D.
   - Age, sex, maternal history of T1D, and viral infections can modify genetic risk. For example:
   - Autoimmunity peaks between 1 and 2 years of age.
   - Boys have a higher early risk, while girls with early-stage T1D progress faster.
   - Children of mothers with T1D have a lower risk compared to those with affected fathers or siblings and non-diabetic mothers.
   - Certain viral infections (e.g., Coxsackie B virus, SARS-CoV-2) have been associated with increased islet autoantibody incidence.
4. Practical Considerations for Screening:
   - Diagnosing early-stage T1D requires high diagnostic certainty due to its asymptomatic nature and the implications of a positive diagnosis.
   - The authors advocate for multiple sequential tests to increase the likelihood that a positive result accurately indicates disease (based on Bayes' theorem).

- "Diagnosing early-stage type 1 diabetes falls into the high-certainty category and is best achieved through multiple sequential tests."
- Decision trees incorporating factors like family history, age, and PRS alongside autoantibody testing are proposed for efficient screening strategies.
- Different autoantibody assay methodologies are available (3Screen ELISA, ECL, ADAP) with varying costs, sensitivities, and capabilities.
- The "2 × 2 × 2 principle" is recommended for robust diagnosis: at least two positive antibodies confirmed by two different tests on one occasion and subsequently in a second occasion.
- "Following the 2 × 2 × 2 rule—requiring at least two positive antibodies confirmed by two different tests on one occasion and subsequently in a second occasion—provides a robust framework for diagnosis."
- Genetic preselection as a primary screening tool requires optimization due to challenges with recall rates. Hybrid strategies combining genetic and autoantibody testing may be viable.

5. Staging and Progression to Clinical Disease:
    - Accurate diagnosis of Stage 1 (normoglycemia) and Stage 2 (dysglycemia) is crucial, especially with the advent of therapies to delay progression.
    - The definition of dysglycemia has evolved to include impaired oral glucose tolerance test (OGTT), HbA1c values, and impaired fasting glucose.
    - Risk stratification within Stage 2 is possible based on the number and persistence of glycemic abnormalities.
    - Alternative markers like c-peptide, proinsulin-c-peptide ratios, and continuous glucose monitoring (CGM) are being investigated for staging and risk prediction.
    - IA-2 autoantibodies (IA-2A) are pivotal in predicting disease progression, with their presence associated with a higher rate of progression to Stage 3.
    - "The presence of IA-2A—either alone or in combination with other islet autoantibodies—is consistently associated with a higher rate of progression to Stage 3 type 1 diabetes."
    - Progression Likelihood Scores incorporating IA-2A, HbA1c, and OGTT glucose values can identify individuals at higher risk of rapid progression within Stage 1.
6. Limitations of Prediction in Early-Stage Type 1 Diabetes:
    - Risk attributed to a group is an average risk, not a precise prediction for an individual.
    - "A common oversight when assessing risk is that the risk attributed to a group of individuals who meet certain criteria represents an average risk, not a precise prediction for any single individual."

- Real-world settings have more variability in testing compared to controlled research environments, potentially affecting diagnostic accuracy.
- Prediction models assume the future will mirror the past, but the incidence of T1D can be influenced by environmental changes.
- Screening in adults presents unique challenges as they often have fewer islet autoantibodies, predominantly single GAD autoantibodies, making identification of true early-stage T1D more complex.
- The significance of single islet autoantibodies remains debated, requiring consideration of the specific antibody, age, and genetic risk.

7. Counseling, Education, and Monitoring:
    - Diagnosis of early-stage T1D necessitates appropriate care, including counseling and education.
    - There are potential psychosocial effects of informing families about a pre-symptomatic condition.
    - "While we acknowledge the potential negative psychosocial effects of informing families that their child may have a disease with no current symptoms…there are also clear benefits to early-stage diagnosis."
    - Genetic pre-screening can lead to more widespread counseling due to the higher proportion of individuals identified at increased risk.
    - Monitoring strategies should consider the likelihood of imminent progression while minimizing the burden of testing.
8. Future Directions and Needs:
    - Continued research is crucial alongside broader application of screening.
    - Key areas for further investigation include:
    - Assessing the psychological impact and behavioral changes associated with screening.
    - Determining the cost-effectiveness of screening.
    - Optimizing screening strategies for adults and individuals with single islet autoantibodies.
    - Adapting screening to diverse global populations.
    - Developing guidelines, communication strategies, and infrastructure for real-world implementation.
    - Expanding screening to a larger scale requires investment in training, staffing, and clinical care infrastructure.

Conclusion:

Significant advancements have been made in understanding and detecting early-stage T1D, paving the way for integrating screening into regular healthcare. However, careful and equitable implementation is essential, requiring ongoing research and addressing logistical challenges. Maximizing the benefits of early

detection and potential therapies necessitates coordinated efforts and substantial investment in screening programs.