10 YEARS:
10 STORIES OF IMPACT

CASE STUDY 1

Pursuing prevention of T1D

Two decades of research have improved our ability to detect individuals who are at risk of type 1 diabetes (T1D) before symptoms develop. Despite being reliable and relatively inexpensive, such testing has not been implemented into routine healthcare anywhere in the world, and most diagnoses still occur after symptoms develop with a high incidence of admission to intensive care and increased risk of long-term complications.

The Australian Type 1 Diabetes Clinical Research Network (T1DCRN) is supporting a pilot to help embed childhood screening for T1D into routine care in Australia. Early identification of people at risk will help protect people who develop T1D from diabetic ketoacidosis (DKA) and assist access to emerging therapies that can delay the progression to symptomatic T1D.

Australian Type 1 Diabetes Clinical Research Network

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

WHAT PROBLEM DO WE NEED TO SOLVE?

More than 30% of childhood T1D diagnoses are only made after the development of life-threatening DKA.[1] Of concern, this percentage is increasing in Australia.[2,3] This start to the condition is traumatic and has lifelong implications for cognitive impairment, higher long-term blood glucose levels, and increased risk of serious complications.

Screening for T1D risk in family members has been underway in Australia through a research program called Type1Screen. However, nine out of 10 individuals presenting with symptoms of T1D have no family history of the condition.[4]

Embedding screening for T1D risk as part of routine care in the general population, before symptoms occur, could change the way T1D is diagnosed and treated. Individuals at high risk who are identified through screening and monitored by healthcare professionals have DKA rates reduced up to 16-fold.[5]

Moreover, early identification of those at risk of T1D could allow them in the future to access therapies such as teplizumab, which has been recently approved by the FDA to delay onset of T1D symptoms for at least three years.

More therapies are on the way and will offer a clear advantage of early access to clinical trials, possibly delaying the symptoms for longer.

WHY IS THIS SUCH AN EXCITING AREA OF RESEARCH?

At present, T1D diagnosis occurs upon clinical presentation of symptoms such as excessive thirst, frequent urination, rapid weight loss and lethargy, all linked to abnormally high blood glucose levels. Further tests are then conducted to confirm T1D and distinguish it from other types of diabetes.

However, two decades of research have demonstrated that T1D begins well before clinical symptoms develop (Figure 1). The autoimmune process that underlies T1D is triggered in genetically susceptible individuals who eventually develop a persistent presence of two of more islet autoantibodies, molecules which are markers of the immune system attacking beta cells in the pancreas (Stage 1).

As the number of functional beta cells diminishes, and insulin production consequently wanes, blood glucose levels start to rise (Stage 2). In Stage 3 T1D, the absence of insulin production leads to an inability of the body to maintain glucose levels in a normal range and this is the stage at which T1D is typically diagnosed.

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1. Diabetic ketoacidosis (DKA) is a potentially fatal complication where low levels of insulin and hyperglycaemia result in the body using fat as an alternative energy source. This leads to dangerously high levels of acidic ketones in the blood. DKA is not only dangerous but leads to worse long-term health outcomes. Birkebaek et al., Impact of the COVID-19 pandemic on long-term trends in the prevalence of diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes: an international multicentre study based on data from 13 national diabetes registries. The Lancet Diabetes & Endocrinology. 2022 Nov 1;10(11):786-94. https://doi.org/10.1016/S2213-8587(22)00246-7

2. ibid.

3. Cherubini, V., et al. Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. Diabetologia 63, 1530–1541 (2020). https://doi.org/10.1007/s00125-020-05152-1

4. Sims EK, et al. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. Diabetes. 2022;71(4):610-623. doi:10.2337/dbi20-0054

5. ibid.

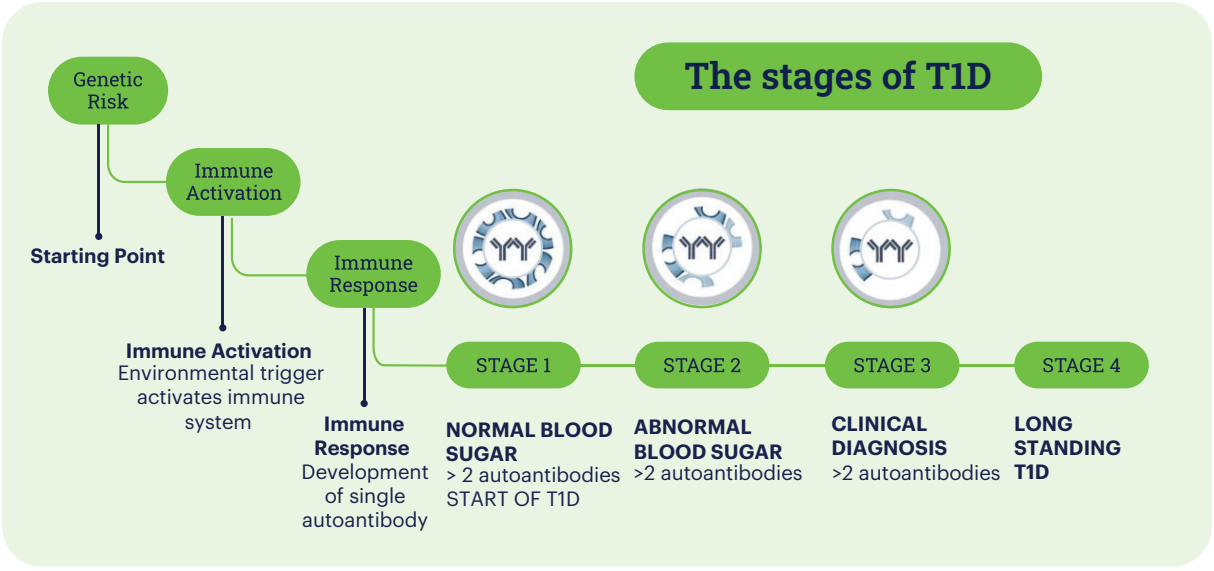

Figure 1: The pre-symptomatic stages of T1D (Stage 1 and 2) are characterised by the presence of autoantibodies, indicative of pancreatic beta cell destruction. Circles above Stages 1-3 represent the presence of autoantibodies and beta cell functional loss (adapted from reference 6).

The presence of islet autoantibodies in these pre-symptomatic stages is a strong indicator of progression towards a clinical diagnosis. The presence of persistent multiple autoantibodies confers a 70% likelihood of progression to symptomatic diabetes within 10 years, and nearly 100% likelihood of developing T1D within a person's lifetime.[6]

WHAT WAS FUNDED BY THE T1DCRN, AND WHY?

The T1DCRN is funding a critical and globally unique pilot project to develop a blueprint for Australia's first general population screening program for T1D. Recognising the immense clinical impact of early identification of people at risk of T1D, the T1DCRN has provided over $1.3 million to **Dr Kirstine Bell** and her team at the University of Sydney to undertake the Australian Type 1 Diabetes National Screening Pilot. This pilot commenced in 2021 and is determining the benefits, feasibility of, and attitudes towards a nationwide T1D population screening program.

An Australian first, Dr Bell's pilot will screen up to 9,000 children and infants across Australia for T1D risk using cutting-edge technologies to identify genetic markers and the presence of islet autoantibodies.

Three different screening methods will be assessed for feasibility, community acceptance and cost-effectiveness to determine which works best in Australia's healthcare settings.

These methods are:

1. **Genetic screening using newborn dried bloodspots,** with autoantibody follow up at 12 months of age for those identified as having higher risk

2. **Genetic screening using saliva** at 6-12 months of age, with autoantibody follow-up of at-risk children at 12 months of age

3. **Autoantibody screening using a capillary dried bloodspot** in children aged two, six and 10 years old

The clinical benefit of this program is that identification of infants and children at risk of or with early-stage T1D could reduce or prevent DKA, and eventually enable access to new therapeutics which can delay or, in the future, halt the condition.

6. Insel RA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. Oct 2015;38(10):1964-74. doi:10.2337/dc15-1419

WHAT WILL THIS PROJECT DELIVER AND WHY IS IT IMPORTANT?

The ultimate vision of this study is for screening for T1D risk to be integrated into routine care in Australia. The results of the pilot will inform recommendations of the best methodology for this to happen.

Australia is well positioned to adopt such a program as we have a well-established and world-recognised health screening infrastructure already in place.

If successful, Australia could become the first country in the world to introduce a general population screening program for T1D.

In the short term, those with pre-symptomatic T1D in Stage 2 could access therapies such as teplizumab as they become approved and available in Australia. Several other therapies such as verapamil, abatacept, baricitinib and alefacept have also shown promise in delaying progression of the immune process and could be offered in a clinical research setting.

The pilot is well on its way to recruiting individuals across the three arms, and results are expected in 2024.

> “Our study is a pivotal first step in achieving our vision for T1D screening to be implemented as a national screening program for all Australian children. Routine screening could have a real benefit for families by diagnosing children early, connecting families to care, and reducing the risk of DKA and its lifelong health impacts. Importantly it would also allow us to identify those in the very early, presymptomatic stages of T1D and offer them preventative therapies as they become available. This means we can essentially stop T1D before it really gets started.
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> **Dr Kirstine Bell**, Principal Investigator of the Australian Type 1 Diabetes National Screening Pilot