

General population screening for childhood type 1 diabetes: is it time for a UK strategy?

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disease of childhood affecting 1:500 children aged under 15 years, with around 25% presenting with life-threatening diabetic ketoacidosis (DKA). While first-degree relatives have the highest risk of T1D, more than 85% of children who develop T1D do not have a family history. Despite public health awareness campaigns, DKA rates have not fallen over the last decade. T1D has a long prodrome, and it is now possible to identify children who go on to develop T1D with a high degree of certainty. The reasons for identifying children presymptomatically include prevention of DKA and related morbidities and mortality, reducing the need for hospitalisation, time to provide emotional support and education to ensure a smooth transition to insulin treatment, and opportunities for new treatments to prevent or delay progression. Research studies of population-based screening strategies include using islet autoantibodies alone or in combination with genetic risk factors, both of which can be measured from a capillary sample. If found during screening, the presence of two or more islet autoantibodies has a high positive predictive value for future T1D in childhood (under 18 years), offering an opportunity for DKA prevention. However, a single time-point test will not identify all children who go on to develop T1D, and so combining with genetic risk factors for T1D may be an alternative approach. Here we discuss the pros and cons of T1D screening in the UK, the different strategies available, the knowledge gaps and why a T1D screening strategy is needed.

INTRODUCTION

Year 2021 marks the centenary of the discovery of insulin, which resulted in 14-year-old Leonard Thompson from Canada, who was at the time dying from diabetic ketoacidosis (DKA), to become the first person to have his life saved by insulin. Severe insulin deficiency, the hallmark of type 1 diabetes (T1D), causes this metabolic decompensation. One hundred years on, insulin is still the gold standard treatment for T1D and 15%–70% children globally present with DKA.^{1–3} Prompt diagnosis improves outcomes by reducing the risks of DKA at presentation. DKA can cause significant morbidity (cerebral oedema, neurocognitive deficits, shock, arrhythmias)³ and is also associated with chronic hyperglycaemia⁴; and if undiagnosed or complicated, it can be fatal.

New developments make it possible to identify presymptomatic T1D. This offers hope to reduce morbidity and mortality at presentation. In future,

it will allow children access to therapies to delay or prevent diabetes onset.

WHAT EVIDENCE DO WE NEED TO CONSIDER IN A SCREENING PROGRAMME?

The UK National Health Service (NHS) screening programme follows specific criteria when assessing whether or not to include a new condition.⁵ These were first formulated by Wilson and Jungner for the World Health Organisation over 50 years ago,⁶ and later revised.⁷ Currently some, but not all, of the screening criteria for T1D are met (table 1). Here we discuss the established evidence, arguments for and against general population screening, screening approaches, and the outstanding scientific, clinical and ethical questions that need to be addressed before widespread adoption.

SCREENING FOR CHILDHOOD T1D: WHAT WE KNOW

Stages of T1D

T1D is a chronic autoimmune disease, affecting 1 in 500 children and young people under 15 years in the UK, with an annual incidence of 25.6:100 000 general population.⁸ There is a long prodromal phase before symptoms develop.⁹ T1D occurs due to a combination of genes and environment, leading to islet-cell autoimmunity, T cell-mediated destruction of pancreatic beta cells followed by glucose intolerance and ultimately osmotic symptoms. This process can take months or even years before symptoms develop. A staging classification has been proposed that has gained widespread acceptance,¹⁰ developed from prospective, longitudinal studies of children and young people at risk of developing symptomatic (insulin-requiring) T1D^{11 12} (figure 1). Stage 1 includes preclinical children who have developed two or more islet-specific autoantibodies (IAb) (anti-insulin (IAA), glutamate decarboxylase (GAD), islet antigen 2 (IA-2) and islet-specific zinc transporter), but who remain normoglycaemic.¹³ These children have a 5-year risk of clinical T1D of 44%, and a 15-year risk of 80%–90%. Stage 2 includes children who remain asymptomatic but have dysglycaemia, with a 5-year risk of clinical disease of 75%, and 100% lifetime risk.¹⁴ Stage 3 includes children who have glycaemic levels diagnostic of T1D.

A child with one IAb is less easy to classify; this may be transient or may indicate evolving seroconversion. The risk of future symptomatic T1D is around 10%–15%.¹³



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Table 1 General population screening for type 1 diabetes (T1D) according to modified Wilson and Jungner criteria

Modified Wilson and Jungner classic screening criteria	Yes	No	Uncertain	Comments
1. The condition sought should be an important health problem.	✓			
2. The target population for screening should be clearly defined and able to be reached.			✓	Ages for testing need to be agreed
3. There should be an accepted treatment or course of action for patients who test positive that results in improved outcomes.			✓	Need to define follow-up for both multiple and single IAb positive Need of T1D preventive treatments
4. Facilities for diagnosis and treatment should be available.		✓		Implementation in routine laboratories needed
5. There should be a recognisable latent or early symptomatic stage.	✓			
6. There should be a suitable test or examination with appropriate performance characteristics.			✓	Test performance needs validation on population level
7. The test should be acceptable to the population.			✓	Will need testing in individual countries and communities
8. The screening test results should be clearly interpretable.			✓	Double IAb positive defined Single IAb positive result not fully established
9. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	✓			
10. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.		✓		UK-specific cost-effectiveness needs to be tested
11. The overall benefit of the programme should outweigh its harms.			✓	More data needed on benefits and harm
12. Case finding should be a continuing process and not a 'once and for all' project, with ongoing monitoring and development of the programme.		✓		National screening programmes embedded in clinical care are required

Why screen for T1D?

Until now, screening for T1D has been limited to research trials recruiting those with a family history. The risk of T1D in a child with a first-degree relative is around 15 times higher than that of the general population, making screening an efficient approach for recruitment into prevention trials. However, more than 85% of newly diagnosed patients lack a family history,¹⁵ and there are advantages for early detection beyond recruitment into trials, which make population screening an attractive option.

DKA reduction

In the UK, around 25% of those with newly diagnosed T1D present with life-threatening DKA, with higher rates in the very young (30% in those under 5 years of age) and in ethnic minority groups. DKA rates have remained unchanged over the

last decade,¹ increasing to 51% during 2020,² likely due to challenges of access and late presentation seen during the COVID-19 pandemic.

Although death from DKA is rare in the UK, it still occurs with three children dying from DKA in England and Wales in 2019 (<https://www.nomisweb.co.uk/>). In 2015, the death of a young boy in Wales with DKA at diagnosis led to a national enquiry.

Identifying children before they present, using IAb alone or in combination with genetic testing, has been shown to reduce DKA by 90%.^{16 17} One advantage of DKA reduction is in avoiding the associated comorbidities, such as cerebral oedema, neurocognitive deficits, shock, arrhythmias and lengthy hospitalisation.^{3 18}

Interestingly, beyond the initial event there appears to be longer term benefit. In the DiPis Study in Sweden, children screened for T1D with longitudinal follow-up before diagnosis had lower glycosylated haemoglobin (HbA1c) up to 5 years following diagnosis.¹⁹ In a recent population-based study of 57 000 children with T1D aged under 20 years, absence of DKA at onset predicted lower HbA1c and fewer episodes of DKA and of severe hypoglycaemia 10 or more years after diagnosis.²⁰ This is supported by the SEARCH Study in the USA, following 1396 children from diagnosis to 13 years, which found DKA at onset to be associated with worsening HbA1c over time.⁴ A causal link between DKA at onset and future long-term complications has not been established, but the association with elevated HbA1c²¹ suggests it worthy of further investigation. Possible mechanisms include a biological effect on beta cells, the trauma of the event adversely affecting subsequent self-management or a psychosocial association between later presentation and self-care.

Reducing stress at diagnosis

The unexpected nature of a T1D diagnosis is challenging for children and families, causing high rates of depression, problems with adjustment and stress; 33% parents report distress at diagnosis.²² Children at high genetic risk of T1D recruited into monitoring programmes demonstrate better family psychological adjustment, parents reported their child had better diabetes-specific quality of life over the first year and there

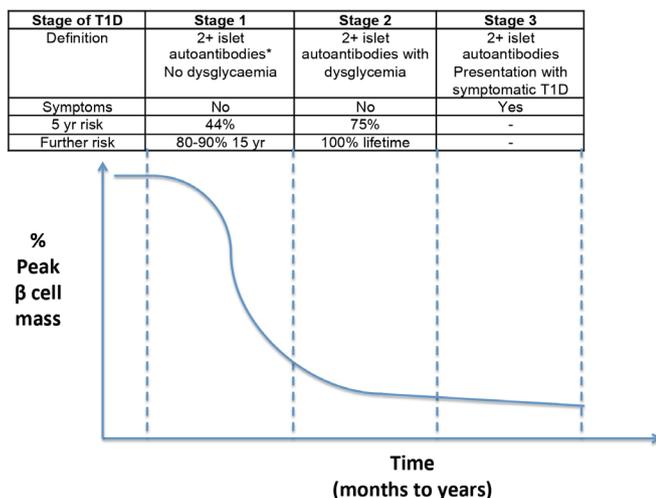


Figure 1 Stages of diabetes and risk of insulin requirement. *Islet autoantibodies include anti-insulin, glutamate decarboxylase, islet antigen 2 and islet-specific zinc transporter. T1D, type 1 diabetes. Adopted from Insel.¹⁰

was lower parental stress following diagnosis compared with community controls (State Anxiety Inventory, Pediatric Quality of Life inventory-Diabetes module and Pediatric Inventory for Parents).²³ The Fr1da Study reported raised stress levels (Patient Health Questionnaire-9) in parents informed that their child was IAb positive; this returned to baseline after 12 months, and even the initial stress levels were only around 50% of those seen in families where children were diagnosed outside of the screening programme.¹⁶

Identifying children for prevention trials

Identification of early stage T1D may provide an important window of opportunity for preventive therapies. Recently, the anti-CD3 therapy (tepluzimab) was shown to be associated with a 3-year delay in progression to symptomatic diabetes in patients who were double antibody positive.²⁴ Regulatory approval is currently being sought.

LIMITED EFFECTIVENESS OF PUBLIC HEALTH AWARENESS PROGRAMMES

Children developing T1D are 6.5 times more likely than controls to have contact with primary care services in the year prior to diagnosis.²⁵ Therefore, to promote greater public and healthcare awareness of the symptoms of T1D (polyuria, polydipsia, tiredness and weight loss) to facilitate earlier diagnosis and reduce rates of DKA, public health awareness programmes have been introduced worldwide, with varying success. These have mostly been modelled on an Italian study,²⁶ using a poster campaign to increase awareness through schools, combined with provision to primary care services of glucose and ketone testing equipment. Interventions in Italy, Australia, Saudi Arabia and Turkey appeared to reduce the rate of DKA at presentation, whereas similar initiatives in Wales and Austria had no observable impact. A systematic review²⁷ determined it was not possible to draw conclusions about the effectiveness of the interventions in these observational studies. Furthermore, a recent international study including four of the countries from which these studies originated¹ reported only a slight decrease in DKA rates at diagnosis of T1D between 2006 and 2016. A further refinement in Wales using a reusable shopping bag to publicise the symptoms of diabetes and delivered to children in schools was shown to be feasible; however, this has not been formally tested.²⁸ In the absence of adequately powered, randomised studies, public health awareness campaigns do not appear adequately effective to reduce DKA, nor do they obviate a need for a screening programme.

PROS AND CONS FOR SCREENING

T1D is typically diagnosed based on symptoms. Rarely do all symptoms highlighted in public awareness campaigns present

at the same time. In young children, symptoms may be non-specific, resulting in missed or late diagnosis.

Some of the arguments for and against screening for T1D are summarised in table 2. The benefit of families having time to prepare for and adjust to the diagnosis before insulin is needed needs to be balanced by the anxiety that this may cause and the challenges of treating those with early or intermittent hyperglycaemia.

POPULATION-BASED SCREENING STRATEGIES

Two strategies have been used for population-based approaches: IAb alone, or in combination with genetic screening for high-risk variants.

IAb alone

The presence of IAb indicates that the autoimmunity has begun and predicts that T1D will develop in over 80% over the next 15 years.¹³ In those with a family history of T1D, islet autoimmunity is commonly detected early in life with most individuals seroconverting by 2–3 years, with a peak incidence between 9 and 12 months.^{29 30}

The Fr1da community surveillance programme in Bavaria is the best-developed population-based screening study and aimed to determine the prevalence of preclinical (stages 1 and 2) T1D in children.¹⁶ The primary outcome was preclinical T1D, defined by two or more IAb. Secondary outcomes were the frequency of DKA and parental psychological stress.

Of 90 632 children aged between 1.75 and 5.99 years screened through the Bavarian community paediatrician network, 280 (0.31%) had preclinical T1D, including 196 (0.22%) with stage 1, 17 (0.02%) with stage 2 and 26 (0.03%) with stage 3. The 261 children confirmed positive for multiple IAb were referred into prevention studies. After a median follow-up of 2.4 years, another 36 children developed stage 3 T1D. Only two children presented in DKA, showing a fivefold reduction in presentation of this complication. The presence of four IAb, IA-2, obesity and HbA1c equal to or greater than 5.7% (39 mmol/mol) was associated with risk of progression.

One other reported IAb study is the Autoimmunity Screening for Kids (ASK) community surveillance programme in Colorado.³¹ Here, children aged 1–17 years were approached through community health fairs and health centres and screened for both T1D and coeliac disease. Approximately, 0.5% of the 10 029 children were found to have 2+ IAb. The proportion of children presenting in DKA fell from a baseline of 46% to less than 10%.

IAb with T1D genetics

The identification of elevated genetic risk for T1D is strongly associated with the development of T1D autoimmunity. The multinational TEDDY Study (The Environmental Determinants

Table 2 Pros and cons of screening for type 1 diabetes (T1D)

Pros	Cons
<ul style="list-style-type: none"> ▶ Potential to prevent DKA at diagnosis by education on symptoms of diabetes ▶ Opportunity for time to adjust to diagnosis ▶ Genetic testing for high-risk genes/genetic risk scores possible at birth for use in combination with autoantibodies ▶ IAb detectable with fingerprick test, so easy test to administer ▶ IAb sensitive and specific ▶ May be intervention studies to delay development or prevent T1D in future 	<ol style="list-style-type: none"> 1. Potential increased anxiety in parents/carers knowing child is at risk 2. High numbers of individuals genetically at risk but who don't develop T1D 3. If using IAb alone: <ul style="list-style-type: none"> – Likely need testing more than once – Will miss those diagnosed before screening and those who seroconvert after screening test 4. Treatment of early hyperglycaemia can be challenging 5. No licensed treatment to prevent T1D at present

DKA, diabetic ketoacidosis.

of Diabetes in the Young) followed 7777 children with high-risk human leucocyte antigen (HLA) alleles from birth to a median of 9.1 years for the development of IAb and T1D.³² A total of 736 (9.5%) children developed one or more persistent IAb (GADA, IAA or IA-2A), 434 developed two or more IAb, and of these 219 (50.5%) developed T1D. HLA genotype was the best predictor for development of IAb, with sensitivity 49.8% and specificity 61.9%.

Recently, T1D genetic risk scores (GRS) have improved the sensitivity and specificity of children who go on to develop IAb.³³ These combine HLA and non-HLA T1D susceptibility single-nucleotide polymorphisms for T1D into a single continuous variable. A GRS threshold or HLA combined with family history is currently being used to recruit the highest risk babies (defined as having >10% risk of islet autoimmunity in the first years of life) into prevention trials, and established in the Global Platform for the Prevention of Autoimmune Diabetes,³⁴ which has successfully recruited infants into the Primary Oral Insulin Trial.¹⁴

SCREENING FOR CHILDHOOD T1D: WHAT DON'T WE KNOW?

There are gaps in our knowledge that need addressing before screening can move from a research-based approach to an integrated programme of service delivery within the NHS.

When to screen, and how

Almost all children with 2+ IAb will develop T1D during childhood. A population screening approach measuring IAb will identify children who have IAb at the time of the test, but is too late for children who already have T1D, and will miss those who have not yet developed IAb unless testing is offered periodically. Since many children seroconvert by 2–3 years of age, the optimal age to screen at a single time point has been suggested as 3–4 years.^{29 30} However, this approach will miss at least one-third of all childhood T1D, and so screening at two time points (2–3 and 5–7 years) will improve sensitivity but this is likely to still miss some children, including the youngest and most vulnerable.^{29 35}

Combining GRS (rather than just with HLA) with IAb testing increases sensitivity; however, as T1D has a prevalence of about 0.3%, even those with high risk are likely not to develop T1D. For example, the top decile of genetic risk for T1D in the UK population (as measured by a T1D GRS) has about 78% sensitivity for childhood T1D, with higher sensitivity for young onset cases in the first few years of life, but the overall risk of T1D within this top decile is about 2.4%.^{33 34} For a genetic screen to have high sensitivity yet still offer accurate future prediction, it must be coupled with IAb screening in those identified as high risk.

Recently, a combined adaptive approach that included assessment of T1D GRS and family history coupled with repeated measurement of IAb in those identified as high risk suggested that an adaptive approach may improve efficiency. This approach recalculates risk at different ages for improved precision; the highest risk children will be screened for IAb at a young age and those with a lower genetic risk can be screened at an older age.³⁶ Follow-up in IAb-negative or single IAb-positive children can be offered according to risk, which will reduce over time.

The technology is now available to measure both GRS and IAb from a small capillary sample that can be collected at home and posted for analysis, which would allow this approach to be tested prospectively.

Follow-up and treatment of early stage T1D

Stratifying multiple IAb-positive patients into slow or fast progressors is needed to decide on the frequency of follow-up. In the Fr1da Study, 26% children progressed from stage 1 to stage 3 disease, despite 2–3 monthly follow-up. The oral glucose tolerance test (OGTT) is the standard method to stage disease, and can be used to provide a score associated with risk of progression.³⁷ The OGTT is an invasive, time-consuming and expensive test, with relatively high variability. Simpler tests exist, such as capillary glucose, or a change in HbA1c within the non-diabetic range,³⁸ but would be of limited use in children who progress rapidly. Continuous glucose monitoring (CGM) is minimally invasive and provides real-time data. A practical approach might be a home capillary test for HbA1c, glucose and C-peptide with CGM. The management of early hyperglycaemia in T1D can be challenging as patients can be insulin sensitive, causing hypoglycaemia with insulin treatment. An agreed management approach is needed.

Cost-effectiveness

Health economic evaluation has suggested that screening using a non-targeted approach may be cost-effective in countries such as the USA where DKA rates are high (>40%). However, what is found to be cost-effective in one country might not be in the UK (and vice versa) even given the same effectiveness, due to different costs of treatment. Cost-effectiveness will need to be assessed, focusing on early case finding, avoidance of DKA and hospital admission, allowing insulin commencement and education as an outpatient. This is particularly relevant to the UK; the DECIDE trial showed no difference in clinical outcomes between children newly diagnosed with T1D managed at home or in hospital, but there were considerable cost savings in managing children out of hospital.³⁹ The benefits of early intervention on psychological burden and improved ongoing self-management need to be evaluated against the costs of an early screening and metabolic surveillance programme.

NEXT STEPS FOR THE UK

A comprehensive research programme is needed to address the unanswered questions before a screening programme is introduced. The goal for the UK will be to gather evidence to determine how to undertake whole population screening (feasibility), and whether screening is acceptable to children and families (acceptability). There is a need to quantify the benefits in terms of DKA prevention and reduction in hospitalisation, the requirement for psychological support for emotional adjustment to the diagnosis and the opportunities for treatments to delay/prevent the progression of the disease.

Since T1D incidence is rising most steeply in children under 5 years old, and this group of children have the highest rates of DKA, an approach to identify young children before clinical onset is needed.

Within the NHS, every child is offered routine health visits, including newborn bloodspot screening, neurodevelopmental checks and immunisations. Costs are likely to be reduced if testing coincides with existing health visits.

IMPLICATIONS FOR PRACTICE: THE NEXT 100 YEARS

Introduction of screening for T1D offers an exciting opportunity to change the way T1D is diagnosed and will impact children, families, primary and secondary care. Primary care health professionals will be best placed to provide genetic and IAb screening but counselling of genetic at-risk and single IAb

children will need careful thought. Paediatricians may be best placed to offer metabolic monitoring to children with two or more IAb until they need insulin. Education and psychological packages for early stage T1D will need to be developed and integrated into NHS practice. New resources will be needed to meet these requirements, but in the longer term the overall workload may not increase substantially. Changes in care pathways will require a frameshift in thinking, as diagnosis will be brought forward to earlier stages of the disease, but where the disease is more manageable.

CONCLUSIONS

Scientific advances have moved the diabetes field forward since Leonard Thompson first received insulin 100 years ago. It is now possible to identify children in the general population before they develop symptoms of T1D. This will involve a change in care pathways, and the opportunity to prevent morbidity and mortality from DKA, allowing children and families time to adjust to the diagnosis before insulin is needed. We need to develop, validate and implement a UK-wide population screening strategy. If this happens, the news that a child has presented with DKA may be consigned to the last 100 years.

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