



Managing adults with screen-detected islet autoantibody positivity: a pragmatic framework

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New disease-modifying therapies, such as teplizumab, offer opportunities to delay the clinical onset of type 1 diabetes but require islet autoantibody screening to identify individuals at increased risk of progression to diabetes. As type 1 diabetes screening programmes expand, clinicians will increasingly encounter a new group of people: adults who test positive for islet autoantibodies but have not yet been diagnosed with diabetes. Although international guidelines outline management for both children and adults, considerable uncertainties remain, particularly for adults. In adults with islet autoantibody positivity, the lower risk of progression to type 1 diabetes compared with children, combined with the high background prevalence of mild non-autoimmune dysglycaemia, presents substantial challenges for clinical management. This Personal View aims to add clarity to international consensus guidelines, proposing a pragmatic framework for managing adults with islet autoantibody positivity. Although fitting within a UK National Health Service setting, we feel this framework is also relevant to other health systems.

Introduction

Teplizumab, the first therapy shown to delay the onset of type 1 diabetes, is now approved in some countries (including the UK, the USA, Canada, and China) and under regulatory review in others. Teplizumab is an anti-CD3 monoclonal antibody that modulates autoreactive T cells by inducing partial T-cell exhaustion and restoring immune tolerance. This mechanism reduces the autoimmune destruction of pancreatic β cells, thereby delaying progression to symptomatic (stage 3) type 1 diabetes.¹ Screening individuals without a diagnosis of diabetes for islet autoantibodies is essential in identifying candidates who could benefit from teplizumab and other future disease-modifying therapies. Screening programmes currently are largely in the research domain, though one country to date, Italy, has an established programme.² People who test positive will require monitoring for progression to symptomatic type 1 diabetes. Although international guidelines,³ published in 2024, provide recommendations for monitoring across age groups, substantial challenges and unanswered questions remain regarding managing adults with islet autoantibody positivity. In this Personal View, we suggest a pragmatic approach for the management of adults with islet autoantibody positivity. Our recommended approach is summarised in a single flowchart (figure), with further detail provided in the appendix.

Challenges and unanswered questions for islet autoantibody screening in adults

Limitations of current research

A major difficulty in implementing islet autoantibody screening in adults and managing those who test positive, is the scarcity of research on type 1 diabetes progression to guide decision making. Islet autoantibodies are specific to pancreatic islet β -cell antigens (eg, GAD65, IA2, insulin, and ZnT8), and their presence signals autoimmune activity that strongly predicts progression to type 1 diabetes.⁴ Adults with multiple islet autoantibodies are

considered to have presymptomatic type 1 diabetes, with around one in six progressing to clinical disease within 5 years.^{5,6} However, screening will also detect adults with a single islet autoantibody, whose 5-year risk is lower but still clinically relevant (approximately one in 20 adults with a single islet autoantibody will progress to clinical disease in 5 years).⁶ Crucially, both estimates are based on studies of adult relatives of people with type 1 diabetes, all recruited younger than 45 years. To the best of our knowledge, no study has yet robustly assessed risk in the general population without a family history of type 1 diabetes or older adults (ie, older than 45 years); therefore, progression is unclear in most of the general population.

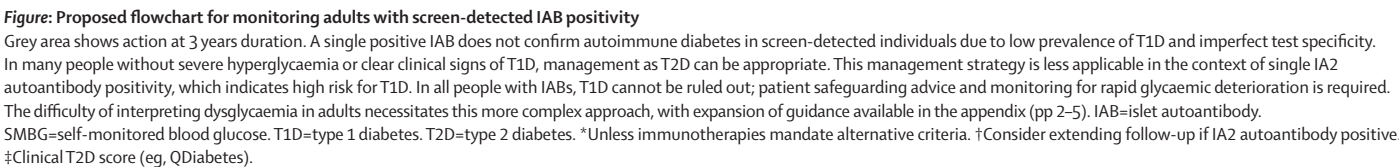
Interpretation of non-diabetic range hyperglycaemia

The presence of non-diabetic range hyperglycaemia (eg, HbA_{1c} 39–47 mmol/mol [5.7–6.4%]) is a strong predictor of progression to type 1 diabetes and is part of the eligibility criteria for teplizumab in individuals with multiple islet autoantibodies.⁷ However, in adults, non-diabetic range hyperglycaemia is common, affecting up to 40% of the general population, making it a less reliable indicator of type 1 diabetes progression than in children.^{8,9} Furthermore, non-diabetic range hyperglycaemia poses a particular challenge in older adults, as applying current thresholds from international guidance could classify a large proportion of this population as at risk of developing type 1 diabetes. Therefore, in adults, thresholds of non-diabetic range hyperglycaemia to predict type 1 diabetes development needs to be further explored.

Type 2 diabetes: common in adults

Although islet autoantibodies have imperfect specificity (ie, false positive results can occur), nearly all children with islet autoantibody positivity who develop diabetes will have type 1 diabetes, as other diabetes types are rare in this age group. By contrast, type 2 diabetes is far more common than type 1 diabetes in adults;¹⁰ the 5-year risk of developing type 1 diabetes in adults with

See Online for appendix



and younger individuals (aged <30 years) or lean adults (where type 2 diabetes is uncommon) are also more likely to have type 1 diabetes, many older adults or adults with overweight or obesity who develop diabetes after testing positive for only a single islet autoantibody (which has lower specificity) are more likely to have type 2 diabetes than autoimmune diabetes. A similar

situation is seen in latent autoimmune diabetes in adults, which likely represents a mixed population of autoimmune (type 1 diabetes) and non-autoimmune (type 2 diabetes) diabetes.^{10,12} Pragmatic strategies are therefore needed to guide the management of adults with diabetes who test positive for a single islet autoantibody.

General guidance for all adults with islet autoantibody positivity

We have summarised our approach in a single flow chart (figure). Islet autoantibodies results can vary substantially between different assays and laboratories. Therefore, as recommended in 2024 international consensus guidelines,³ islet autoantibody positivity should be confirmed with the rule of twos: positivity on two different assays from two separate samples, where possible.³ We suggest repeat testing is ideally done in a laboratory participating in the international islet autoantibody standardisation programme, using population-derived positivity thresholds to maintain test specificity.¹³ Many screening studies use high-specificity thresholds (ie, >99th percentile) to define positivity; however, routinely available clinical assays, predominantly used to confirm type 1 diabetes, often define positivity at lower thresholds.

We recommend that to avoid diagnostic delay and minimise risk of presentation in ketoacidosis, all confirmed adults with islet autoantibody positivity (single or multiple) should be provided with written education on diabetes symptoms (ie, the four Ts: toilet, tired, thirsty, thinner). Given the possibility that exercise could preserve β -cell function in early type 1 diabetes, and proven benefits to cardiovascular, mental, and general health, we emphasise healthy lifestyle guidance at initial contact.^{14,15}

In international guidance, a range of measures have been proposed for measuring glycaemia, including repeated oral glucose tolerance testing.³ Although less sensitive than oral glucose tolerance testing, we propose HbA_{1c} as the preferred glycaemic measure due to its accessibility and familiarity among clinicians. International guidelines have recommended that HbA_{1c} of 39–47 mmol/mol (5.7–6.4%) indicates non-diabetic range hyperglycaemia and increased risk of progression to diabetes, warranting more frequent monitoring.³ However, this value is present in approximately 40% of adults 40 years or older in the general population.⁸ Therefore, to guide monitoring frequency in adults with islet autoantibody positivity, and while awaiting prospective studies that address this issue to define an optimal cut-off for adults, we propose use of a higher threshold (≥ 42 mmol/mol [$\geq 6\%$]), aligning with glucose thresholds used to define non-diabetic range hyperglycaemia advocated by WHO and used in many countries, including the UK.¹⁶ In younger adults, especially those transitioning from paediatric care, maintaining the lower threshold might be more appropriate.

Moving forward, additional glycaemic and non-glycaemic measures for predicting progression to type 1 diabetes, validated in adults with islet autoantibody positivity, are required.

The frequency of glycaemic monitoring should balance the need to detect progression in individuals with islet autoantibody positivity against the financial, time, and resource costs of repeated testing. Monitoring frequency should vary according to the likelihood of progression in different risk groups and account for the generally slower rate of progression in adults compared with children, for individuals with single and multiple islet autoantibody positivity.^{5,6}

Given islet autoantibody screening in individuals who have not yet been diagnosed with diabetes is in its infancy, and the complexity of differentiating the cause of dysglycaemia in adults, we favour monitoring initially being coordinated by secondary care teams (rather than primary care), contrary to some guidance.^{3,17} We anticipate this changing over time as this area becomes more familiar to primary care practitioners and risk stratification improves. Genetic testing for type 1 diabetes is not widely available in clinical practice, so we have not included this in our recommendations. However, as it becomes more routine, genetic testing could help inform progression risk in individuals with islet autoantibody positivity, although further research is needed.

Specific guidance

Adults with islet autoantibody positivity with HbA_{1c} concentrations less than 48 mmol/mol (6.5%)

Adults with single islet autoantibody positivity

Given the low risk of progression in most adults with single islet autoantibody positivity, further research is urgently needed to improve risk stratification. This group is heterogeneous and includes: individuals who previously tested positive for multiple islet autoantibodies but have lost antibodies over time; false positive results or people with islet autoantibodies not strongly associated with type 1 diabetes (eg, islet autoantibodies targeting only the first 95 amino acids of the glutamic acid decarboxylase antigen);¹⁸ and people with true persistent single positivity,¹⁹ for whom the duration of islet autoantibody positivity, whether originating in childhood or more recently, is typically unknown.

Current evidence suggests that within individuals with single islet autoantibody positivity, those with non-diabetic range hyperglycaemia have a higher risk of progressing to type 1 diabetes than those with normal glucose concentrations.⁶ Risk is further elevated in those who have first-degree relatives with type 1 diabetes, IA2 autoantibody positivity, and previous gestational diabetes.^{20,21} Additionally the importance of good prenatal glycaemic control warrants more frequent testing in this scenario, irrespective of HbA_{1c}, to reduce the risk of entering pregnancy with unrecognised diabetes.

We therefore recommend testing HbA_{1c} once per year where the individual has HbA_{1c} of 42–47 mmol/mol (6·0–6·4%; inclusive), and has a first-degree relative with type 1 diabetes, has IA2 autoantibody positivity, is planning pregnancy, or had previous gestational diabetes. If none of these factors apply, we recommend testing HbA_{1c} every 3 years and if HbA_{1c} is 48 mmol/mol (6·5%) or higher, follow the guidance discussed later in this Personal View.³ In those who do not develop diabetes within 3 years of testing, we suggest one-off repeat islet autoantibody testing 3 years after initial screening. Where islet autoantibodies become negative, people can be reassured and discharged. If additional islet autoantibodies develop, we suggest management as outlined for those with two or more positive islet autoantibodies.

In adults with persistent single positive islet autoantibodies, we suggest management according to HbA_{1c} concentrations 3 years after initial screening. For individuals with HbA_{1c} concentrations less than 42 mmol/mol (6·0%), reassure the individual, reiterate diabetes symptoms, and discharge from routine follow-up, with management under primary care no different from the general population. If an individual subsequently develops diabetes, we recommend considering management as type 2 diabetes, unless high clinical suspicion of type 1 diabetes or progression to insulin within 3 years of diabetes diagnosis.²² We suggest this pragmatic approach because of the increased incidence of type 2 diabetes in adults in the context of unclear relevance of persistent single islet autoantibody positivity and type 1 diabetes progression. When managed as type 2 diabetes, we recommend considering intermittent capillary glucose monitoring in adults who otherwise would not routinely require it (eg, those treated with lifestyle measures alone). For individuals with HbA_{1c} concentrations of 42–47 mmol/mol (6·0–6·4%), continue annual HbA_{1c} testing. We suggest assessment of risk factors for type 2 diabetes, for example, with clinical prediction risk scores such as QDiabetes.²³ For those identified as being at high risk of type 2 diabetes, we suggest ongoing monitoring with annual HbA_{1c} testing and education, in line with UK practice for those at high risk of type 2 diabetes. If HbA_{1c} remains less than 48 mmol/mol (6·5%) 6 years after initial screening, we suggest the individual is reassured and discharged to primary care for ongoing follow-up as pre-type 2 diabetes. For individuals with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher, follow guidance outlined later in this Personal View.

Adults with two or more positive islet autoantibodies

The presence of multiple islet autoantibodies indicates presymptomatic type 1 diabetes, staged by glycaemia; stage 1 normoglycaemia and stage 2 dysglycaemia have the highest risk of type 1 diabetes.^{3,24} All adults with multiple positive islet autoantibodies should receive a capillary blood glucose meter (for self-monitored blood

glucose testing) and education on testing when unwell or symptomatic. We suggest they receive the following advice on result interpretation: where glucose concentration is greater than 14 mmol/L, call clinical team urgently (within 24 hours) and attend hospital if feeling unwell; where glucose concentration is 11–14 mmol/L, start regular capillary glucose testing (ie, first thing in the morning and before bed) and call the clinical team within working hours.

Until further adult natural history data are available, we suggest undertaking lifelong follow-up in this group. No further islet autoantibody testing is needed after confirmation, as loss of islet autoantibodies after testing positive for multiple antibodies does not materially alter future type 1 diabetes risk.²⁵ The benefit of continuous glucose monitoring in presymptomatic management (stage 1 and 2) remains unclear and requires further study. Therefore, we do not recommend its use, especially given, in our clinical experience, the potential anxiety caused by constant awareness of minor glucose fluctuations of uncertain significance.

We recommend HbA_{1c} monitoring frequency based on the individual's most recent HbA_{1c} concentrations, following international consensus guidance.³ For individuals with HbA_{1c} of less than 42 mmol/mol (6·0%), we recommend annual testing; consider reducing to once every 2 years if HbA_{1c} is less than 42 mmol/mol (6·0%) for 5 years. For individuals with HbA_{1c} of 42–47 mmol/mol (6·0–6·4%) or history of gestational diabetes,²¹ we recommend repeat testing every 6 months. For individuals with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher, follow guidance outlined later.

Adults with islet autoantibody positivity with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher

In adults, islet autoantibody screening often leads to diabetes being diagnosed much earlier than it would be through symptomatic presentation, typically in an age group where type 2 is common (eg, in people older than 30 years, the prevalence of type 2 diabetes is >5% in the UK and higher in many other countries).²⁶ Although the default management of adults with islet autoantibody positivity with diabetes is as type 1, in line with consensus recommendations for latent autoimmune diabetes in adults,²⁷ a trial of non-insulin therapies with close monitoring could be appropriate in asymptomatic individuals with moderate glycaemia just above the diabetes range, as discussed later. This approach is especially relevant for those with single islet autoantibody positivity and high type 2 diabetes risk, as a considerable proportion are likely to have diabetes driven by non-autoimmune type 2 diabetes mechanisms.¹⁰

For adults with single islet autoantibody positivity with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher who have clinical features otherwise consistent with type 2 diabetes, we suggest consideration of initial management as type 2 diabetes with HbA_{1c} testing every

6 months; capillary glucose monitoring when unwell, with the advice as outlined previously; and education on severe symptoms that should prompt urgent medical review.

Our recommendation to manage some adults with single islet autoantibody positivity with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher as having type 2 diabetes differs from current international consensus guidelines,³ which define type 1 diabetes by the presence of one or more islet autoantibodies in individuals with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher. We emphasise that, in asymptomatic individuals identified as having islet autoantibody positivity through screening, a diagnosis of type 2 diabetes might often be more appropriate, given the imperfect specificity of single positive islet autoantibodies for autoimmune aetiology diabetes^{10,12} and the high population prevalence of type 2 diabetes in adults, particularly where type 2 diabetes risk factors (older age or high BMI) are present. This recommendation contrasts with current clinical practice, where islet autoantibody positivity is typically identified retrospectively in individuals presenting with symptoms consistent with type 1 diabetes, in whom the high pre-test probability of type 1 diabetes means even a single positive islet autoantibody will usually confirm the clinical diagnosis.^{11,22,28}

For other adults with islet autoantibody positivity, our recommendation is to manage as type 1 diabetes, provide education, and consider continuous glucose monitoring. Although insulin is typically necessary, initial non-insulin therapy can be considered alongside close monitoring.^{26,29} When treatment is initiated, the target HbA_{1c} concentration is less than 48 mmol/mol (6·5%). We predominantly recommend metformin as initial therapy, and suggest caution regarding use of GLP-1 receptor agonists and SGLT2 inhibitors due to concerns around diabetic ketoacidosis risk in the context of potential insulin deficiency. Moreover, it is important to note that neither treatment is licensed for type 1 diabetes management.^{30,31} Further research is needed given the likely low risk (for diabetic ketoacidosis) of these therapies in early type 1 diabetes and their known cardiovascular and renal benefits.³²

At 3 years after diagnosis in adults treated with insulin who have single islet autoantibody positivity, we recommend measuring non-fasted (ie, within 5 hours of a meal) C-peptide concentration, with interpretation consistent with international guidance on classification of adult onset type 1 diabetes.²² For individuals with C-peptide concentration less than 600 pmol/L, continue type 1 diabetes treatment. For individuals with C-peptide concentration of 600 pmol/L or higher, consider non-insulin agents and discontinuing insulin (if not previously had inadequate glycaemic response to oral therapy alone).²² However, in line with international guidance, ongoing additional glycaemic monitoring is

needed, as a partial remission of type 1 diabetes (ie, a temporary period after diagnosis when the body's remaining β cells can still produce some insulin, leading to improved glucose control and a reduced need for insulin therapy, also known as the honeymoon period)³³ could potentially extend beyond 3 years, especially where the disease might have been diagnosed before the appearance of symptoms.²²

Pregnancy

Few data exist on monitoring women with islet autoantibody positivity during pregnancy but associated increased insulin resistance is a risk factor for glycaemic progression.³⁴

Pre-pregnancy

We recommend women of reproductive age with islet autoantibody positivity should be asked about pregnancy and where planned, have annual HbA_{1c} and thyroid stimulating hormone testing, reflecting the coexistence of type 1 diabetes and thyroid disorders and importance of recognition in early pregnancy.³⁵ For individuals with HbA_{1c} concentrations of 48 mmol/mol (6·5%) or higher, we recommend following diabetes in pregnancy pre-conception guidelines,³⁶ including prescribing 5 mg folic acid.

Confirmed pregnancy

All pregnant women with islet autoantibody positivity with pre-conception HbA_{1c} less than 48 mmol/mol (6·5%), regardless of number of islet autoantibodies detected, should receive a capillary glucose meter and education to test if they feel unwell. If glucose values are greater than 14 mmol/L, individuals should call their clinical team urgently (within 24 hours) and attend hospital if they feel unwell. If glucose value is 11–14 mmol/L, individuals should start regular capillary glucose testing (first thing in the morning and before bed) and call their clinical team within working hours. If glucose value is 7·8 to less than 11 mmol/L, individuals should inform their clinical team within working hours.

Where pre-pregnancy HbA_{1c} is less than 48 mmol/mol (6·5%), we recommend following guidelines for previous gestational diabetes: 75 g 2-hour oral glucose tolerance testing as soon as possible, ideally within 8 weeks.^{3,36} Where initial oral glucose tolerance testing is normal, repeat at 24 weeks. Where oral glucose tolerance testing is abnormal, management should be in a specialist antenatal diabetes clinic. Initial glucose monitoring should follow gestational diabetes protocols: fasting and post-meal glucose testing. We recommend initiating treatment to reach local pregnancy diabetes targets, favouring insulin, but we consider metformin where individuals are at high risk of developing type 2 diabetes (eg, high QDiabetes risk score).²³ Continuous glucose monitoring should be considered if mealtime insulin injections are required. We recommend measuring

Search strategy and selection criteria

We searched PubMed for publications from database inception to June 12, 2025. We referenced studies based on an unstructured search of the literature as well our personal knowledge and experience and did not undertake a formal literature search.

thyroid stimulating hormone when pregnancy is confirmed, mirroring current international guidelines for type 1 diabetes.³⁵

Postpartum

As per gestational diabetes guidelines, after delivery we recommend discontinuing treatment when started in pregnancy. However, we recommend undertaking an additional 2 weeks of capillary fasting glucose monitoring after childbirth. Where fasting glucose is consistently (as per clinician judgement) greater than 7.0 mmol/L, we recommend management as for those with an HbA_{1c} concentrations of 48 mmol/mol (6.5%) or higher outside of the context of pregnancy. Where fasting glucose is lower than 7.0 mmol/L, no additional action is required. We recommend repeat HbA_{1c} testing at 13 weeks postpartum in all individuals and then continue routine care as per the figure.

Conclusion

This Personal View provides a pragmatic approach to managing adults with screen-detected islet autoantibodies but is not exhaustive for all clinical scenarios and should not replace clinical judgment. We have based this approach on the best available data and our clinical experience, and have highlighted often overlooked issues in adults. These guidelines are developed with the UK's National Health Service in mind but we believe they are relevant to other health systems because they address the universal challenge of differentiating between diabetes phenotypes. Further research is clearly needed, as there are few published data on natural history and risk stratification in adults, particularly in older adults where type 2 diabetes is more common, and data on management of presymptomatic type 1 diabetes and pregnancy management are scarce.³ Addressing these issues will be fundamental to developing robust evidence-based guidance for the management of adults with presymptomatic type 1 diabetes.

Contributors

NT and PN conceived the manuscript. NT, AJ, DT, and PN met and discussed the best approach for the management of preclinical type 1 diabetes. NT wrote the first draft. NT, AJ, DT, and PN reviewed and edited the first draft.

Declaration of interests

NT has submitted a research funding application to Sanofi through their institution and serves on advisory boards for Sanofi. NT holds current research funding from a Gillings-funded Academic Clinical Lectureship

at Exeter University, the Medical Research Council (MRC), and the Academy of Medical Science. AJ reports institutional research funding and travel and subsistence support from the National Institute for Health and Care Research, MRC, Diabetes UK, Breakthrough T1D, Novo Nordisk Foundation, and the European Foundation for the Study of Diabetes. AJ has also received travel and subsistence support and speaking honoraria from the Association of British Clinical Diabetologists. DT is an unpaid trustee of the Novo Nordisk UK Research Foundation and holds a consultancy agreement with Quell Therapeutics, though has not engaged with the company nor received any payment. DT holds current research grants from Breakthrough T1D in partnership with the Steve Morgan Foundation, the Helmsley Charitable Trust, and the MRC. DT serves on advisory boards for Sanofi, from whom they have also received support for conference attendance. PN has served on advisory boards for Sanofi and Abbott and has received speaker fees and obtained research funding from Sanofi—all through their institution. PN has received grants from Helmsley Charitable Trust, Breakthrough T1D, and Diabetes UK.

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