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RESEARCH ARTICLE

Clinical care advice for monitoring of islet autoantibody positive individuals with presymptomatic type 1 diabetes

A. Emile J. Hendriks[1,2] | M. Loredana Marcovecchio[1,2] | Rachel E. J. Besser[3,4] | Ezio Bonifacio[5,6] | Kristina Casteels[7,8] | Helena Elding Larsson[9,10] | Gita Gemulla[5,11] | Markus Lundgren[10,12] | Olga Kordonouri[13] | Roberto Mallone[14,15] | Flemming Pociot[16] | Agnieszka Szypowska[17] | Jorma Toppari[18,19] | Thekla von dem Berge[13] | Anette G. Ziegler[6,20,21] | Chantal Mathieu[22] | Peter Achenbach[6,20,21] | on behalf of the INNODIA consortium, the Fr1da Study Group and the GPPAD Study Group

[1]Department of Paediatrics, University of Cambridge, Cambridge, UK

[2]Department of Paediatric Diabetes and Endocrinology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[3]Diabetes and Inflammation Laboratory, Wellcome Centre for Human Genetics, Nuffield Department of Medicine, Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

[4]Department of Paediatrics, University of Oxford, Oxford, UK

[5]Technische Universität Dresden, Center for Regenerative Therapies Dresden, Dresden, Germany

[6]German Center for Diabetes Research (DZD e.V.), Munich, Germany

[7]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[8]Department of Development and Regeneration, KU Leuven, Leuven, Belgium

[9]Department of Pediatrics, Skåne University Hospital, Malmö/Lund, Sweden

[10]Department of Clinical Sciences Malmö, Lund University, Malmö/Lund, Sweden

[11]Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[12]Department of Pediatrics, Kristianstad Hospital, Kristianstad, Sweden

[13]Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover, Germany

[14]Université Paris Cité, Institut Cochin, CNRS, INSERM, Paris, France

[15]Assistance Publique Hôpitaux de Paris, Service de Diabétologie et Immunologie Clinique, Cochin Hospital, Paris, France

[16]Department of Clinical Research, Translational Type 1 Diabetes Research, Steno Diabetes Center Copenhagen, Herlev, Denmark

[17]Department of Pediatrics, Medical University of Warsaw, Warsaw, Poland

[18]Institute of Biomedicine, Centre for Integrative Physiology and Pharmacology and Population Health Research Centre, University of Turku, Turku, Finland

[19]Department of Pediatrics, Turku University Hospital, Turku, Finland

[20]Institute of Diabetes Research, Helmholtz Munich, German Research Center for Environmental Health, Munich, Germany

[21]Technical University of Munich, School of Medicine, Forschergruppe Diabetes at Klinikum Rechts der Isar, Munich, Germany

[22]Department of Endocrinology, UZ Gasthuisberg, Katholieke Universiteit, Leuven, Belgium

Correspondence
A. Emile J. Hendriks, Department of Paediatrics, University of Cambridge, Box 116 Level 8, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK.
Email: aejh6@medschl.cam.ac.uk

Abstract

Background/Aim: Type 1 diabetes is an autoimmune disease that involves the development of autoantibodies against pancreatic islet beta-cell antigens, preceding clinical diagnosis by a period of preclinical disease activity. As screening activity to identify autoantibody-positive individuals increases, a rise in presymptomatic type 1 diabetes individuals seeking medical attention is expected. Current guidance on how to monitor these individuals in a safe but minimally invasive way is limited. This article aims to provide clinical guidance for monitoring individuals with presymptomatic type 1 diabetes to reduce the risk of diabetic ketoacidosis (DKA) at diagnosis.

Methods: Expert consensus was obtained from members of the Fr1da, GPPAD, and INNODIA consortia, three European diabetes research groups. The guidance covers both specialist and primary care follow-up strategies.

Results: The guidance outlines recommended monitoring approaches based on age, disease stage and clinical setting. Individuals with presymptomatic type 1 diabetes are best followed up in specialist care. For stage 1, biannual assessments of random plasma glucose and HbA1c are suggested for children, while annual assessments are recommended for adolescents and adults. For stage 2, 3-monthly clinic visits with additional home monitoring are advised. The value of repeat OGTT in stage 1 and the use of continuous glucose monitoring in stage 2 are discussed. Primary care is encouraged to monitor individuals who decline specialist care, following the guidance presented.

Conclusions: As type 1 diabetes screening programs become more prevalent, effective monitoring strategies are essential to mitigate the risk of complications such as DKA. This guidance serves as a valuable resource for clinicians, providing practical recommendations tailored to an individual's age and disease stage, both within specialist and primary care settings.

KEYWORDS
monitoring, presymptomatic type 1 diabetes, primary care, screening, specialist care, staging

1 | INTRODUCTION

Type 1 diabetes is a chronic autoimmune disease that leads to insulin dependence due to immune-mediated loss of beta-cell function.[1,2] The disease affects particularly children and adolescents, but more than half of those diagnosed with type 1 diabetes are older than 18 years at clinical the onset.[3] Our understanding of the underlying autoimmune process is evolving, especially with regards to the development of autoantibodies against antigens of the pancreatic islet beta-cells and the risk of requiring insulin therapy.[4] As such, it is clear that the clinical diagnosis of type 1 diabetes, through presence of hyperglycaemia and classical symptoms, is preceded by weeks, months or years of preclinical disease activity.[5] Biomarkers of this disease activity are continuously being refined, but the presence of autoantibodies against beta-cell antigens has been shown to predict the clinical disease onset in family members of people with type 1 diabetes, as well as in the general population,[6–8] thus leading to a novel classification of type 1 diabetes, including preclinical stages.[9] A hallmark paper in 2015 introduced the concept of staging of type 1 diabetes,[10] which has been incorporated into current clinical practice guidelines, where stage 1 is presymptomatic with multiple positive islet autoantibodies and normoglycaemia, stage 2 is presymptomatic with (usually) multiple islet autoantibodies and dysglycaemia, and stage 3 is the onset of clinical type 1 diabetes with hyperglycaemia.[9–11] Further sub-classifications, such as stage 1a and 1b but also stage 3a (asymptomatic) and 3b (symptomatic), are likely to become more widely used as more and more individuals are identified in the early stages and the risk to progression is better understood. For example, individuals in stage 1b (based on progression likelihood score calculation, including HbA1c, OGTT 90 min glucose and insulinoma-like antigen-2 autoantibody [IA-2A] titre) have been shown to have similar rapid progression to stage 3 as individuals in stage 2.[11,12] Current staging of type 1 diabetes is

shown in Figure 1. The risk and rate of developing stage 3 type 1 diabetes varies depending on islet autoantibody status and age at seroconversion. Children with two or more islet autoantibodies (stage 1 or 2) have a >99% lifetime risk of stage 3 type 1 diabetes with 84% developing insulin dependence within 15 years.[8] Children with single positive islet autoantibodies who revert back to islet autoantibody negative within 2 years of seroconversion have a risk of only 12% to develop stage 3 type 1 diabetes over the next 15 years, while this risk is 30% in those children that remain single islet autoantibody positive after 2 years.[6] Time to stage 3 type 1 diabetes is shorter in children who develop islet autoantibodies before the age of 10 years than in adolescents and adults.[8,13] The risk to develop multiple islet autoantibodies is high in the first 2 years from seroconversion, depending on the age of the child and the type of autoantibody.[14,15] IA-2A positivity and its titre are associated with an increased rate of progression to clinical diabetes.[7,16–18] Children who are single autoantibody positive have therefore been followed in research studies with repeated antibody testing to identify those who develop multiple autoantibodies or IA-2A positivity.

Several screening studies have been rolled out in recent years with the aim of identifying individuals at risk and monitoring their progression to stage 3 type 1 diabetes.[19] Initial screening studies have focused on first-degree relatives of people with type 1 diabetes who have a 15-fold higher risk of developing type 1 diabetes compared to the general population.[20] However, 90% of newly diagnosed type 1 diabetes individuals do not have a first-degree relative with the condition. More recently, general population screening programs have been introduced across Europe and the USA.[7,19,21] These initiatives identify individuals with presymptomatic type 1 diabetes based on the detection of islet autoantibodies, with or without prior genetic risk screening. At risk individuals identified through these studies are educated and followed over time to avoid diabetic ketoacidosis (DKA) by early diagnosis of stage 3 type 1 diabetes. Whilst the incidence of DKA in newly diagnosed type 1 diabetes has remained unacceptably high in recent years,[22,23] screening programmes have recently shown to be successful in reducing the incidence of DKA at diagnosis.[24–28]

We are now entering a new era where disease-modifying therapies are becoming part of the therapeutic arsenal of type 1 diabetes. Recently, the American Food and Drug Administration approved Teplizumab for the treatment of people with stage 2 type 1 diabetes based on the evidence of delaying progression to stage 3 type 1 diabetes.[29] Further immunotherapy and other drug trials in presymptomatic type 1 diabetes are on the horizon as this may be an important therapeutic window to halt the progression of disease and avoid insulin dependence.

The increase in screening initiatives will lead to a growing number of individuals, especially children and adolescents, diagnosed with presymptomatic type 1 diabetes. While at present these individuals will be offered follow-up as part of the research protocols, it is likely that not all will want to take this up. Some may find the research protocols too labour intensive; others may have issues with travel or have other objections to further participate in research. However, individuals with presymptomatic type 1 diabetes are currently not routinely seen in the healthcare setting. Therefore, a new situation for clinicians, in particular specialist care teams and primary care physicians, is created where clinical advice is needed on how to follow up these individuals in a safe but minimally invasive way. Suggestions for follow-up have been included in the ISPAD guidelines of 2022,[11] but there is a need for a structured approach

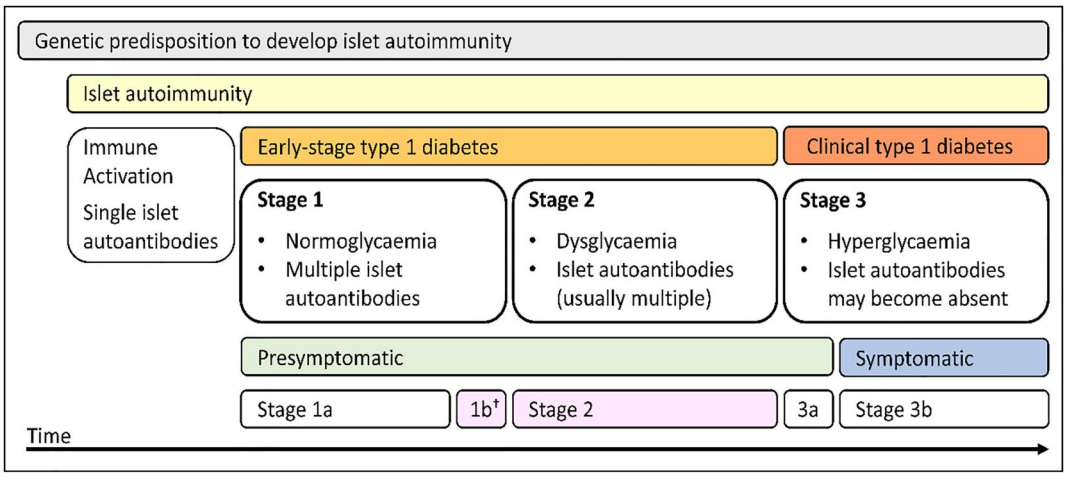

FIGURE 1 Stages of type 1 diabetes.[9–12] The figure shows a schematic representation of the pathogenesis and staging of type 1 diabetes. Based on a genetic predisposition, autoimmunity against the beta cells in the islets of Langerhans of the pancreas may occur (islet autoimmunity). The confirmed-positive detection of autoantibodies in the blood directed against several different beta cell antigens (multiple islet autoantibodies) marks the presence of an early stage of the disease type 1 diabetes in individuals who have not yet shown any diabetes symptoms. Early stage type 1 diabetes may be associated with normoglycemia (stage 1) or dysglycaemia (stage 2). Individuals with presymptomatic early stage develop clinical type 1 diabetes with hyperglycaemia (stage 3) over an individual-variable period of time, leading to the onset of diabetes symptoms if untreated. The rate of progression can be estimated by immunologic and metabolic testing. †Individuals with Stage 1b show similar rapid progression to Stage 3 as individuals in Stage 2.

based on age, disease stage and clinical setting. An important aspect to consider is that the reimbursement of the costs involved with the monitoring of these individuals may vary from country to country, depending on the specific regulations of each health care system. As, to date, this has not been established in most countries, we advocate that this should be done as soon as possible.

2 | AIM

To create clinical advice for healthcare professionals to guide the monitoring of individuals, in particular children and adolescents, with presymptomatic type 1 diabetes to limit their risk of presenting with DKA at diagnosis of stage 3 type 1 diabetes using minimally invasive testing to enhance concordance and limit the burden for these individuals.

2.1 | Target population

Physicians caring for individuals with presymptomatic type 1 diabetes.

2.2 | Consensus group

This clinical advice is written by a group of experts who are members of three European diabetes consortia that have come together to discuss the need and contents of this guideline: Fr1da, GPPAD and INNODIA (Supporting Information S1).[30–32] The Fr1da study was designed as a model project in order to introduce public health screening of multiple islet autoantibodies in Bavaria, Germany. The Fr1da study has shown that early staging of type 1 diabetes in childhood is feasible and leads to a reduction in DKA incidence.[7,28,31] GPPAD is the Global Platform for the Prevention of Autoimmune Diabetes that was established in 2015 with the intention to establish an infrastructure for primary prevention trials in type 1 diabetes and that currently includes five European countries.[32–35] The **Inno**vative approach towards understanding and arresting type 1 **dia**betes (INNODIA) consortium was established through the Horizon 2020 initiative of the European Union in 2015 (https://www.innodia.eu/) with the purpose of developing a European infrastructure for the recruitment, detailed clinical phenotyping and bio sampling of a large cohort of newly diagnosed individuals with type 1 diabetes and unaffected family members using the INNODIA Master protocol, generating a bio resource for type 1 diabetes discovery science.[30]

3 | DEFINITIONS

Presymptomatic type 1 diabetes is defined as an individual without symptoms who is persistently confirmed positive for two or more islet autoantibodies on at least two independently drawn blood samples.[7,9]

Staging of presymptomatic type 1 diabetes is based on the ADA criteria to define dysglycaemia and hyperglycaemia using fasting plasma glucose (FPG), 2 h PG during OGTT and HbA1c (Table 1).[9] HbA1c should be measured using an NGSP certified method.[9] Random plasma glucose (RPG) can also be used to diagnose hyperglycaemia if symptoms are present. In addition to the ADA criteria, many research studies use intermediate time points during OGTT to diagnose dysglycaemia, as defined by glucose values ≥200 mg/dL (≥11.1 mmol/L) at 30-, 60- or 90-min (Table 1).[10] Diabetes specialists may use these intermediate time points when interpreting OGTT data.

Further stratification of the risk and rate of progression is an ongoing topic of research in type 1 diabetes. Some have shown the value of stratification based on advanced indices that include C–peptide measured during OGTT, such as Index 60 or DPTRS.[36,37] Others have shown that autoantibody type and titre, especially IA-2A, affect the likelihood of progression.[7,12,16–18] In the TrialNet study, it was shown that HLA typing and genetic risk scores can also

TABLE 1 ADA criteria for normoglycaemia, dysglycaemia and hyperglycaemia.[9]

	Normoglycaemia (stage 1)	Dysglycaemia (stage 2)	Hyperglycaemia (stage 3)
Fasting plasma glucose	FPG <100 mg/dL (<5.6 mmol/L) OR	FPG 100–125 mg/dL (5.6–6.9 mmol/L) OR	FPG ≥126 mg/dL (≥7.0 mmol/L) OR
Haemoglobin A1c	HbA1c <5.7% (<39 mmol/mol) OR	HbA1c 5.7%–6.4% (39–47 mmol/mol) OR HbA1c ≥10% increase from previous visit OR	HbA1c ≥6.5% (≥48 mmol/mol) OR
Oral glucose tolerance test	2 h PG <140 mg/dL (<7.8 mmol/L)	2 h PG 140–199 mg/dL (7.8–11.0 mmol/L)	2 h PG ≥200 mg/dL (≥11.1 mmol/L) OR
Additional criteria used in research studies [10]		30-, 60- or 90-min PG ≥200 mg/dL (≥11.1 mmol/L)	
Random plasma glucose			Symptoms + PG ≥200 mg/dL (≥11.1 mmol/L)

Abbreviations: FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; PG, plasma glucose.

stratify the risk of progression in presymptomatic type 1 diabetes, although this was not observed in young children in the Fr1da study.[7,38] Further research is required to establish which of these factors should be included in clinical care. For this guidance, we have included metabolic markers that are currently widely used by primary care and specialist care physicians managing type 1 diabetes.

There is a need for less labour-intensive methods than the OGTT for metabolic staging of islet autoantibody-positive individuals at risk of progression to type 1 diabetes to limit the burden of testing for individuals with presymptomatic type 1 diabetes and increase their acceptability of testing. Evidence is emerging on the value of continuous glucose monitoring (CGM) to detect dysglycaemia early and to predict the risk of progression to type 1 diabetes.[21,39,40] In this clinical guidance, CGM is being suggested for use only in specialist care monitoring of those with stage 2 presymptomatic type 1 diabetes, as careful interpretation by a diabetes specialist is required when using this relatively new method that has not yet been fully validated to diagnose dysglycaemia or stage 3 type 1 diabetes.

3.1 | Pathway for individuals identified with presymptomatic type 1 diabetes

Figure 2 shows the recommended pathway for individuals identified with presymptomatic type 1 diabetes as they present to clinical care for the first time (Figure 2). Considering the relatively low numbers of individuals who will present with presymptomatic type 1 diabetes, the fast evolution in monitoring possibilities and the advent of disease modifying therapies, we strongly advocate for individuals with stage 1 or stage 2 type 1 diabetes to be followed in specialist care. In the next section, we discuss the recommended follow-up in this setting.

Not all individuals diagnosed with presymptomatic type 1 diabetes may agree to be monitored in specialist care. Concerns such as travel time, travel costs or co-payment for specialist clinic visits may deter individuals from being monitored in specialist care, but they may be open to being seen in primary care instead. Not all primary care settings will be suitable for this, but in the cases where primary care can support individuals who are not engaging with specialist care, this may help to recognise progression to stage 2 or stage 3 type 1 diabetes earlier and avoid complications. To support primary care physicians who encounter presymptomatic type 1 diabetes individuals in their clinic, we have included guidance for monitoring in the primary care setting in the last section of this paper.

3.2 | Specialist care advice for follow-up

In Figure 3 we present the advice for clinical follow-up of individuals with presymptomatic type 1 diabetes in specialist care (Figure 3). Education of the individual and their family should always take priority and include signs and symptoms of type 1 diabetes, DKA, how to use a glucometer and what is healthy eating. Teams may also want to deliver teaching on the pathophysiology of type 1 diabetes and explain the staging of type 1 diabetes. Information on licenced treatments or ongoing intervention studies in the area where the person lives should be shared with the individual and their family.

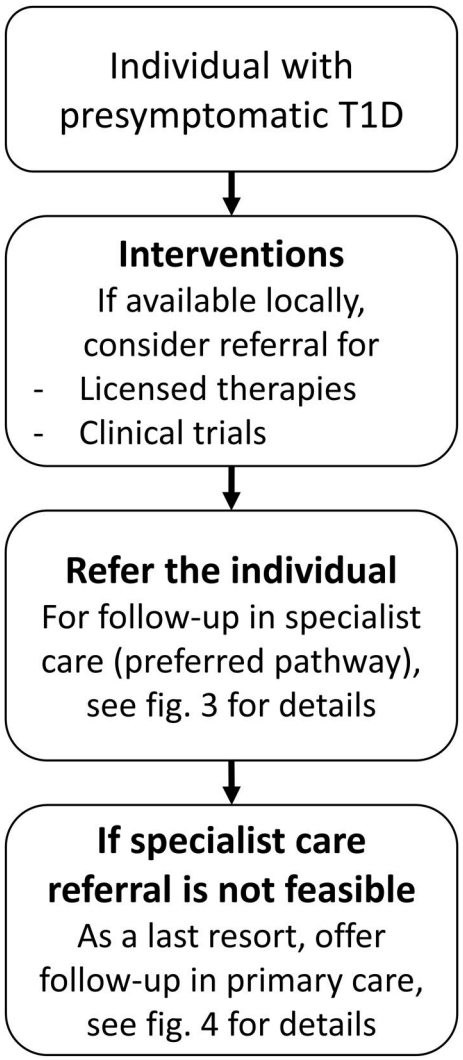

FIGURE 2 Pathway for individuals with newly diagnosed presymptomatic type 1 diabetes.

Individuals with unknown stage of type 1 diabetes should have a staging OGTT to: 1. Identify those with stage 1, stage 2, or stage 3 type 1 diabetes; and 2. To inform the monitoring frequency during further follow-up. Individuals with stage 3 type 1 diabetes should be monitored as per local type 1 diabetes guidelines, and insulin therapy should be considered. However, the timing of initiating insulin therapy is outside the remit of this clinical advice.[41] Individuals with stage 1 or stage 2 type 1 diabetes should be monitored in specialist care and we present the type of tests and frequency here (Figure 3). OGTT in children <2 years of age can be challenging and monthly

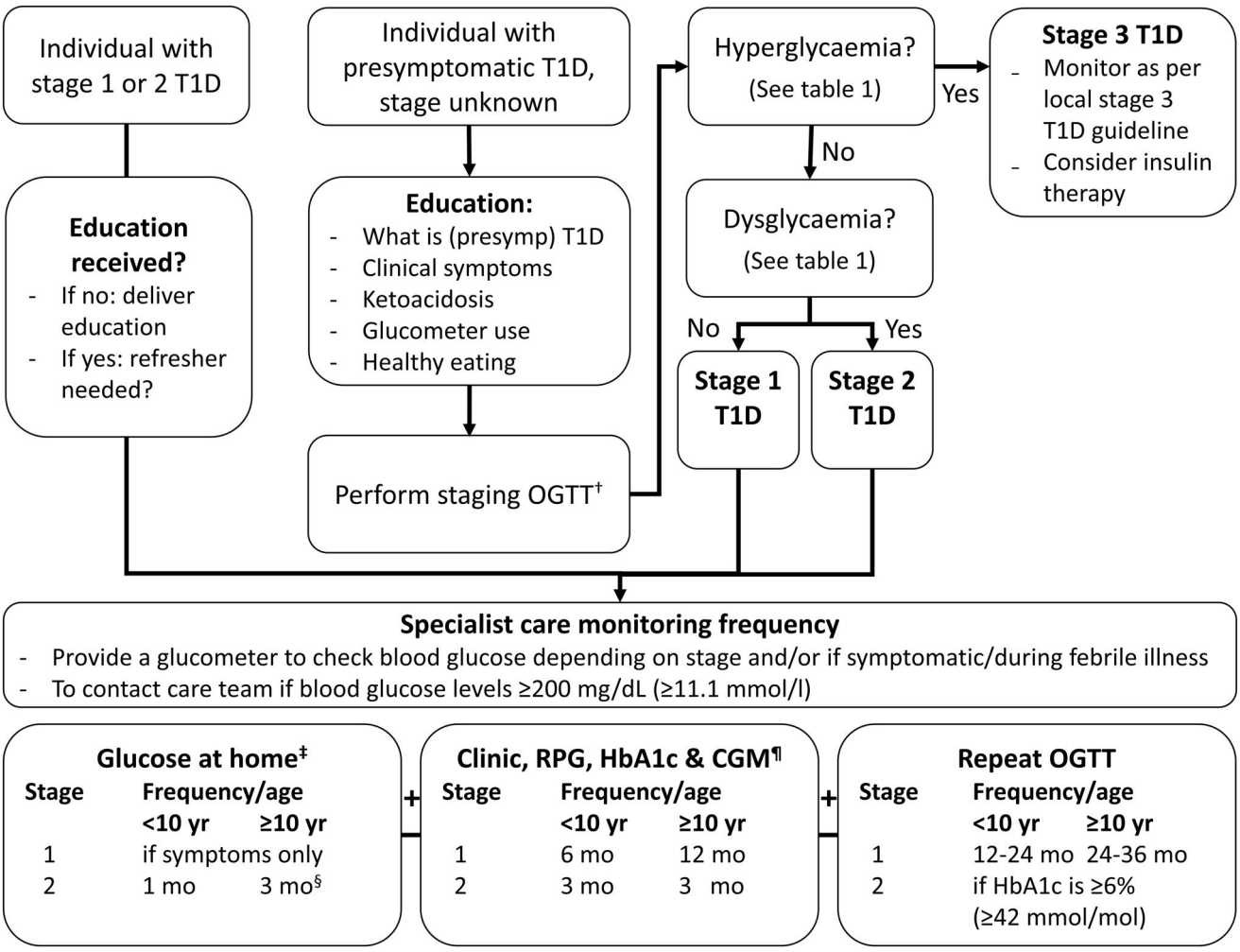

FIGURE 3 Advice for follow-up of individuals with presymptomatic type 1 diabetes in specialist care. †OGTT in children <2 years of age can be challenging, consider monthly monitoring of glucose at home post carbohydrate-rich meal as an alternative until OGTT is feasible. ‡1–2 h post carbohydrate-rich meal. §In between clinic visits. ¶CGM in stage 2 for 10 days if feasible, CGM T1D criteria not validated, interpretation by specialist. Abbreviations: CGM, continuous glucose monitoring; HbA1c, haemoglobin A1c; OGTT, oral glucose tolerance test; PG, plasma glucose; RPG, random plasma glucose; T1D, type 1 diabetes.

monitoring of glucose at home post carbohydrate-rich meal can be considered as an alternative until (staging) OGTT is feasible. OGTT glucose cut-off levels for staging (Table 1) can be used as guidance when interpreting these glucose levels.[9]

All individuals in early stages of type 1 diabetes should be given a glucometer to measure finger prick blood glucose levels if symptomatic or during febrile illness and advised to seek help from their care team if any blood glucose levels are ≥200 mg/dL (≥11.1 mmol/L). Based on the increased rate of progression to clinical diabetes in children <10 years of age and in individuals with stage 2 diabetes, we have stratified our advice on the frequency of at home and in the clinic testing by age and stage of presymptomatic type 1 diabetes.

For all individuals with stage 2 type 1 diabetes, regardless of age, we advise frequent monitoring with 3-monthly clinic visits with measurement of RPG, preferably post carbohydrate-rich meal, and HbA1c. These individuals should also be advised to check glucose levels at home 1–2 h post a carbohydrate-rich meal monthly if they are <10 years of age and every 3 months, in between clinic visits, if they are 10 years and over. Repeated OGTTs at follow-up are not routinely indicated in individuals with stage 2. Instead, we recommend performing an OGTT once HbA1c is ≥6% (42 mmol/mol) to identify those who have progressed to stage 3 early on. If stage 3 is not confirmed, then OGTT should not be repeated until HbA1c level is again ≥6% (42 mmol/mol) at a subsequent visit and no sooner than 6 months following the previous OGTT. If individuals are found to meet the criteria for hyperglycaemia (Table 1), the start of insulin treatment should be considered.

With the rise in the use of CGM, diabetes teams may choose to use this in addition to measuring RPG and HbA1c in stage 2 individuals to monitor the risk of progression to stage 3 type 1 diabetes. However, CGM-specific diagnostic cut-offs are not yet validated and therefore careful interpretation by a diabetes professional experienced in CGM technology is required.

For children with stage 1 type 1 diabetes, we recommend that they be seen twice a year by their specialist team for testing of RPG and HbA1c. Adolescents and adults can be seen once a year for these assessments. We recommend repeating OGTT every 1–2 years in children under the age of 10 years and every 2–3 years in adolescents and adults to identify those who have progressed to stage 2 early on.

Individuals may occasionally revert from stage 2 to stage 1 type 1 diabetes during follow-up. If this is suspected based on an HbA1c level <5.7% (39 mmol/mol), we recommend following up the individual from that moment onwards according to the stage 1 monitoring guidance (Figure 3). Dietary changes after a diagnosis of early stage type 1 diabetes may be one of the contributing factors. Individuals who revert from stage 3 to stage 2 type 1 diabetes require bespoke advice from a specialist team.

3.3 | Primary care advice for follow-up

In general, diabetes teams will be best equipped to monitor individuals with any stage of type 1 diabetes and we strongly recommend that presymptomatic type 1 diabetes individuals are followed in specialist care. However, individuals and their families may not wish to engage with specialist care until insulin therapy is indicated and may prefer monitoring by their primary care physician. In Figure 4 we present the advice for follow-up of individuals with presymptomatic type 1 diabetes in primary care (Figure 4). The first and most important step in this advice is to ensure that teaching on the clinical signs and symptoms of type 1 diabetes is delivered. Classic symptoms include polyuria, polydipsia, nocturia, fatigue and weight loss, commonly referred to as the 4Ts: toilet, thirsty, tyred and thinner. Changes in behaviour, mood, or appetite are also commonly seen. Vomiting or a change in the breathing pattern is sometimes the reason to seek medical attention, especially in younger children where the classic symptoms may be subtle and often hard to recognise. In adults, type 1 diabetes can have a more insidious onset.

Individuals presenting with presymptomatic type 1 diabetes to primary care should have an HbA1c and RPG measured at presentation to ensure that those already progressed to stage 3 are quickly identified. All individuals should be given a glucometer to measure finger prick blood glucose levels if symptomatic or during febrile illness, and education on how to use a glucometer should be provided. Individuals should be instructed to contact their primary care team if the random finger prick blood glucose levels are ≥200 mg/dL (≥11.1 mmol/L).

We use the same stratification by age and stage as for our specialist care advice. We recommend that children with stage 1 type 1 diabetes are seen twice a year by their primary care physician for HbA1c and RPG, preferably post carbohydrate-rich meal. Some may choose to measure FPG for staging (Table 1), but this is often a late marker of disease progression. Adolescents and adults can be seen once a year for these assessments. When interpreting HbA1c results, clinicians will need to take into consideration that certain conditions

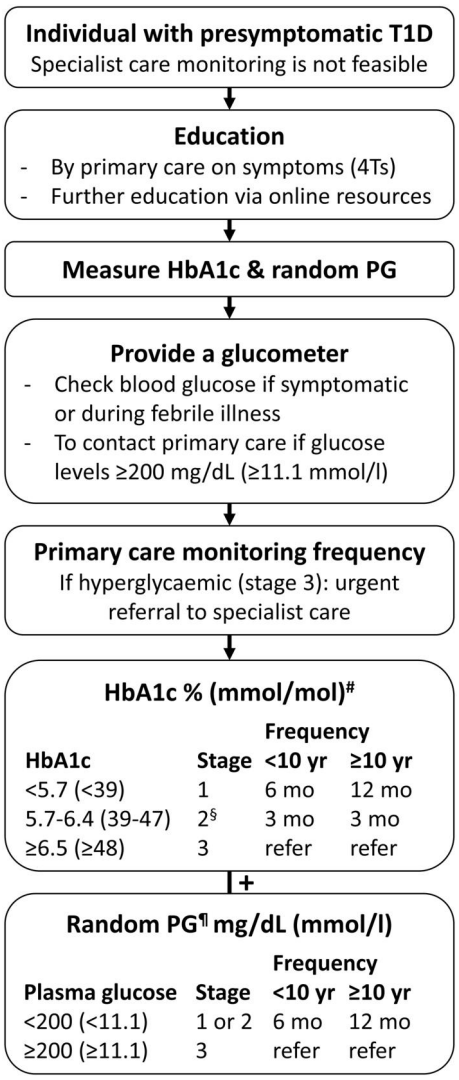

FIGURE 4 Advice for follow-up of individuals with presymptomatic type 1 diabetes in primary care. #Certain conditions may affect HbA1c clinical utility.[42] §Individuals with dysglycaemia are preferably monitored in specialist care, see Figure 3. ¶preferably 1–2 h post carbohydrate-rich meal. Abbreviations: HbA1c, haemoglobin A1c; PG: plasma glucose; T1D: type 1 diabetes.

associated with altered rates of erythrocyte turnover will affect HbA1c levels.[42] Some primary care providers might be able to offer an OGTT, but we would recommend that these should be preferably performed in specialist care for presymptomatic type 1 diabetes.

If individuals are found to develop dysglycaemia during follow-up, they should be preferably referred to specialist care for further monitoring, especially young children <10 years of age. If due to circumstances specialist care monitoring is not feasible, we would recommend 3-monthly clinic visits for HbA1c and random glucose levels in primary care for all individuals with stage 2 presymptomatic type 1 diabetes.

If individuals are found to meet the criteria for hyperglycaemia (Table 1), they should be urgently referred to specialist care for consideration of insulin treatment. Home ketone monitoring is not

recommended in presymptomatic type 1 diabetes to avoid delays in presentation as all individuals with hyperglycaemia should be immediately referred irrespective of whether ketones are present or not. We would recommend that primary care physicians have easy access to a specialist care team for advice and guidance as they are likely to encounter presymptomatic only type 1 diabetes sporadically in their clinics.

4 | CONCLUSION

With the progressive increase in screening programs or future self-diagnosis tools, there will be a rise in the diagnosis of individuals with presymptomatic type 1 diabetes. Many will be offered monitoring through research initiatives and potentially will have the opportunity to be enroled into intervention trials. However, not all individuals will want to continue participating in research, and they should be offered some form of follow-up to identify those at risk of progressing to stage 3 type 1 diabetes and diagnose them early to prevent DKA and initiate insulin at the right time, especially in children and adolescents. Currently, few specialist care clinicians have experience with individuals with presymptomatic type 1 diabetes. This expert advice is aimed at providing a simple and safe clinical care pathway based on the evidence available to date. We also provide guidance for primary care physicians to monitor those individuals who refuse to engage with specialist care. Other important areas for consideration in islet autoantibody-positive individuals, such as when to start insulin, antibody monitoring of single autoantibody-positive individuals, or psychological aspects of presymptomatic type 1 diabetes, are not covered in this clinical care advice but will be part of an ongoing JDRF initiative to develop a consensus statement on the wider care and management of autoantibody-positive individuals (https://www.jdrf.org/). Evidence emerging from ongoing and future studies assessing the feasibility and acceptability of novel monitoring tools (eg., home OGTT, CGM) will provide invaluable information for future updates of this advice.

AUTHOR CONTRIBUTIONS

A Emile J Hendriks, M Loredana Marcovecchio and Peter Achenbach wrote and edited the manuscript. Rachel E J Besser, Ezio Bonifacio, Kristina Casteels, Helena Elding Larsson, Gita Gemulla, Markus Lundgren, Olga Kordonouri, Roberto Mallone, Flemming Pociot, Agnieszka Szypowska, Jorma Toppari and Thekla von dem Berge contributed to writing and reviewing the manuscript. Anette G Ziegler and Chantal Mathieu designed the work and critically reviewed the manuscript. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Nothing to declare. This consensus statement did not require any sources of funding to be written.

ETHICS STATEMENT

Ethics opinion has not been sought for this consensus statement.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

A. Emile J. Hendriks https://orcid.org/0000-0002-0795-1832

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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