



# WHITE PAPER

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Paediatric screening for Type 1  
autoimmune diabetes and  
celiac disease

**sanofi**





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# EXECUTIVE SUMMARY

On October 10, 2023, Law no. 130/2023 came into force, approved unanimously by Parliament and promoted by the Vice President of the Chamber of Deputies, the Hon. Giorgio Mulè. The Law establishes a multi-year screening program for identifying Type 1 Diabetes and Celiac Disease in the paediatric population.

Italy is the first country in the world to have introduced this type of screening regulated by a State Law. A record that places Italy at the centre of international attention: all states will observe the implementation phase to evaluate the adoption of similar regulations.

The implementation of the national program is preceded by a preparatory phase conducted by the Istituto Superiore di Sanità (ISS) based on an agreement signed with the Ministry of Health. This phase involves 4 Regions (Lombardy, Marche, Campania and Sardinia). It aims to highlight the sustainability of costs, potential, organisational criticalities and cost-benefits of a screening conducted on a national scale. After this preparatory phase, the screening will be launched nationally.

The White paper entitled “Paediatric Screening for Type 1 Autoimmune Diabetes and Celiac Disease” was created to establish an active dialogue between the main actors involved in the implementation phase of Law No. 130/2023. To this end, the Working Group, composed of the main spokespersons engaged in diagnosing and caring for the paediatric patient, discussed the most urgent priorities to ensure a correct and uniform application of the future multi-year screening program.



The document identified 16 recommendations that aim to promote an organisational model capable of satisfying and managing screening at a national level in the best possible way:

- 1.** Identify an age range for screening;
- 2.** Enrol the paediatric population in the care of General Practitioners;
- 3.** Provide measures to encourage Primary Care Paediatricians;
- 4.** Overcome the difficulties of capillary sampling;
- 5.** Define laboratory governance;
- 6.** Centralize communication between laboratories, Primary Care Paediatricians and Diabetes Reference Centres;
- 7.** Ensure the presence of a multidisciplinary team in the Regional Diabetes Reference Centres;
- 8.** Rule the follow-up phase by adopting ad hoc guidelines;
- 9.** Train all the actors involved in the screening;
- 10.** Highlight and value the role of Patient Associations;
- 11.** Implement the coordination of the screening activities;
- 12.** Create regional registries;
- 13.** Conduct a survey among Primary Care Paediatricians involved in the preparatory project;
- 14.** Provide an exemption code for pre-symptomatic Type 1 Diabetes;
- 15.** Include screening in the Essential Levels of Care;
- 16.** Ensure complete care in case of positive test result.

# REGULATORY FRAMEWORK

With the coming into force of **Law No. 130 of 15 September 2023**<sup>1</sup>, published in the Official Gazette on 27 September 2023, Italy has established and financed for the first time at an international level a multi-year screening program for Type 1 Diabetes and Celiac Disease, to identify clinically asymptomatic cases through early paediatric diagnosis.

Italy is the first country in the world to have introduced a screening regulated by a State Law. It is a success recognised by the international scientific community, and the articles in the most prestigious journals, such as Lancet<sup>2</sup> and Science<sup>3</sup>, have confirmed it. This record means that all states will carefully observe the implementation phase in Italy to evaluate the adoption of similar regulations.

In detail, the implementation of a multi-year national screening program in the paediatric population (1-17 years) is provided for the identification, through measurement of autoantibodies, of subjects at risk for the development of **Type 1 Diabetes and/or of undiagnosed Celiac Disease**, to reduce the complications associated with a late diagnosis of these diseases.

## The Law specifically pursues the following objectives:

- prevention of diabetic ketoacidosis at the onset of Type 1 Diabetes;
- identification of cases of Type 1 Diabetes in the pre-symptomatic stage, susceptible to interventions to delay the progression of the disease;
- timely treatment with a gluten-free diet in new cases of Celiac Disease;
- prevention of non-gastroenterological complications of Celiac Disease, such as slow growth, iron deficiency and delayed puberty.

<sup>1</sup> Law No. 120, 15 September 2023, "Provisions concerning the definition of a diagnostic program for the identification of type 1 diabetes and celiac disease in the pediatric population".

<sup>2</sup> Lancet Diabetes Endocrinol. 2024 Jan;12(1):12-14. Universal screening for early detection of chronic autoimmune, metabolic and cardiovascular diseases in the general population using capillary blood (UNISCREEN): low-risk interventional, single-centre, pilot study protocol - <https://bmjopen.bmj.com/>

<sup>3</sup> Science. 2024 Mar 15;383(6688):1164-1165

## 01 REGULATORY FRAMEWORK

The implementation of the Law involves the following actions:

- promotion of screening activities through regular **information and awareness campaigns**;
- establishment of the **Type 1 Diabetes National Observatory**, composed of **thirteen members**<sup>4</sup>, appointed by Decree of the Minister of Health, with the task of studying and processing the results of the national screening and publishing an annual report on the Ministry of Health website;
- issuing a **decree from the Minister of Health** to adopt the **multi-year screening program nationally**, following the opinion of the State-Regions Conference, after consulting the most representative associations of people with Diabetes and Celiac Disease. Before adoption, the draft of the ministerial decree is submitted based on the opinion of the competent parliamentary commissions on the subject matter.

To implement the multi-annual screening program, **3.85** million euros have been allocated singularly for **2024 and 2025** and 2.85 million euros per year starting from 2026. The actual implementation of the national

program is preceded by a preparatory study called **D1Ce Screen<sup>5</sup> (Screening Type 1 Diabetes and Celiac Disease)**, conducted by the Istituto Superiore di Sanità (ISS) based on an agreement signed with the Ministry of Health.

This study highlights the sustainability of the National Health Service (SSN), the potential, the organisational criticalities and the cost-benefit profiles of a nationwide screening for the two diseases. The **preparatory project is carried out in 4 Regions: Lombardy, Marche, Campania and Sardinia.**

In these Regions, the Primary Care Paediatricians who have joined the project will recruit, on a voluntary basis, **children aged 2, 6 and 10** to be screened through capillary blood sampling using a finger prick for the detection of antibodies predictive of Type 1 Diabetes and/or Celiac Disease. With specific reference to Type 1 Diabetes, the identification of subjects at risk is essential as it allows the prevention of the development of ketoacidosis as a complication associated with the clinical development of the disease and, at the same time, recognises those who may benefit from new therapies to delay the disease onset. **Too often, the diagnosis of Type 1 Diabetes occurs with the acute onset of ketoacidosis. This severe metabolic imbalance requires the patient to be admitted to the Emergency Room quickly and can leave permanent neurological damage or even endanger the life of the child.**



## Key Point

Law No. 130 of 15 September 2023 established a multi-year screening program for Type 1 Diabetes and Celiac Disease to identify clinically asymptomatic cases through early diagnosis at paediatric age. Italy is the first country in the world to have introduced a screening regulated by a State Law.

In detail, the implementation of a multi-year screening program on a national basis in the paediatric population (1-17 years) is planned for the identification, through measurement of autoantibodies, of subjects at risk for developing **Type 1 Diabetes and/or with undiagnosed Celiac Disease**, to reduce the complications associated with a late diagnosis of these diseases.

The actual implementation of the national program is preceded by a preparatory study called **D1Ce Screen (Screening Diabete di tipo 1 e Celiachia)**, conducted by the Istituto Superiore di Sanità (ISS) based on an agreement signed with the Ministry of Health.

<sup>4</sup> Composition of the Observatory: a) a representative of the Ministry of Health, who assumes the role of president; b) two representatives of the Istituto Superiore di Sanità (ISS); c) six doctors with proven experience, specialized in the diagnosis and treatment of Type 1 Diabetes and Celiac Disease; d) two representatives, for each pathology, of the most renowned Associations of people affected by Type 1 Diabetes and Celiac Disease and their families and, of the foundations of national importance in the field, also in fulfilment of Title VII of the Third Sector Code, pursuant to Legislative Decree 3 July 2017, no. 117

<sup>5</sup> The D1Ce study was developed with the aim of addressing the feasibility issues of the screening program for Type 1 Diabetes and Celiac Disease. Source: Il progetto D1Ce Screen - ISS





## 02

# METHODOLOGY

The Diabetes Type 1 Vision of Screening (DIVE) project, created by Sanofi in collaboration with UTOPIA, was designed to establish an active dialogue between the main spokespersons involved in the implementation phase of the Law No. 130/2023.

To this end, on 7 May 2024, a specific Working Group was established, composed of the main actors involved in diagnosing and caring for the paediatric patient, who discussed the most urgent priorities to ensure the correct and consistent application of the future multi-year screening program.

### **In this perspective, the Working Group:**

- has preliminarily analysed the state of the art to identify the pre-existing strengths and critical points in the management of patients;
- has then established a comparison to identify a path for the screening and the post-screening phase.

After a series of one-to-one meetings, a second meeting of the Working Group was held on 16 July 2024 to share the framework of the final document to reach an approved text to present in the context of a specific institutional conference.

This white paper clearly articulates the proposals that emerged during this dialogue space, with the proposals aiming to promote an organisational model capable of satisfying and managing screening at a national level in the best possible way.



The members of the Working Group are listed below:

- **Osama Al Jamal**, National Secretary of the Treasury of the Italian Federation of Paediatricians (FIMP)
- **Emanuele Bosi**, Head of Medicine and Diabetology at the IRCCS San Raffaele Hospital in Milan
- **Raffaella Buzzetti**, President-Elect of the Italian Society of Diabetology (SID)
- **Riccardo Candido**, National President of the Association of Diabetologists (AMD)
- **Ugo Cappellacci**, President of the Social Affairs Commission of the Chamber
- **Valentino Cherubini**, President of the Italian Society of Endocrinology and Diabetology
- **Antonio D'Avino**, President of the Italian Federation of Paediatricians (FIMP)
- **Paolo Di Bartolo**, Director of the Diabetological Assistance Program of the AUSL of Romagna and past National President of the Association of Diabetologists (AMD)
- **Alessia Fugazzola**, Vice President of the Italian Diabetes Foundation (FID)
- **Concetta Irace**, Member of the Teaching Committee of the Italian Society of Diabetology (SID)
- **Fabiano Marra**, Vice President of Diabete Italia
- **Enza Mozzillo**, Researcher, Department of Medical and Translational Sciences, University of Naples Federico II, representing the Italian Society of Pediatrics
- **Giorgio Mulè**, Vice President of the Chamber of Deputies
- **Annarita Patriarca**, Secretary of the Chamber of Deputies
- **Annamaria Staiano**, President of the Italian Society of Paediatrics (SIP)
- **Francesca Ulivi**, General Director of the Italian Diabetes Foundation (FID)
- **Nicola Zeni**, President of the Italian Diabetes Foundation (FID)

## 03

# TOWARDS THE NATIONAL SCREENING PROGRAM: STATE OF THE ART AND AREAS FOR IMPROVEMENT

## 3.1

## STATE OF THE ART

## 3.1.a

**Type 1 Diabetes and Celiac Disease**

**Type 1 Diabetes** is a chronic disease that is currently incurable and results from the destruction of the beta cells that produce insulin in the pancreatic islets. The disease manifests itself with hyperglycaemia and requires lifelong insulin therapy. The cause of Type 1 Diabetes remains unknown, although the mechanism has long been identified as autoimmune.

The incidence and prevalence of Type 1 Diabetes have steadily increased over the last few decades throughout the world, making it **the most widespread** chronic disease, although not exclusive, **of childhood and adolescence**. The disease can manifest itself at any age. However, in adults, the clinical presentation may be more variable and generally less acute, so it can go unnoticed for a long time or be confused with Type 2 Diabetes.

**In Italy, approximately 300,000 people suffer from it.** Although the initial cause is not yet known, the natural history of Type 1 Diabetes during its pre-symptomatic phase is now well characterised: the autoimmune process responsible for the disease is associated with the presence of autoantibodies in the blood, which appears entirely silently years before the clinical symptoms of the disease. Autoantibodies are, therefore, blood markers that, if found in the absence of Type 1 Diabetes onset, can predict its possible future development and quantify the risk.

The clinical manifestations of the disease depend on the progressive exhaustion of the function of pancreatic beta cells and, therefore, of the production of insulin, a hormone essential for regulating the metabolism. The lack or scarcity of insulin does not allow the body to use the sugars introduced through food, which are then eliminated in the urine. In this situation, the body is forced to produce energy in other ways, mainly through the metabolism of fats, leading to the **production of so-called ketone bodies**.

**In Italy,  
approximately  
300,000 people  
suffer from it**

### 3.1.a TYPE 1 DIABETES AND CELIAC DISEASE

When insulin deficiency becomes critical, ketone bodies are produced in large quantities, causing a metabolic acidosis called **diabetic ketoacidosis**, which, if not recognised in time, can lead to a medical emergency requiring immediate hospitalisation in the Emergency Room or even Intensive Care and, in extreme cases, to **death** or **permanent damage** in the person affected.

In any case, diabetic ketoacidosis also negatively impacts the progression of Type 1 Diabetes after the diagnosis, making it more difficult the glycaemic control with insulin therapy, causing a reduction in cognitive performance in the long term, and generating an increase in costs.

**In Italy, the incidence of Type 1 Diabetes in 2021 was 26.7 cases per 100,000 children, with a clinical trend every 4 years<sup>6</sup>. In 43.2% of cases, the onset occurred with diabetic ketoacidosis<sup>7</sup>.**

**Celiac Disease** is a chronic autoimmune disease that causes an immune reaction of the body against the small intestine in response to gluten, a protein complex present in many cereals such as barley, wheat, and rye. It affects approximately 1% of the general population; in Italy, approximately **9,000 diagnoses** are made yearly, with a disease incidence of **0.41%**. According to the 2021 Ministry of Health Report data, **241,729 celiac subjects** have been diagnosed in Italy, of which 70% (168,385) and 30% (73,334) are female and male, respectively.

Even if they are distinct pathologies, Type 1 Diabetes and Celiac Disease can coexist in the same person, adding up to 5% of **total cases**. There are also numerous **similarities**: they are both chronic autoimmune conditions associated with the presence of autoantibodies specific to the disease in the blood. Furthermore, they partly share a common genetic susceptibility linked to polymorphisms of the HLA (Human Leukocyte Antigens) complex.

<sup>6</sup> <https://dom-pubs.onlinelibrary.wiley.com/doi/epdf/10.1111/dom.15024>

<sup>7</sup> 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



### 3.1.a TYPE 1 DIABETES AND CELIAC DISEASE

**There is no cure for both diseases:** in the case of Celiac Disease, it is necessary to eliminate gluten permanently from the diet; in the case of Type 1 Diabetes, insulin therapy is used for life. This therapy involves the administration of insulin through multiple daily injections using pens or micro-infusors for continuous delivery over 24 hours.

#### Insulin therapy aims to:

- maintain for 24 hours circulating blood glucose values as much as possible within the range of normal levels, ideally:
  - pre-prandial values of 80–130 mg/dL and post-prandial values <180 mg/dL;
  - glycated haemoglobin (an indicator of overall glycaemic control) < 7.0%;
  - time in the range of 70–180 mg/dL measured during continuous glucose monitoring (CGM) >70%;
- **prevent episodes of hypoglycaemia**, whether minor (blood sugar 70–54 mg/dL), more significant (<54 mg/dL), or severe, i.e. associated with sensory alteration and need for external intervention;
- maintain **optimal glycaemic values and**, at the same time, **prevent hypoglycaemia**, reducing to the point of avoiding the risk of chronic complications such as retinopathy, nephropathy, diabetic neuropathy and cardio- and cerebrovascular diseases that over time can be very disabling;
- **prevent** episodes of **acute complications** (hyperglycaemia, ketoacidosis, hypoglycaemia) and consequently **the number of visits to the Emergency Room**, as the patient with Type 1 Diabetes is constantly exposed to the risk of acute complications, some of which are predictable, such as during intercurrent interventions, others utterly unpredictable due to accidents or interference of any kind. About this, it is essential to highlight that, if on the one hand, the management with modern integrated micro-infusor-sensor systems allows the optimisation of glycometabolic control, drastically reducing the risk of chronic complications, on the other hand, it requires in-depth knowledge and continuous training for the correct use of the devices mentioned above by caregivers to minimise access to the Emergency Room.



## Key Point

**Type 1 Diabetes** is a chronic disease currently incurable, resulting from the destruction of the beta cells that produce insulin in the pancreatic islets. In Italy, approximately 300,000 people suffer from it. **The incidence of Type 1 Diabetes in 2021 was 26.7 children out of 100,000, with a clinical trend every 4 years. In 43.2% of the cases, the onset occurred with diabetic ketoacidosis.**

**Celiac disease** is a chronic autoimmune disease that causes an immune reaction of the body against the small intestine in response to gluten.

**There is no cure for either disease:** while with Celiac Disease, it is necessary to eliminate gluten permanently from the diet, with Type 1 Diabetes, insulin therapy is used for life.



#### Type 1 diabetes

is a chronic disease that results from the distribution of true cells that produce insulin



**Therapy:** lifelong use of insulin



At the time  
**300.000**  
people



2021  
out of **100.000** people

**26,7**  
children

→ **43,2%**

are cases with diabetic  
ketoacidosis at the  
onset of the disease



#### Celiac disease

Chronic autoimmune disease that causes an immune reaction in response to aluminis



**Therapy:** it is necessary to eliminate gluten from the diet forever

### 3.1.b

#### The preparatory project for the national screening program

As already noted in the introduction, the D1Ce Screen preparatory project was launched following **an agreement signed between the Istituto Superiore di Sanità (ISS) and the Ministry of Health**. This project involves 4 Regions (Lombardy, Marche, Campania and Sardinia). It aims to highlight the sustainability of costs, potential, organisational criticalities and cost-benefits of a screening conducted on a national scale.

The Primary Care Paediatricians joining the project recruited **children aged 2, 6 and 10 years old** on a voluntary basis to measure auto-antibodies related to Type 1 Diabetes and Celiac Disease. Furthermore, the same blood test also provides a sample used for genetic typing of the predisposition to Celiac Disease.

The recruitment phase began under the supervision of the Istituto Superiore di Sanità (ISS) in April 2024: the paediatricians received all the appropriate instructions and the kit for the sample, and there was very high participation. The total expected enrolment is 5,363 children.

#### As part of this project, paediatricians took care of:

- **inform families** and obtain informed consent from parents;
- acquire the **availability of the parents through a questionnaire** for the collection of the children's personal and clinical data (name, surname, date and place of birth, weight and height) and anamnestic data (possible diagnosis of diabetes and specific type of diabetes, possible diagnosis of Celiac Disease, country of birth, schooling levels);
- perform a blood sampling using a finger prick to **collect a capillary blood sample** in a microtube for the measurement of autoantibodies and on paper for HLA typing;
- carry out the **administrative registration activities** (access to the personal area of the D1Ce online platform, filling in the "enrolment proposal" section by registering the recruited subject and also entering the code present in the kit for the sample to be used, which will correspond to the subject entered).



Primary Care Paediatricians are responsible for direct contact with families, fulfilling requests from the central platform, collecting and shipping capillary blood sampling and subsequent communications with families.

### 3.1.b.1)

#### The execution phase and the antibody measurement method

After collection, the sample, to which an identification code is assigned, is immediately sent by courier to the centralised Autoimmunity Laboratory of the I.R.C.C.S. Ospedale “San Raffaele” to carry out the initial assessment of the presence or absence of autoantibodies specific for Type 1 Diabetes and Celiac Disease.

The method used to measure antibodies in capillary blood is **ELISA** (*Enzyme-Linked Immunosorbent Assay*), which requires 15 microliters of blood. **LIPS** (*Luciferase Immunoprecipitation System*) is used for further confirmation and requires a microliter of blood volume. In particular, it is worth pointing out that the screening test provides an inconclusive result. In the presence of even a single antibody, the Regional Diabetes Reference Centres are called to do a **new venous or capillary blood check**.

The laboratory results are communicated to the paediatrician through the online platform on which the enrolled minor was registered. In case of a positive result, the paediatrician would communicate the outcome and inform the parents about the possibility of the child being taken over by the Diabetes Centre. Suppose the parents, for personal or logistical reasons, refuse the Diabetes Centre option. In that case, the paediatrician will take care of the **follow-up** phase and provide information on the Diabetes Reference Centres, to which the parents can turn to guarantee synergic care of the child.

### 3.1.b.2)

#### How to evaluate screening results


The most important element of evaluation is the **incidence of future cases of diabetic ketoacidosis** in association with the onset of Type 1 Diabetes in children who test positive for antibodies.

To verify the impact of the pathology and its geographical distribution, the following **criteria** could be taken into consideration:

- ratio between the number of **children screened** and the total number of children **residing** in a given Region by age groups;
- incidence of **positive cases in the screened population** and incidence vs the total number of children in that given Region;
- **comparison** of the numbers of **positive cases**, in other words, the prevalence of autoimmunity between the various Regions.







## **FOCUS**

### **National screening preparatory project:**

The D1Ce Screen preparatory project involves 4 Regions - Lombardy, Marche, Campania and Sardinia - and aims to highlight the sustainability of costs, potential, organisational criticalities and cost-benefits of a screening conducted on a national scale.

#### **The Primary Care Paediatricians joining the project, therefore:**

- have recruited children aged 2, 6 and 10 voluntarily for the measurement of autoantibodies;
- are responsible for direct contact with families, fulfilling the requests of the online central platform, and performing, collecting, and subsequently shipping the capillary blood sample from a finger prick.

After the capillary blood sample is taken using a finger prick lancet, the sample is immediately sent to the centralised Autoimmunity Laboratory of the I.R.C.C.S. Ospedale "San Raffaele", to carry out the initial assessment of the presence or absence of specific autoantibodies. The laboratory results are communicated to the paediatrician through the platform where the enrolled minor was registered. In case of positive results, the paediatrician communicates the outcome and informs the parents about the possibility of being cared for by the Specialist Clinical Centre.

**The goal of the screening is to avoid the onset of ketoacidosis.**

## 3.2

### AREAS FOR IMPROVEMENT

Starting from the results that emerged within the preparatory project, the Working Group has identified some **areas for improvement** to be addressed, given the extension of the screening at a national level.

#### Blood sampling

Simplify blood sampling by collecting the blood only on paper after a finger prick, thus avoiding pricking the child's fingertip several times.

#### Identification of laboratories

In the preparatory project, the analysis of the collected samples was centralised. With the extension of the screening, an efficient identification of qualified regional laboratories is recommended to reach a consistent methodology for analysing the samples in the various regions.

#### Presence of a multidisciplinary team in the Diabetes Reference Centres

In Italy, there is a network of facilities specialised in Diabetology, made of 650 units (diabetes centres and clinics), 350 diabetology<sup>8</sup> centres with a multidisciplinary team and 300 clinics with a single diabetologist.

However, as highlighted in the 2022 Report to Parliament *"on the state of knowledge and new acquisitions on the subject of diabetes mellitus - Law 16 March 1987, n. 115, containing Provisions for the prevention and treatment of diabetes mellitus"*, only in a limited number of centres there is a multidisciplinary team composed of diabetologists, nurses, dieticians, psychologists and podiatrists who are diabetes experts<sup>9</sup>.

In particular, the figure of the psychologist is crucial, especially in the phase of communicating to the families that the child's result is positive. Furthermore, a shortage of diabetologists and experienced and dedicated healthcare staff has recently been observed.



<sup>8</sup> [https://www.salute.gov.it/imgs/C\\_17\\_pubblicazioni\\_3365\\_allegato.pdf](https://www.salute.gov.it/imgs/C_17_pubblicazioni_3365_allegato.pdf)

<sup>9</sup> Report to Parliament 2022 on the state of knowledge and new acquisitions on Diabetes Mellitus. [https://www.salute.gov.it/imgs/C\\_17\\_pubblicazioni\\_3365\\_allegato.pdf](https://www.salute.gov.it/imgs/C_17_pubblicazioni_3365_allegato.pdf)

## 3.2 AREAS FOR IMPROVEMENT

### Attribution of the costs incurred by the Diabetes Reference Centres

The Reference Centres must carry out the test to confirm the positivity for Type 1 Diabetes through a second blood sample, venous or capillary, and care for the minor.

In this context, it should be noted that an initial analysis of the provisions of Law No. 130/2023 does not clarify whether the National Health Service (SSN) covers the costs incurred by the Diabetes Reference Centres. In this direction, the recent update of the international classification of diseases (2024 ICD-10), also adopted by the WHO, which recognised pre-symptomatic Type 1 Diabetes, assigning it three new specific codes<sup>10</sup>, is of great importance:

- E10.A0 (Type 1 Diabetes, presymptomatic, not otherwise specified);
- E10.A1 (Type 1 Diabetes, presymptomatic, stage 1);
- E10.A2 (Type 1 Diabetes, presymptomatic, stage 2).

The official inclusion of pre-symptomatic Type 1 Diabetes in the ICD-10/11 should also facilitate its recognition in terms of DRG, being at this point in all respects assimilable to clinically manifest Type 1 Diabetes.

### Age group identification

The Law no. 130/2023 provides that screening be carried out on minors aged 1 to 17. Given this, three age groups were prioritised in the preparatory project: 2, 6 and 10 years, as they correspond to the peaks of seroconversion in clinical trials published in Europe.

Given the resources allocated by the Law and considering the national program, evaluating whether to favour a specific age group with which to start and then expand the target population is appropriate.

### Framework of the Primary Care Paediatrician's activities

As is known, the National Collective Agreement regulates the relationships with the Primary Care Paediatricians, defines their tasks and delegates the creation of additional levels of care to regional agreements.

In light of this, assuming the adoption of national reference guidelines for individual regions, it would be appropriate to include the screening for Type 1 Diabetes and Celiac Disease within the scope of clinical governance at a national level to have a well-balanced recruitment of paediatricians throughout the territory, for the national program.

### Involvement of the General

Some minors, especially those in the age group between 7 and 14 years, are followed by the General Practitioner for reasons mainly related to problems of territorial organisation.

<sup>10</sup> <https://www.icd10data.com/ICD10CM/Codes/E00-E89/E08-E13/E10->



### KEY POINT

**Given the extension of the screening at a national level, the Working Group found the following areas for improvement:**

- make blood sampling easier through a more straightforward method, such as collecting the sample on paper;
- identify laboratories to have a consistent method for analysing samples in the various Regions;
- guarantee the presence of multidisciplinary teams in the Diabetes Reference Centres, also including a psychologist;
- clarify in the event of a positive test whether the National Health Service covers the costs incurred by the Diabetes Reference Centres or not;
- evaluate whether to favour a specific age group with which to start screening and then extend it to the target population;
- involve General Practitioners who follow minors between 7 and 14 years of age;
- include screening for Type 1 Diabetes and Celiac Disease in clinical governance at a national level to ensure uniform recruitment of paediatricians throughout the country.





## 04

# RECOMMENDATIONS

The following recommendations emerged from the discussion established within the Working Group.

The objective to be pursued is to promote an organisational model suitable for ensuring correct and uniform application of the screening program, as well as a practical follow-up phase and care of children who have tested positive.

## 01

## Identify an age range for screening

Law no. 130/2023 provides that screening be conducted on minors aged 1 to 17. Given this, three age groups were favoured in the preparatory project: 2, 6 and 10 years, since they correspond to the seroconversion peaks found in European studies. Given the resources allocated by the law to the national program, it is appropriate to evaluate whether to favour, within this range, one or more age groups with which to start and then expand the target population. The risk of developing autoantibodies against insulin-producing cells is most concentrated from 2 to 7 years.

## 02

## Enrol the paediatric population in the care of General Practitioners

Within the paediatric population, there is a minority group in the care of General Practitioners. For this reason, it is appropriate to involve them in the active call phase, possibly through the relevant Scientific Society and/or the Federation representing them.

## 03

## Provide measures to encourage Primary Care Paediatricians

The family paediatrician plays a fundamental role in patient enrolment and conscious adherence to the screening program. His activity does not end with the blood sample but also continues in the follow-up phase in case of a positive test in conjunction with the Diabetes Reference Centre. It is, therefore, clear that the screening program will be more effective with a higher participation of Primary Care Paediatricians. For this reason, it is appropriate to provide specific measures to encourage paediatricians to perform the screening.

## 04

## Overcome the difficulties of capillary sampling

In light of the challenges encountered in performing blood sampling through the finger prick, it seems appropriate to prepare a specific vademecum that can direct the execution of this activity by the Paediatrician. To simplify, one could use the so-called "card test", in which collecting drops of blood on paper is more manageable than collecting them in microtubes. Currently, no biological samples other than blood, such as saliva, can be used to measure autoantibodies.



## 05

### Define laboratory governance

To ensure a prompt start of the national program, it is necessary to define the governance of the laboratories responsible for processing the samples taken as part of the screening. It could be assumed that several laboratories with regional or macro-regional coverage should be identified as possessing the necessary quality requirements.

## 06

### Centralize communication between laboratories, Primary Care Paediatricians and Diabetes Reference Centres

To ensure effective management by the Diabetes Reference Centre, it is appropriate to provide a centralised telematic system that allows the laboratory that processed the sample to communicate the autoantibody-positive case concurrently to the Primary Care Paediatrician and the Regional Diabetes Reference Centre. In any case, the Primary Care Paediatrician is in charge of communicating the screening results.

## 07

### Ensure the presence of a multidisciplinary team in the Regional Diabetes Reference Centres

It is crucial to ensure the presence in each Region of one or more Diabetes Reference Centres characterised by the presence of a dedicated multidisciplinary team composed of a Paediatric Diabetologist, a Nurse with experience in the use of technologies and a Nutritionist. It is also necessary to provide each Diabetes Reference Centre with a Psychologist to adequately support the family of the child whose result tested positive. The number of healthcare professionals in the centre must align with the indications of the International Society for Paediatric and Adolescent Diabetes (ISPAD).

## 08

### Rule the follow-up phase by adopting ad hoc guidelines

To ensure treatment consistency, nationwide guidelines to direct the management and care phase of the paediatric population that tested positive for the screening test should be adopted. These guidelines, to be followed with the involvement of members of patient associations, should include:

- a. ruling the follow-up phase (i.e., frequency of autoantibody testing, identification and scheduling of further control analyses, etc.);
- b. identifying minimum requirements for Regional Diabetes Reference Centres, as in recommendation no. 7;
- c. defining a Clinical Protocol, which would classify the paediatric population into risk categories based on the number of positive antibodies found;
- d. running a shared national therapeutic education program;
- e. adopting a Diagnostic Therapeutic Care Pathway (PDTC).

A consensus document<sup>12</sup> among experts recently published defines the references, summarised in 10 key points, to draw the guidelines. In the guideline composition phase, it is recommended to take into account the indications contained in the international guidelines of future adoption by ISPAD<sup>13</sup> and the consensus document<sup>14</sup> of the Juvenile Diabetes Research Foundation (JDRF)<sup>15</sup>.

<sup>11</sup>[MOU1]Limbert C et al. ISPAD Clinical Practice Consensus Guidelines 2022: The delivery of ambulatory diabetes care to children and adolescents with diabetes. *Pediatr Diabetes*. 2022 Dec;23(8):1243-1269. doi: 10.1111/pedi.13417. PMID: 365375

<sup>12</sup>Cherubini V et al. *Diabetes Obes Metab*. 2024 Jul 26. doi: 10.1111/dom.15779. Epub ahead of print. PMID: 39054936.

<sup>13</sup>[MOU1]Limbert C et al. ISPAD Clinical Practice Consensus Guidelines 2022: The delivery of ambulatory diabetes care to children and adolescents with diabetes. *Pediatr Diabetes*. 2022 Dec;23(8):1243-1269. doi: 10.1111/pedi.13417. PMID: 365375

<sup>14</sup>Breakthrough T1D - *Diabetes Care*. 2024 Aug 1;47(8):1276-1298. PMID: 38912694.

<sup>15</sup>JDRF is a foundation born and supported by people with Type 1 Diabetes and their families in the United States. It is the leading international agency for funding Type 1 Diabetes research.

## 09

### **Train all the actors involved in the screening**

For the correct execution of Law No. 130/2023, it is critical to implement ad hoc training programs that should include all key spokespersons, from the Primary Care Paediatrician to the hospital Paediatrician and the Diabetes Centre Healthcare Team. The Scientific Societies engaged can manage the training programs.

## 11

### **Implement the coordination of the screening activities**

In general terms, a screening program, to be effective, must be able to reach the entire target population and ensure informed participation in the test. The Observatory established by Article 2 of the Law No. 130 of 15 September 2023 will play a fundamental role in supervising the achievement of these goals.

## 13

### **Conduct a survey among the Primary Care Paediatricians involved in the preparatory project**

To promote an effective start of the screening program on a national scale, it would be helpful to administer a survey to the Primary Care Paediatricians involved in the preparatory project to collect feedback and insights.

## 10

### **Highlight the value and role of Patient Associations**

Patient Associations can play a decisive role in spreading the importance of having people of developmental age screened to ensure the broadest possible adherence through:

- information activities on diabetic disease and the importance of preventing complications related to a late diagnosis;
- ad hoc training time for volunteers will also help gain the desired participation of the associative component at the institutional tables.

## 12

### **Create Regional Registries**

Currently, under the management of the Istituto Superiore di Sanità (ISS), a national register is established in which all screening results converge, both for Type 1 Diabetes and for Celiac Disease. Alongside it, the opportunity to develop regional registries linked to the national one could be evaluated to have aggregated and disaggregated data.

### 14

#### **Provide an exemption code for pre-symptomatic Type 1 Diabetes**

To date, the SSN benefits recognised to patients with diabetes do not apply to minors at risk who have tested positive for screening. It is therefore recommended that an ad hoc exemption code be introduced for the condition of pre-symptomatic Type 1 Diabetes (stage 1 or stage 2) and updated based on the 2024 ICD-10/ICD-11 international diagnostic codes that also identify the pre-symptomatic form of Type 1 Diabetes. This could also represent an opportunity to review the coding of all cases of diabetes.

While waiting for an ad hoc code to be approved, it could also be appropriate to extend the existing exemption to pre-symptomatic Type 1 Diabetes.

### 15

#### **Include screening in the Essential Levels of Care (LEA)**

To ensure a consistent application of the national program and avoid a variable trend from Region to Region, it would be appropriate to include paediatric screening for Type 1 Diabetes and Celiac Disease within the LEA.

### 16

#### **Ensure complete care in case of positive test result**

The resources allocated by Law no. 130/2023 are insufficient to meet the clinical needs of those who would test positive at the screening. In particular:

##### **In particolare:**

- since the onset of the disease has not yet been confirmed, there is no exemption code suitable for covering the services needed to support the patient in the monitoring and discovery phase of the disease;
- it must be considered that screening does not only include the capillary blood sampling but, in the event of a positive result, also the need to subject the child to further check-ups;
- there is a need to:
  - offer psychological support;
  - establish the parameters in the presence of which it is necessary to guarantee the use of a sensor for glycemia monitoring;
  - carry out control blood tests;
  - guarantee the administration of pharmacological therapies;
- some children may need occasional day hospital admissions.

In addition to the above, the cost of dedicated healthcare personnel must also be added. All the services mentioned earlier are currently not codified. The lack of coverage by the SSN could discourage adherence to the diagnostic pathway, with the risk of multiplication of social and healthcare costs related to late diagnosis and complications. For these reasons, to ensure the complete application of the Law No. 130/2023 to screen all minors (the Law expressly provides that screening be carried out on minors aged 0 to 17) and guarantee complete care of the paediatric patient throughout the follow-up phase, it is necessary to increase the resources allocated by the Law above. The Working Group believes that to ensure the above purposes, the resources allocated by the Law No. 130/2023 could be increased by one million euros, starting from 2025.





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