

7th Symposium on
General Population Screening for T1D
Barbara Davis Centre fo Diabetes, Denver, 14 November 2024

Italian National Program

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San Raffaele Hospital, Milano



I.R.C.C.S. Ospedale
San Raffaele

Non c'è cura, senza ricerca.



Disclosures

Emanuele Bosi

received advisory board and lecture fees from:

Abbott

Medtronic

Roche

Sanofi

Challenges for T1D screening in Italy

- **Cultural**: low public perception of impact of science on society (among the lowest in UE; perhaps improving after pandemic), diffuse skepticisms to medical research, lack of collaboration by the physician communities;
- **Organizational**: lack of tradition, no dedicated infrastructures, few physician scientists and research nurses, multiple and unfocused interests of scientific societies and patient organizations;
- **Legal/Political**: pervasive Privacy Law, demanding Ethics Committees, AIFA tortuous procedures, insufficient private and public advocacy;
- **Economical**: limited research funds.

Action:

- To establish screening programs by Law and incorporate them into public health managed by the Health Ministry through the National Health System (SSN). This action was advocated by FID (Fondazione Italiana Diabete)

Italian Republic National Law on type 1 diabetes and celiac disease screening in infants and adolescents. Approved Sep 2023

Advocated by **Fondazione Italiana Diabete**



Press release after approval by the House. Mr. Giorgio Mulé, Author and first signer of the Law

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SOMMARIO

LEGGI ED ALTRI ATTI NORMATIVI

LEGGE 15 settembre 2023, n. 130.

Disposizioni concernenti la definizione di un programma diagnostico per l'individuazione del diabete di tipo 1 e della celiachia nella popolazione pediatrica. (23G00140) Pag. 1

DECRETI PRESIDENZIALI

DECRETO DEL PRESIDENTE DELLA REPUBBLICA
31 agosto 2023.

DECRETO DEL PRESIDENTE DELLA REPUBBLICA
31 agosto 2023.

Scioglimento del consiglio comunale di Besenzone. (23A05245) Pag. 4

DECRETI, DELIBERE E ORDINANZE MINISTERIALI

Ministero dell'agricoltura,
della sovranità alimentare
e delle foreste

DECRETO 4 agosto 2023.

Modalità di accertamento della legittimità e regolarità delle operazioni finanziate dal FE-ASR per i tipi di intervento che non rientrano nel campo di applicazione del Sistema integrato di



Ministero della Salute

Italian Republic National Law on type 1 diabetes and celiac disease screening in infants and adolescents: a summary

Comment

Sponsor

- Ministry of Health

General Objective

- Nationwide, Public Health Program in the childhood and adolescent general population (age 1-17 yr) in Italy to identify individuals at risk for type 1 diabetes and/or undiagnosed celiac disease, in order to reduce the complications associated with late diagnosis of these diseases.

Specific Aims

- Prevention of diabetic keto-acidosis (DKA) at the clinical onset of type 1 diabetes;
- Identification of pre-symptomatic type 1 diabetes suitable to disease modifying therapies.
- Prompt treatment of newly diagnosed celiac disease by gluten free diet;
- Prevention of non gastrointestinal complications of celiac disease including impaired growth or short stature, iron deficiency, osteopenia, delayed puberty, etc.;

Screening type 1 diabetes and celiac disease by law

On Sept 17, 2023, the Italian Parliament approved with unanimous vote a law ([Italian Republic Law 130/2023](#)) introducing a nationwide screening for type 1 diabetes and coeliac disease in the general population aged 1–17 years as part of the public health program aimed at reducing the effects of these chronic diseases. This law was successfully passed because of the commitment of many people from the diabetes and scientific community and was advocated for by Fondazione Italiana Diabete.

Type 1 diabetes and coeliac disease are two distinct, but sometimes coexisting, autoimmune conditions that share some common features, including an underlying immune-mediated pathogenetic mechanism; a partially shared genetic predisposition associated with HLA polymorphisms; associations with disease-specific autoantibodies, being detectable in the circulation years before clinical onset; an identifiable long presymptomatic phase; and progression to clinical stage that can be predicted.^{1,2} In addition, both conditions have continuously increased in incidence over the past five decades in high-income countries.^{1,2}

There are two specific aims of the new Italian law. First is the identification of children and adolescents during the presymptomatic phase of type 1 diabetes.

children and adolescents, positivity for two or more islet autoantibodies is associated with the greatest risk (almost certainty) of future disease; positivity for one autoantibody indicates an intermediate risk, and a negative autoantibody status is associated with no risk. Similarly, the development of coeliac disease—either typical or clinically silent—is associated with IgA class transglutaminase and endomysial autoantibodies that are also easily measurable and are sensitive and specific markers of the disease.⁴ Type 1 diabetes and coeliac disease-specific autoantibodies can be tested together in combined screening procedures, as indicated in the new law.

Available information on presymptomatic type 1 diabetes and its natural history derives from screening programmes done in relatives or other groups of genetically predisposed individuals, for reasons of higher efficiency and feasibility. However, since most people developing type 1 diabetes have no family history, any action aiming at reducing disease burden at the public health level requires moving to screening in the general population.⁵ In the general childhood and adolescent population, the prevalence of islet antibodies is around 1–2%, with 0.3–0.5% of the population deemed high risk due to having two or more autoantibodies.⁶ For coeliac



Lancet Diabetes Endocrinol 2023

Published Online

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[https://doi.org/10.1016/S2213-8587\(23\)00354-6](https://doi.org/10.1016/S2213-8587(23)00354-6)

For the Italian Republic Law 130/2023 see <https://www.gazzettaufficiale.it/eli/gu/2023/09/27/226/sg/pdf>



Law implementation Propaedeutic project: the D1CE SCREEN

Collaboration between Ministry of Health and Istituto Superiore di Sanità (ISS) for a Propaedeutic Project on national screening of T1D and CD in the pediatric general population



D1CE SCREEN - Propaedeutic project on smaller scale to assess feasibility, acceptability, operative, technical and administrative issues of the nationwide project, conducted by ISS

Time of conduction:
April-November 2024



Ministero della Salute
DIREZIONE GENERALE PER L'IGIENE E LA SICUREZZA
DEGLI ALIMENTI E LA NUTRIZIONE
Ufficio 5

ACCORDO di collaborazione tra pubbliche amministrazioni per la realizzazione del
PROGETTO denominato

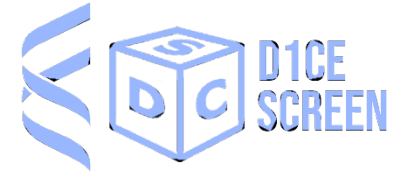
*“Progetto Propedeutico per la realizzazione di un programma di screening nazionale nella
popolazione pediatrica per il diabete di tipo 1 e della celiachia”*

*Il Ministero della salute
Direzione generale per l'igiene e la sicurezza degli alimenti e la nutrizione
e
l'Istituto Superiore di Sanità*

di seguito indicati rispettivamente come *Ministero*, costituito con legge n. 172/09, sulla base dell'organizzazione di cui al D.P.C.M. n. 59/14 e con sede in Roma, viale Giorgio Ribotta, 5 – 00144, codice fiscale n. 97969380589, rappresentato dal Direttore generale della *Direzione per l'igiene e la sicurezza degli alimenti e la nutrizione*. *Dr. Ugo Della Marta*.



Law implementation Propaedeutic project: the D1CE SCREEN



Organization summary

Participating Regions:

Lombardia, Marche, Campania, Sardinia, each with a coordinating center for T1D and CD

Children to be screened:

Total 5,363

Screening ages: 2+1, 6+1, 10+1 years

Operating network:

Family Pediatricians

Ethics Committee:

Central, Ministry of Health

Central Platform: ISS

Sponsor: Ministry of Health

Screening tests on capillary blood:

Autoantibodies to GAD, IA-2, ZnT8, insulin, transglutaminase-IgA and -IgG on capillary blood; HLA-DQ2 and DQ8 typing on Guthrie Cards.

Central Lab, San Raffaele: Vito Lampasona, Paola Carrera

Operating Body: ISS Istituto

Superiore di Sanità

P.I.: Flavia Pricci, Olimpia Vincentini (ISS)

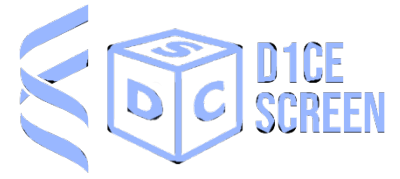
ISS supervision: Marco Silano, Umberto Agrimi

Scientific consultants:

Emanuele Bosi, Carlo Catassi, Valentino Cherubini, Antonio Davino, Vito Lampasona, Graziano Barera, Riccardo Troncone, Dario Iafusco, Enza Mozzillo, Carlo Ripoli, Mauro Congia, Renata Auricchio, Riccardo Bonfanti



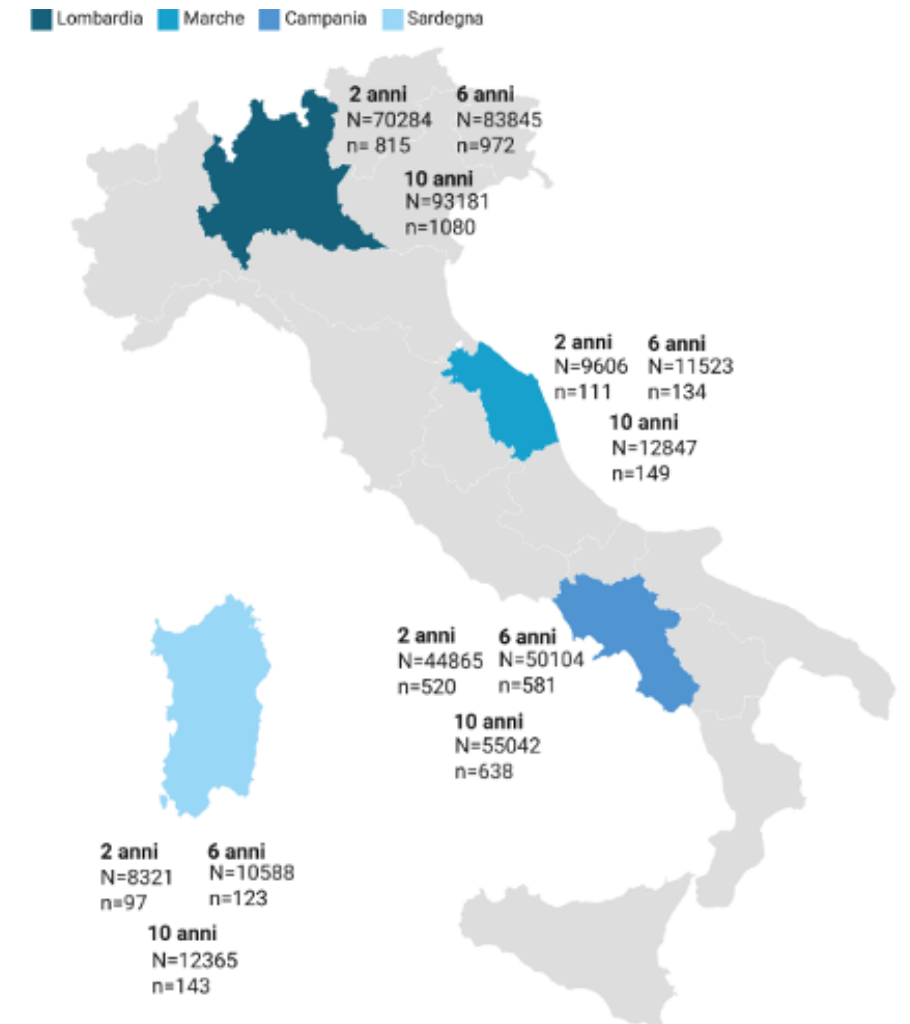
Law implementation Propaedeutic project: the D1CE SCREEN



Participating Regions and Children

Screening of 5363 children resident in 4 Regions (1.6% of reference Italian population), proportionally distributed according to population, stratified for 3 age ranges (2+1, 6+1, 10+1) corresponding to reported peaks of islet autoimmunity seroconversion

Age (yr)	Lombardy	Marche	Campania	Sardinia	Total
2+1	815	111	520	97	1543
6+1	972	134	581	123	1810
10+1	1080	149	638	143	2010
total	2867	394	1739	363	5363



Lancet Diabetes Endocrinol
2022; 10: 589–96

Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study



Mohamed Ghalwash, Jessica L Dunne, Markus Lundgren, Marian Rewers, Anette-G Ziegler, Vibha Anand, Jorma Toppari, Riitta Veijola, William Hagopian, on behalf of the Type 1 Diabetes Intelligence Study Group*

Interpretation Our results show that initial screening for islet autoantibodies at two ages (2 years and 6 years) is sensitive and efficient for public health translation but might require adjustment by country on the basis of population-specific disease characteristics.

Optimal screening at 2 and 6 years

Islet autoantibody screening in at-risk adolescents to predict type 1 diabetes until young adulthood: a prospective cohort study



Mohamed Ghalwash, Vibha Anand, Olivia Lou, Frank Martin, Marian Rewers, Anette-G Ziegler, Jorma Toppari, William A Hagopian, Riitta Veijola, the Type 1 Diabetes Intelligence Study Group*

Interpretation Screening of adolescents at risk for type 1 diabetes only once at 10 years of age for islet autoantibodies was highly effective to detect type 1 diabetes by the age of 18 years, which in turn could enable prevention of diabetic ketoacidosis and participation in secondary prevention trials.

Lancet Child Adolesc Health
2023; 7: 261–68

Optimal screening at 10 years



Law implementation Propaedeutic project: the D1CE SCREEN The Family Pediatricians



Family Pediatricians are a public medical organization, part of the NHS and unique to Italy, extended as a nationwide network, responsible for prevention, cure and rehabilitation of children in the age ranges 0-6 years (mandatory) and 7-14 years (optional in alternative with adult GPs), sometime up to 16 yr.

In D1CE SCREEN Family Pediatricians are responsible for:

- direct contact of participants and families
- presentation of project rational and objectives
- administration of informed consent and informative materials
- execution of capillary blood drawing by fingerprick
- blood collection in microtubes and cards
- preservation of samples until shipping by courier
- communication to families of screening results and referral of positive cases to Regional centers
- questionnaires on feasibility and acceptability



Law implementation Propaedeutic project: the D1CE SCREEN



Capillary blood Sampling and Assays

Capillary blood drawings from fingerprick was chosen vs venous sampling:

- Collected in Microvette (at least 25 μ l) for autoantibody measurement:
GAD, IA-2, ZnT8, insulin, transglutaminase-IgA and -IgG (6 specificities)
- Two drops on paper (Guthrie Cards) for HLA typing



Assays centralized at San Raffaele:

- Autoantibodies measured by ELISA and LIPS, with comparative evaluation
- HLA DQ2 and DQ8 typing by HLA typing by Reverse Dot Blot Hybridization

Acceptability and feasibility of capillary vs venous blood drawing in children and adolescents evaluated in the former UNISCREEN study



Family Pediatrician

Screening for early-stage type 1 diabetes and celiac disease
In children aged **2+1, 6+1, 10+1 years** - Informed consent
Capillary blood up to 200 µl + dried blood spot + questionnaire

Screening/Core lab

3-ELISA and LIPS screening:
GADA, IA-2A, ZnT8A (combined)
LIPS confirmation on positive,
plus IAA

ELISA and LIPS screening:
TGA-IgA, TGA-IgG
LIPS confirmation on positive
Real Time-PCR HLA typing
HLA-DQ2 and HLA-DQ8

Pseudonymised registration in
EDENT1FI (age, gender,
autoantibodies)

GADA, IA-2A, ZnT8A, IAA negative
No risk for type 1 diabetes
No more action or follow up

Type 1 diabetes track

Celiac disease track

TGA-negative, no DQ2, no DQ8
No latent/potential celiac disease
No more action or follow up

Any confirmed GADA, IA-2A,
ZnT8A, IAA (single or multiple)
Risk for type 1 diabetes

Either confirmed TGA positivity or
DQ2 and/or DQ8
Latent/potential celiac disease

**Type 1 diabetes pediatric
expert regional center**
Follow up and monitoring

**Celiac disease pediatric
expert regional center**
Follow up and monitoring

Family Pediatrician

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In children aged **2+1, 6+1, 10+1 years** - Informed consent
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Risk for type 1 diabetes

Either confirmed TGA positivity or DQ2 and/or DQ8
Latent/potential celiac disease

Type 1 diabetes pediatric expert regional center
Follow up and monitoring*:
T1D staging
Education/Training
Random glucose, HbA1c, CGM
OGTT (optional)
Psychological assessment/support
Intervention options

Type 1 diabetes pediatric expert regional center
Follow up and monitoring

Celiac disease pediatric expert regional center
Follow up and monitoring

Celiac disease pediatric expert regional center
Follow up and monitoring:
Protocol on development

*Cherubini V et Al. Diabetes Obes Metab. 2024 Oct;26(10):4197-4202



D1Ce Screen study

Current state of recruitment (27 September 2024)



392 pediatric primary care physicians currently participating

The screenshot shows the dashboard of the D1Ce Screen study. The top navigation bar is blue and contains the Istituto Superiore di Sanità logo, the text 'Istituto Superiore di Sanità Progetto D1Ce Screen', and a user profile for 'admin AMMINISTRATORE'. The main content area is titled 'Dashboard' and features a summary card for 'Totale anagrafiche inserite' with a value of 4331 (highlighted in a red box) and a note that 80.1% of the total are to be screened. Below this are three cards showing the number of records for different age groups: 1211 for 2-year-olds, 1384 for 6-year-olds, and 1508 for 10-year-olds. At the bottom, there are two more cards: 'Ultime anagrafiche inserite' and 'Elenco pediatri'. A left sidebar contains navigation links for Home, Archivio Utenti, Anagrafiche, Statistiche, Cambio password, and Logout.

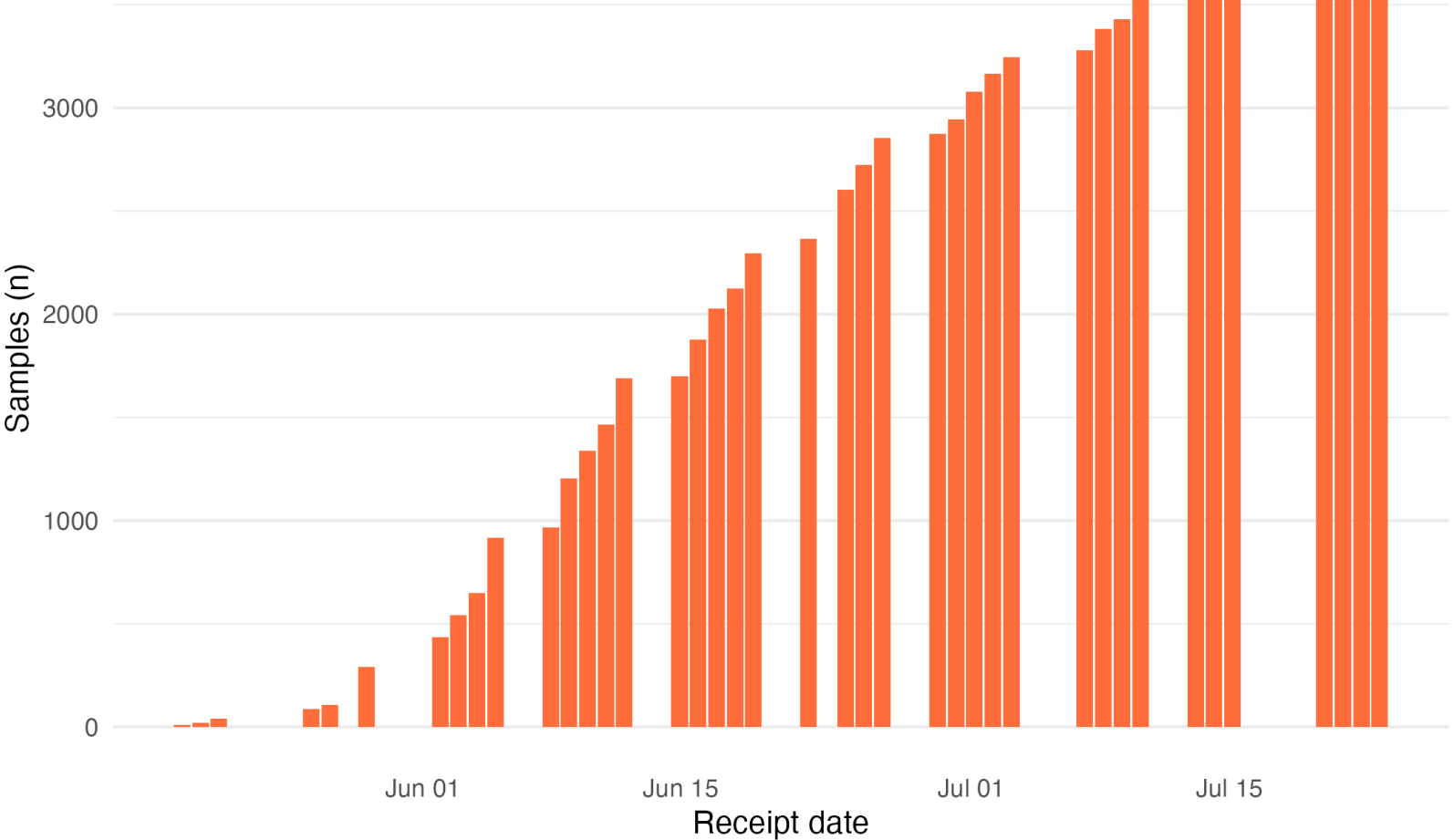
Totale anagrafiche inserite **4331** **80.1% of total to be screened**

Anagrafiche inserite Età 2 anni	Anagrafiche inserite Età 6 anni	Anagrafiche inserite Età 10 anni
1211	1384	1508

Ultime anagrafiche inserite **Elenco pediatri**

Cumulative number of received samples (n = 3673)

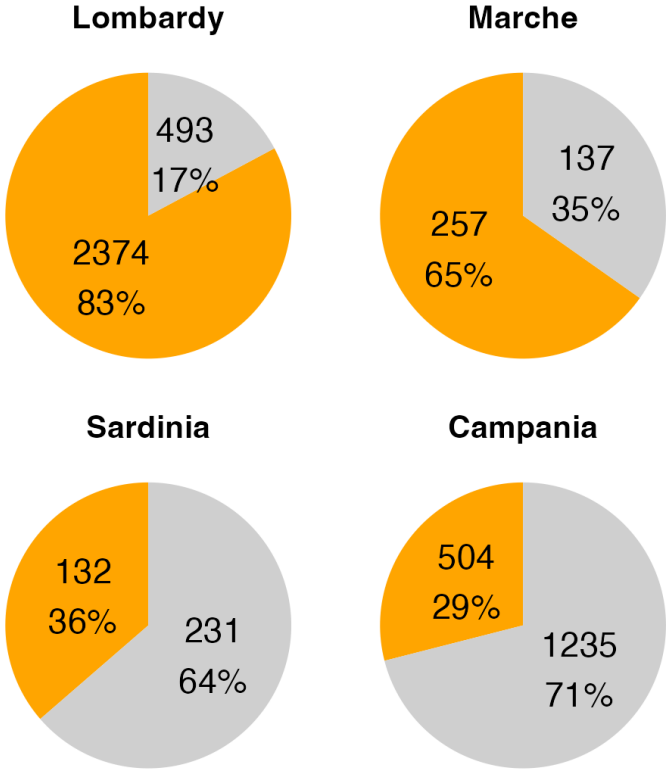
includes samples with insufficient serum volume



D1Ce Screen Status: Update at 31st July 2024

Samples collected so far (n, % of expected)

includes only samples with actionable serum volume



collected still pending

D1Ce Screen study

Feasibility issues

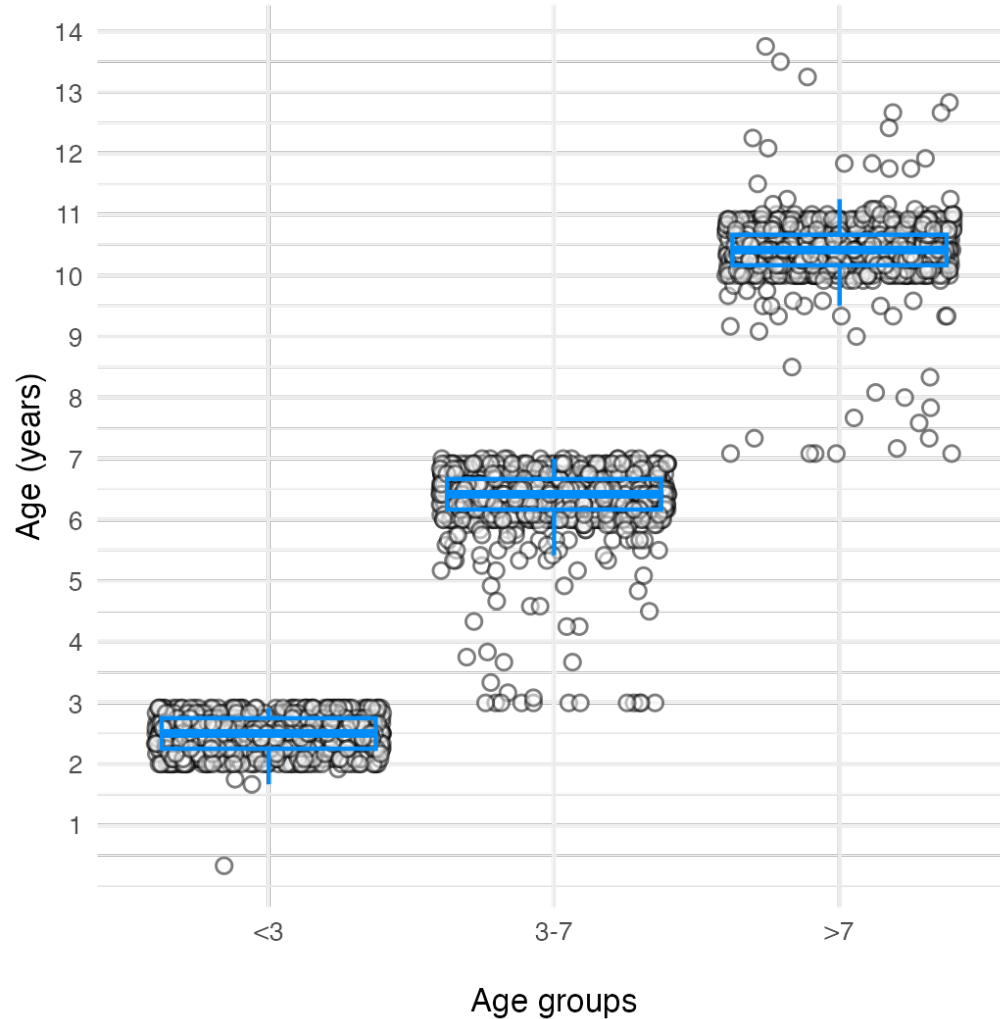
Serum volume adequacy of received capillary samples

PEDIATRICIANS (N)	SUBJECTS (N)	Adequate		Partly met		Insufficient	
		N	%	N	%	N	%
306	3673	3013	82.0%	254	6.9%	406	11.1%

D1Ce Screen Status: Update at 31st July 2024

Age of children tested for autoantibodies

children are stratified into the targeted age groups



Distribution of children into age groups stratified by sex

	AGE (YEARS)	SUBJECTS (N)	SUBJECTS (%)
female	<3	452	13.8%
	3-7	572	17.5%
	>7	577	17.7%
all ages		1601	—
male	<3	458	14.0%
	3-7	562	17.2%
	>7	643	19.7%
all ages		1663	—
total		3264	—

Frequency of children with a T1D first degree relative

AFFECTED FDR	N	%
no	3156	96.7%
yes	108	3.3%

Frequency of children with a CD first degree relative

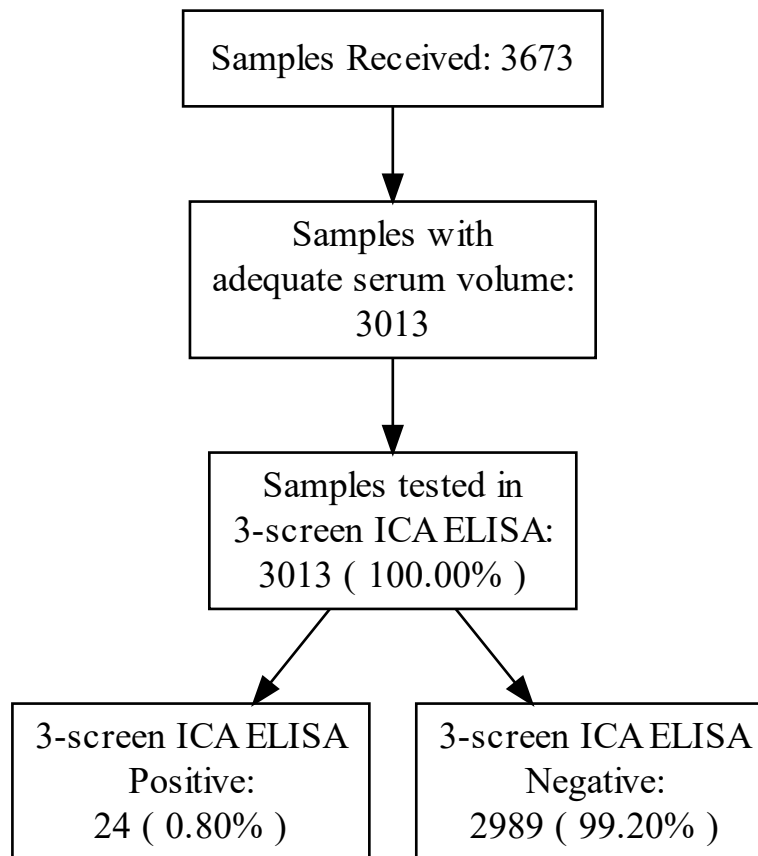
AFFECTED FDR	N	%
no	3122	95.6%
yes	142	4.4%

D1Ce Screen Status: Update at 31st July 2024



D1CE SCREEN

T1D autoantibody testing



D1Ce Screen Status: Update at 31st July 2024



D1CE SCREEN

T1D autoantibody testing



3-screen islet autoantibody ELISA:

- 24 of 3013 positive (0.80%)

Confirmed by LIPS:

- ≥ 2 autoantibodies: 7 (0.23%)

- single autoantibodies: 8 (0.27%)

- not confirmed: 9 (0.30%)

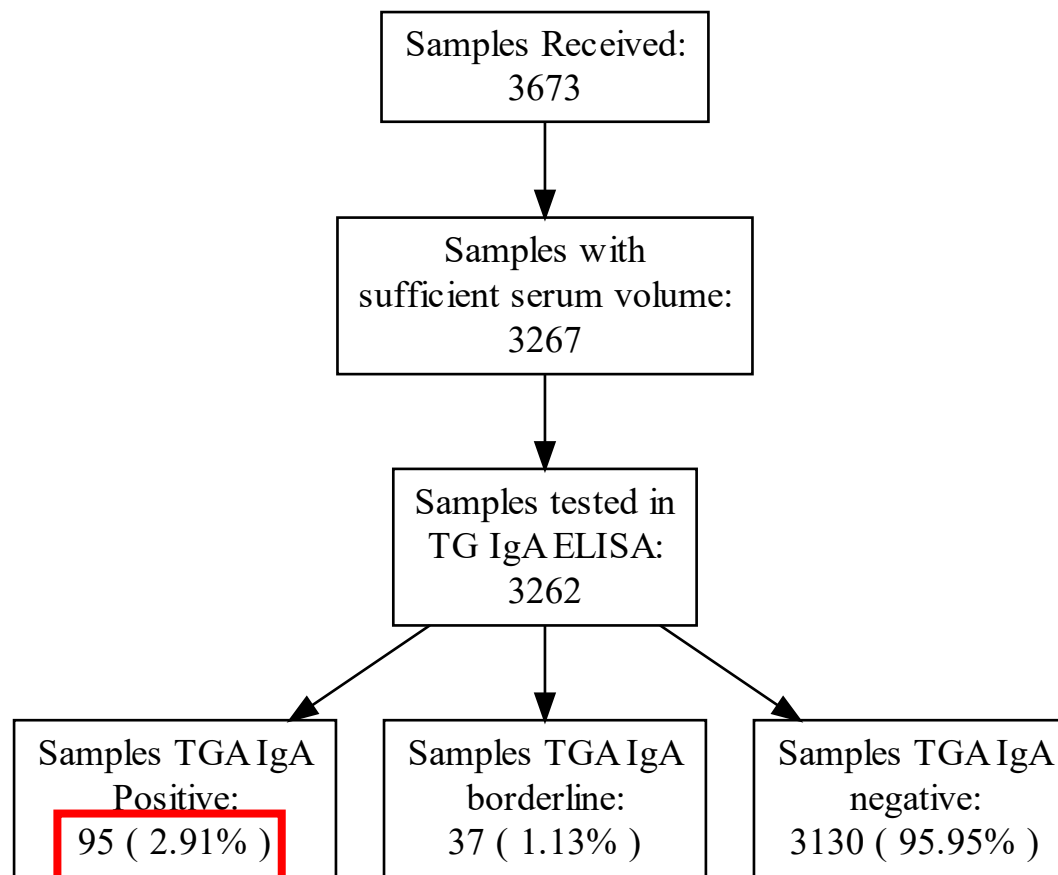
Individual autoantibodies:

GADA 14 (0.46%), ZnT8A 7 (0.26%), IAA 3 (0.1%), IA2A 3 (0.1%)



D1CE SCREEN

CD autoantibody testing



D1Ce Screen Status: Update at 31st July 2024

D1Ce Screen – Questionnaires from EDENT1FI WP2

- In the original protocol

Evaluation of feasibility and acceptability of screening for type 1 diabetes

Feedback questionnaire for paediatric diabetes care centres

- **Amendment to introduce questionnaires on feedback from families** – approved 10 Sept 2024 by the National Ethics Committee for public health clinical trials. Three existing validated measures will be administered to parents/guardians of who consider their children screened, as well as to parents whose children have completed screening,

HADS - Hospital Anxiety and Depression Scale: developed to identify cases (possible and probable) of anxiety disorders and depression among patients in nonpsychiatric hospital clinics. It was divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), both containing seven intermingled items.

SAI-6 – State Anxiety Inventory 6 items: short form of 20-items STAI adapted for parents of at risk of developing diabetes children. The question wording is: ‘When you think of your child’s risk of developing diabetes do you feel?’ and the 6 items which is assessed on 4-point Likert scale describes the states: calm, worried, relaxed, tense, at ease, nervous.

EQ-5D-5L: to assess quality of life self-reported as of ‘today’. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The new Italian law on screening type 1 diabetes and celiac disease: the current status

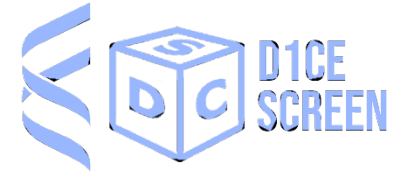
Initial feed backs:

- **Generally well received** as a program by the political, scientific, stake holders and family communities;
- Prompt action by the Italian Government after law approval, through the implementation of the **propaedeutic D1Ce Screen study**, conducted by the Istituto Superiore di Sanità: the study (4 Regions, 5363 children to be screened) is ongoing and expected to be completed by Nov 2024
- **Critical feed backs** on feasibility and acceptability are expected by D1Ce Screen in order to finalize operation and functionality of the National Screening Program starting in Dec 2024. Anticipated issues include:
 - Technical difficulties in capillary blood drawing (tutorial to see)
 - Agreement with Regions (very political !)



D1Ce Screen

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others)**

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more that 500
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Lombardy, Marche,
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Central Lab**

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Iafusco, Enza Mozzillo, Carlo Ripoli,
Mauro Congia, Renata Auricchio,
Riccardo Bonfanti, Raffaella
Buzzetti**