8th Symposium on General Population Screening for T1D

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Selected International General Population Screening Programs: The Italian Experience

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I.R.C.C.S. Ospedale San Raffaele
Non c'è cura, senza ricerca.

EDENT1FI
European action for the Diagnosis of Early Non-clinical Type 1 diabetes For disease Interception

INNODIA

UniSR
Università Vita-Salute San Raffaele

Emanuele Bosi - Disclosures

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

Ministero della Salute

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 o 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.;

Comment

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 December 1, 2023
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

Bosi E, Catassi C. Lancet Diabetes Endocrinol. 2024 Jan;12(1):12-14

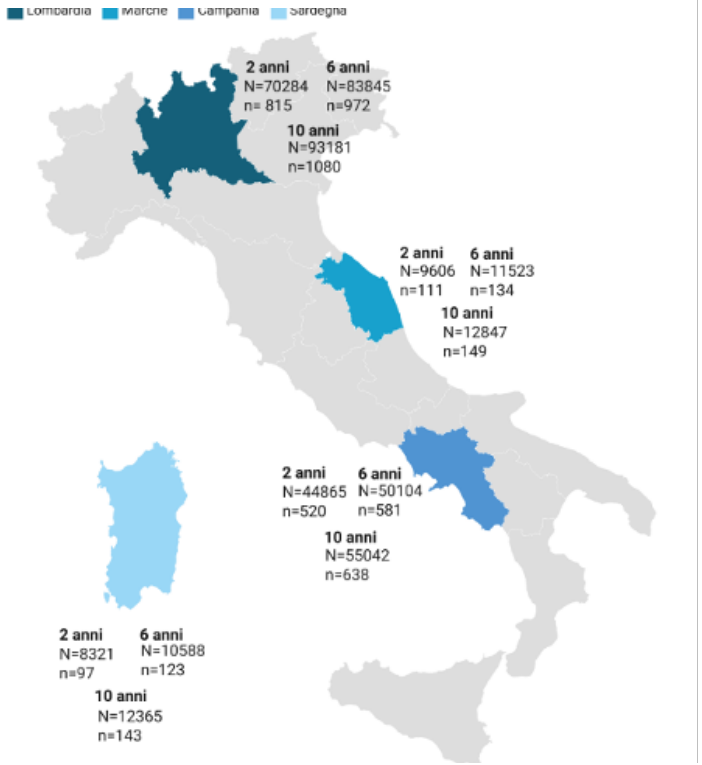
Law implementation pilot project: the D1Ce Screen

Participating Regions and Children

April 2024 – March 2025

3 pillars:
The Family Pediatricians Nationwide Network
Capillary blood sampling
Centralized laboratory assays

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



Vincentini O et al. PLoS One. 2025 Aug 13;20(8):e0328624

Law implementation Propaedeutic project: the D1Ce Screen

The Family Pediatricians Network

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.

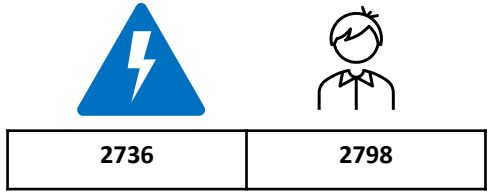
In D1CE SCREEN Family Pediatricians were responsible for:

- 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

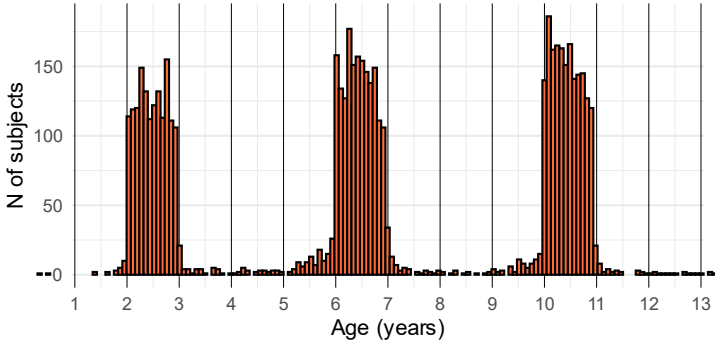
Vincentini O et al. PLoS One. 2025 Aug 13;20(8):e0328624

D1Ce Screen study

Final enrollment (April 2024 – March 2025)



Region	Planned (n)	Enrolled (2+6+10 years)	Enrolled (other ages)	Total
Campania	1739	1488 (85.6%)	190	1678 (96,5%)
Lombardy	2867	2807 (97.9%)	186	2993 (104.4%)
Marche	394	351 (89.1%)	19	370 (93.9%)
Sardinia	363	359 (98.9%)	61	420 (115.7%)
Totale	5363	5005 (93,3%)	456	5461 (102%)



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 µl) for autoantibody measurement:

  GADA, IA-2A, ZnT8A, insulin (IAA), transglutaminase-IgA and –IgG

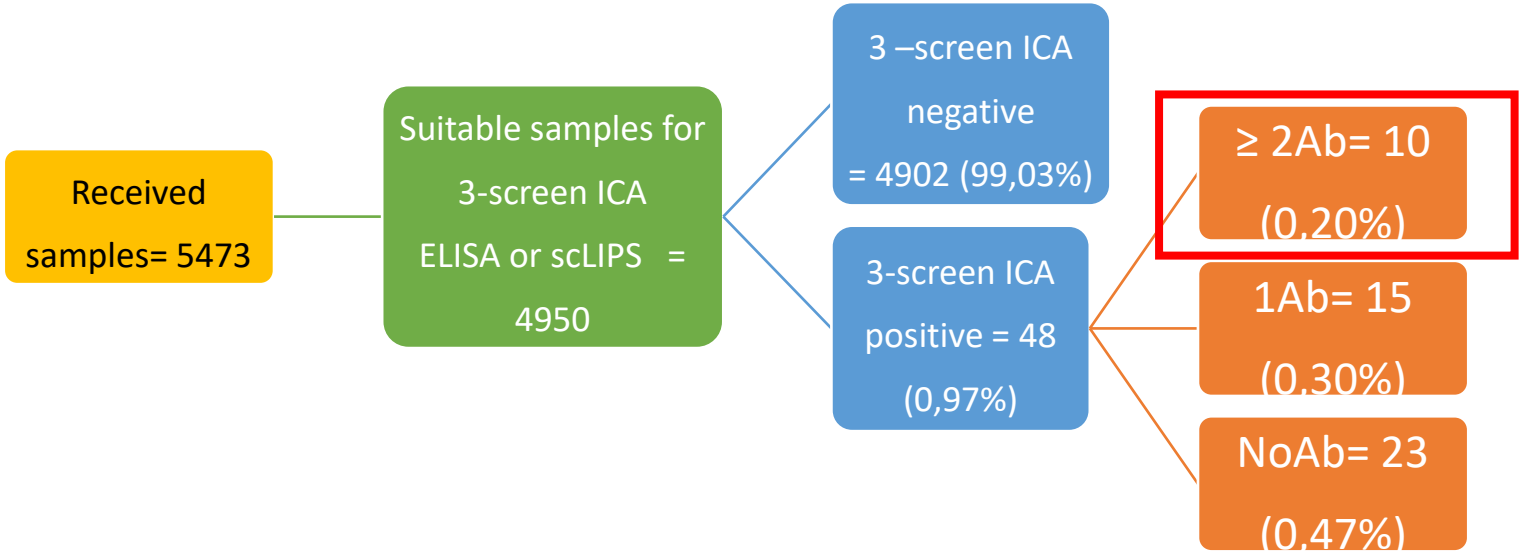
- Two drops on paper (Guthrie Cards) for HLA typing

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

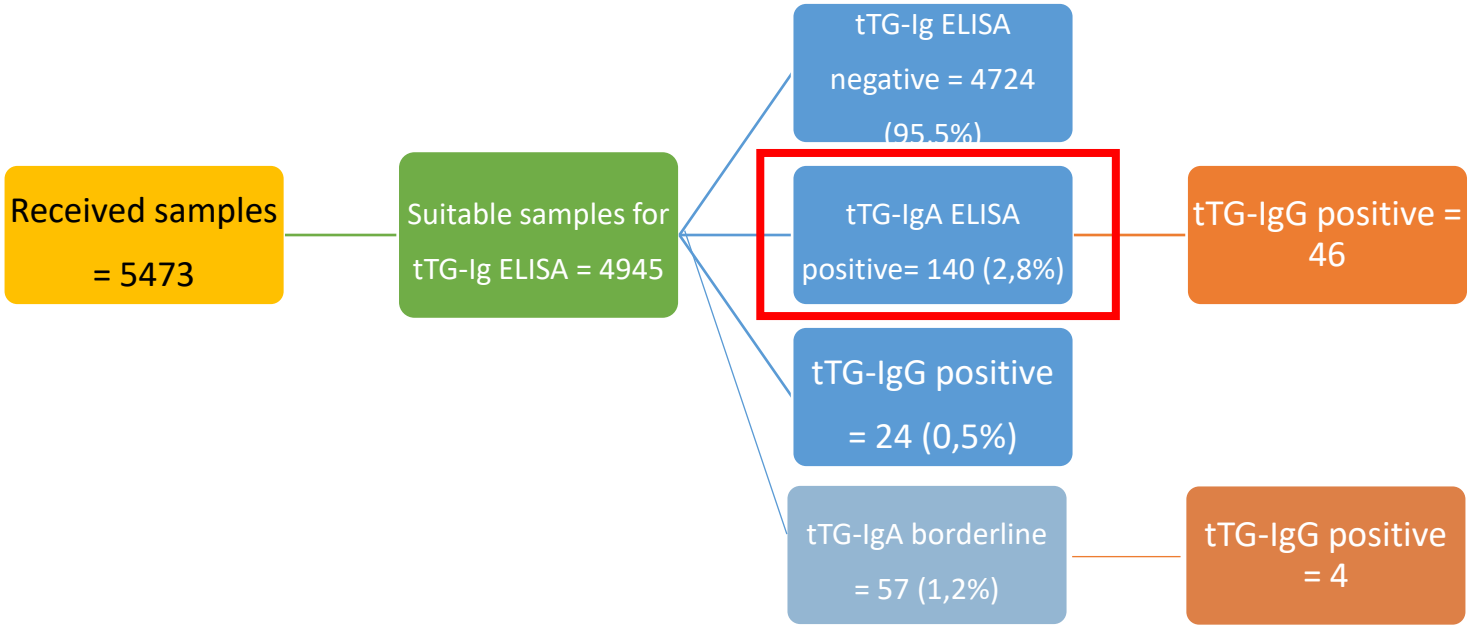
D1Ce Screen

prevalence of type 1 diabetes autoantibodies in the general pediatric population in Italy

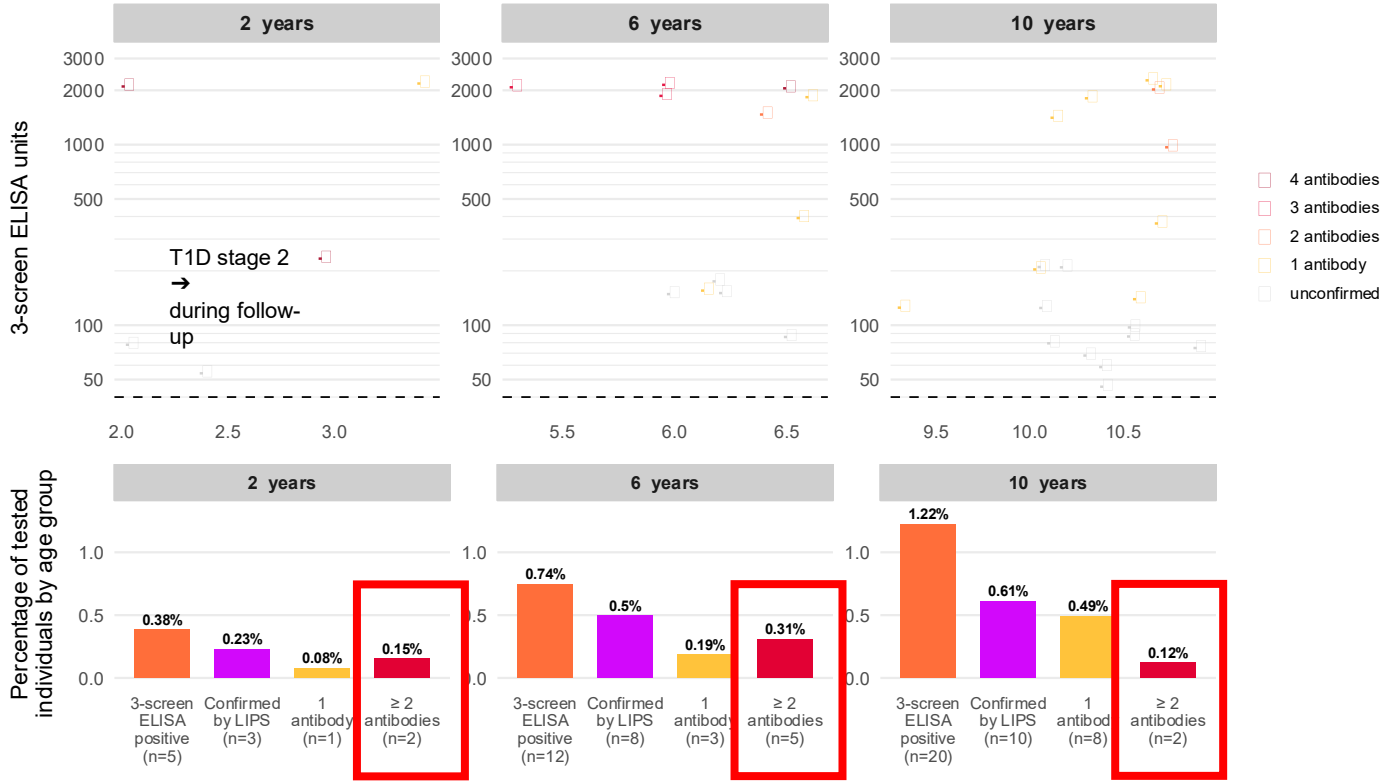


D1Ce Screen

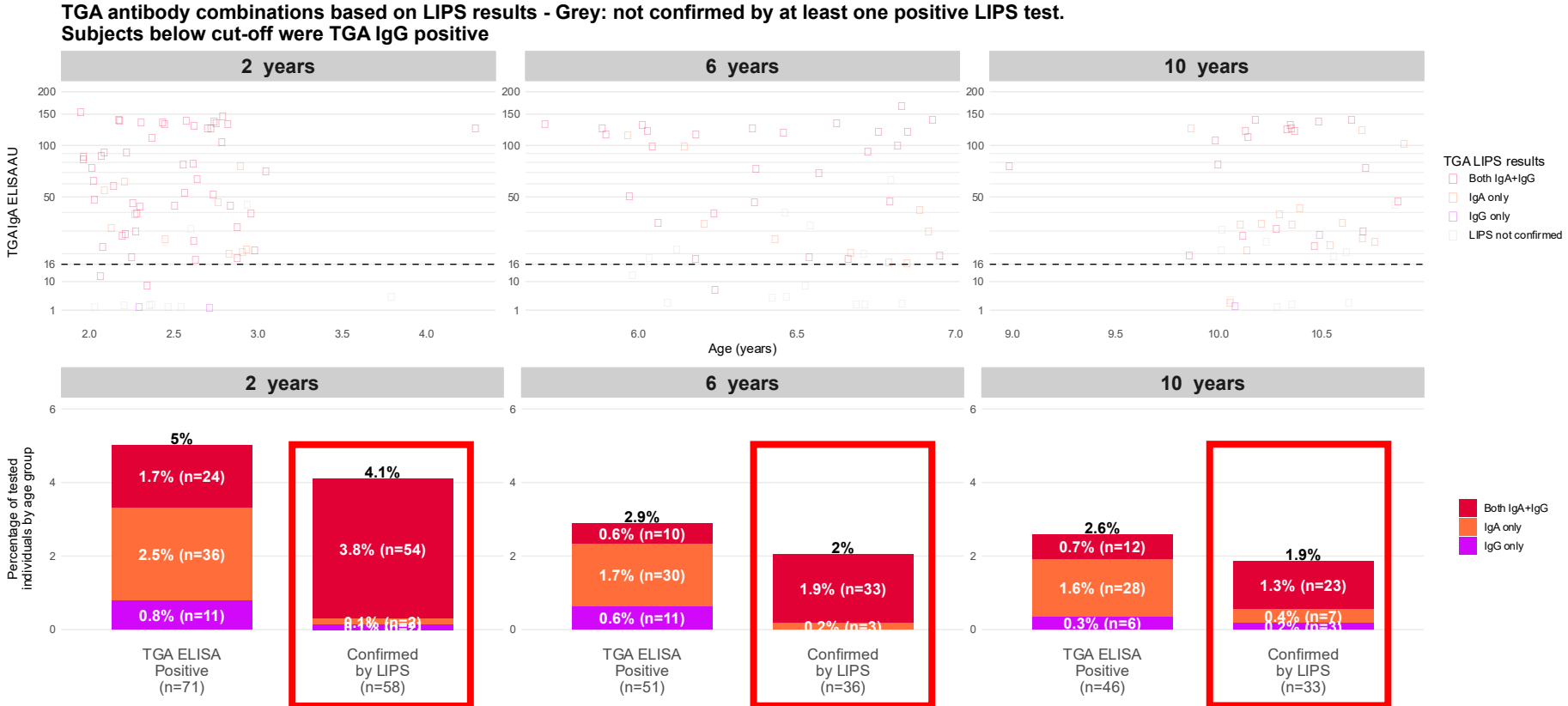
prevalence of celiac disease autoantibodies in the general pediatric population in Italy



D1Ce Study: T1D autoantibodies
Antibody levels, multiple antibodies, and age groups: stable with ages



D1Ce Study: CD autoantibodies
TGA IgA and IgG and age groups: decreasing with ages



Summary of D1Ce Screen genetic analysis

Region	Total enrolled subjects	HLA tested samples	High CD risk (n)	High CD risk (%)
Campania	1,682	1,433	322	22.5
Lombardy	2,998	2,632	611	23.2
Marche	371	327	73	22.3
Sardinia	422	385	143	37.1
Total	5473	4777	1149	24.0

High CD risk: HLA-DQ2.5 homozygous/ heterozygous, DQ2.5 + DQ2.x, DQ2.5 + DQ8

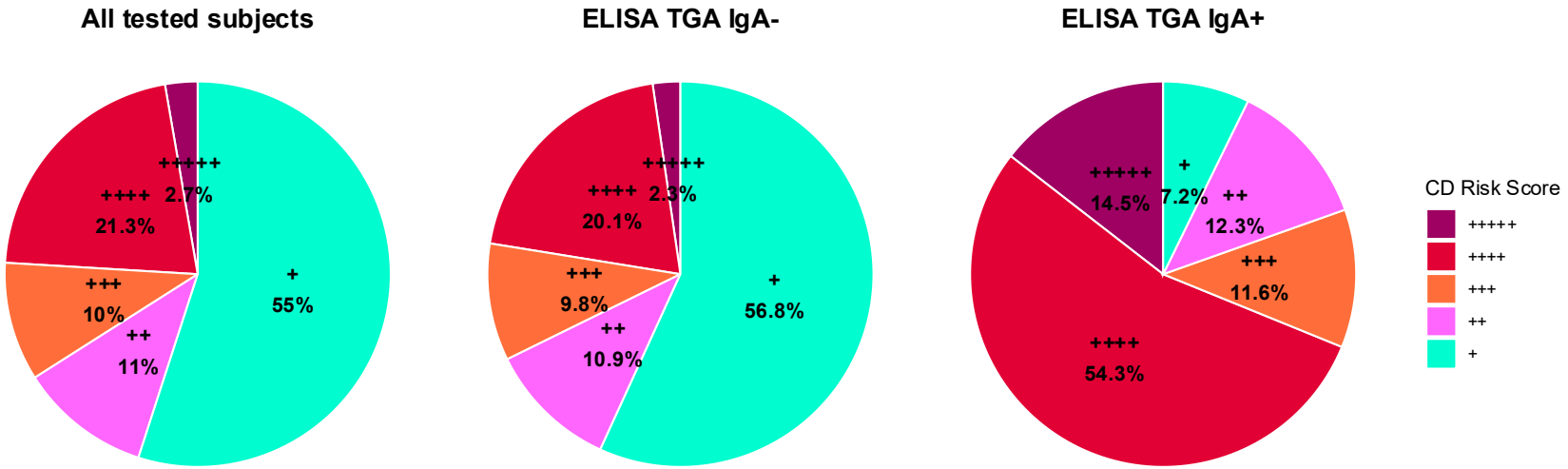
Alternative version with CD risk categories

CD Risk Score	Corresponding genotype
+++++	DQ2.5 homozygous / DQ2.5 + DQ2.x
++++	DQ2.5 + DQ8
++++	DQ2.5 heterozygous
+++	DQ2.x + DQ8
+++	DQ8
+++	DQ8 + DQX.5
++	DQ2.x heterozygous
++	DQ2.x homozygous
+	DQ2/DQ8 negative
+	DQX.5

Alternative version with CD risk categories

Region	Total enrolled subjects	HLA tested samples	+++++ CD risk (n)	++++ CD risk (n)	+++ CD risk (n)	++ CD risk (n)	+ CD risk (n)
Campania	1,682	1,433	25	297	120	169	822
Lombardy	2,998	2,632	71	540	284	297	1,440
Marche	371	327	10	63	24	36	194
Sardinia	422	385	24	119	48	24	170
Total	5473	4777	130	1019	476	526	2626

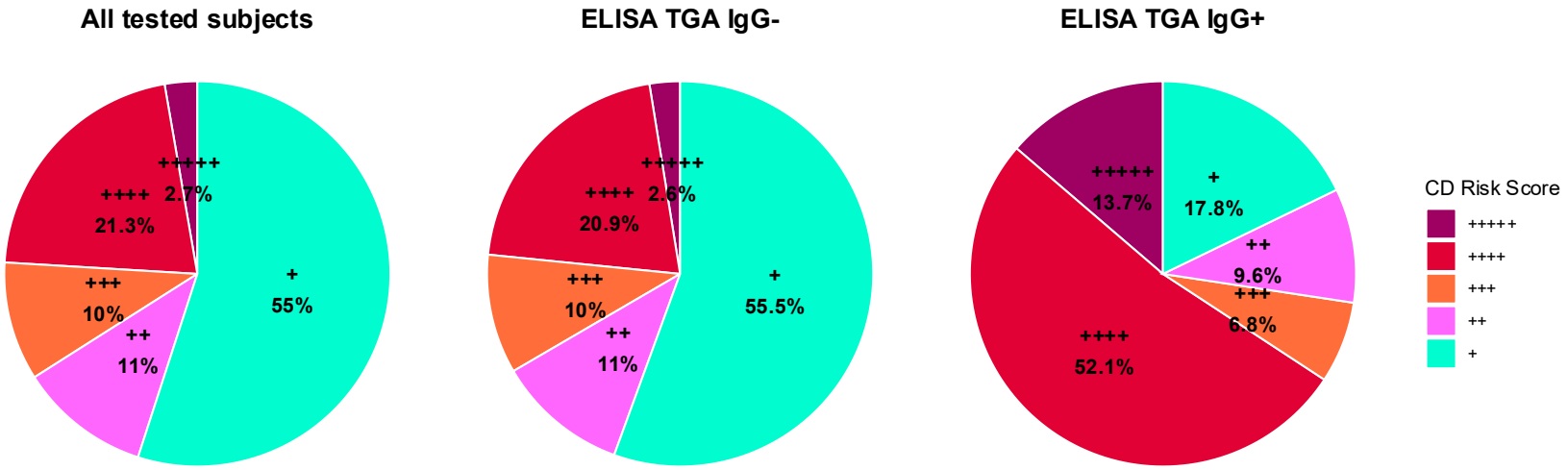
TGA IgA-positive subjects showed significant enrichment for high CD genetic risk compared to TGA IgA-negative subjects



(Cochran-Armitage trend test, $p < 2.2 \times 10^{-16}$)

(OR = 7.52, 95% CI: 5.18-10.99)

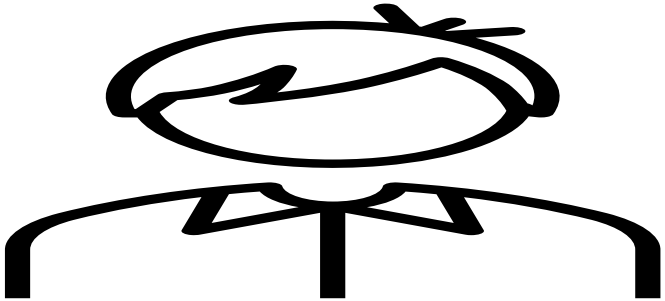
TGA-IgG ELISA and CD HLA risk

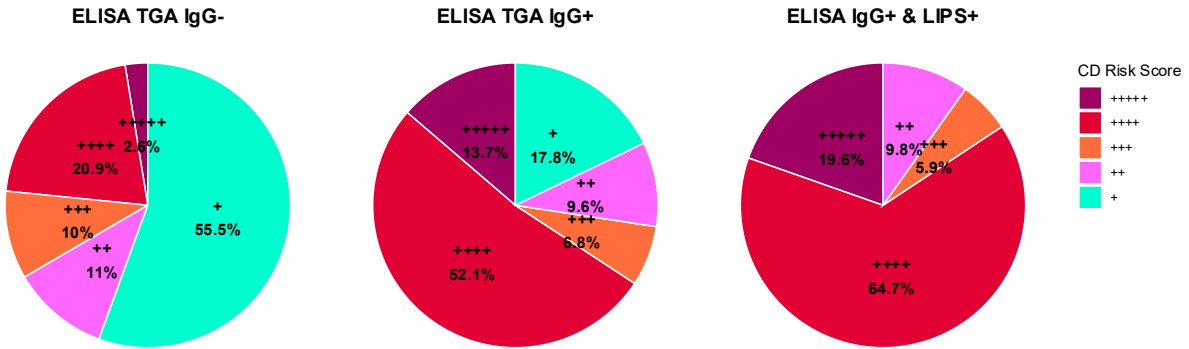


(Cochran-Armitage trend test, $p < 2.2 \times 10^{-16}$)

(OR = 6.33, 95% CI: 3.83-10.64)

Double positivity by ELISA and LIPS (2nd level test) is associated with an even higher prevalence of CD genetic risk traits





D1Ce Screen – Questionnaires

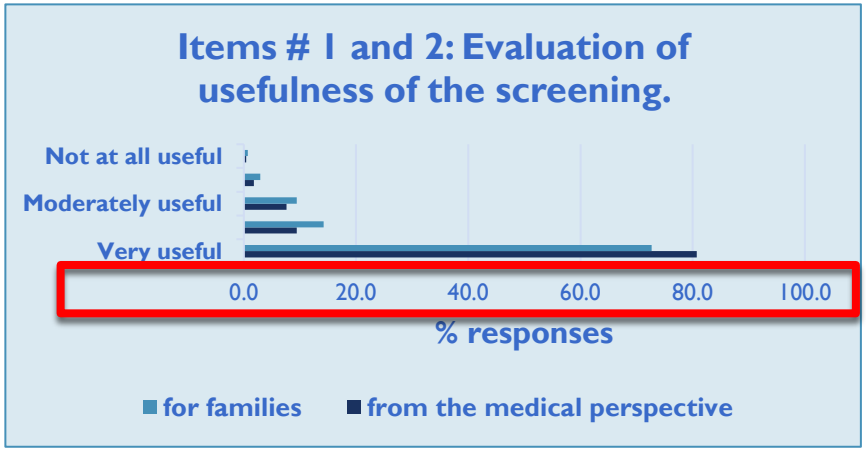
Feasibility and acceptability by physicians:

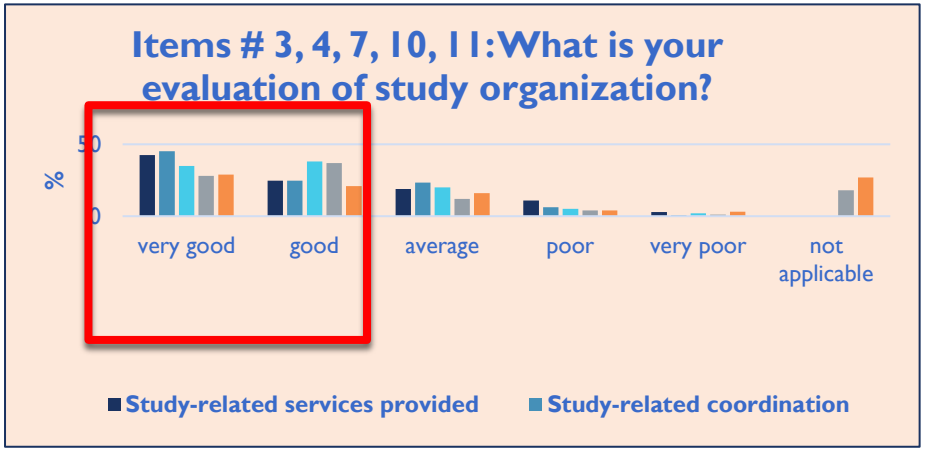
- feed-back questionnaires (from Fr1da, modified) from participating (N= 309) and non participating (N=60) Primary Care Pediatricians

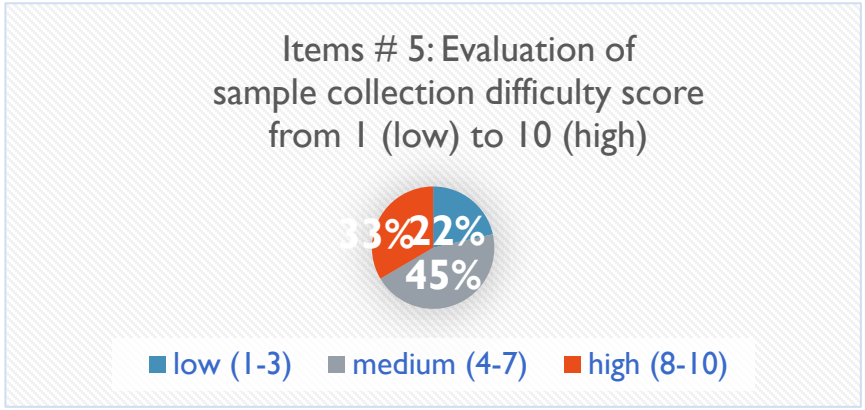
Impact on families:

- on line questionnaires (from EDENT1FI) on anxiety and depression (SAI-6, N=64; and HADS, N=49) and quality of life (EQ-5D-5L, N=46) at time of screening and 3 months later.

Evaluation of screening by Primary Care Pediatricians in D1Ce

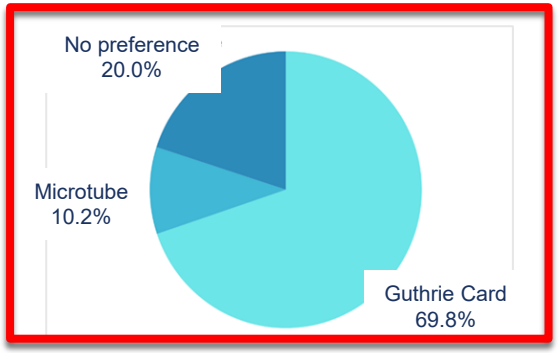






Pricci F et al. EASD poster 2025

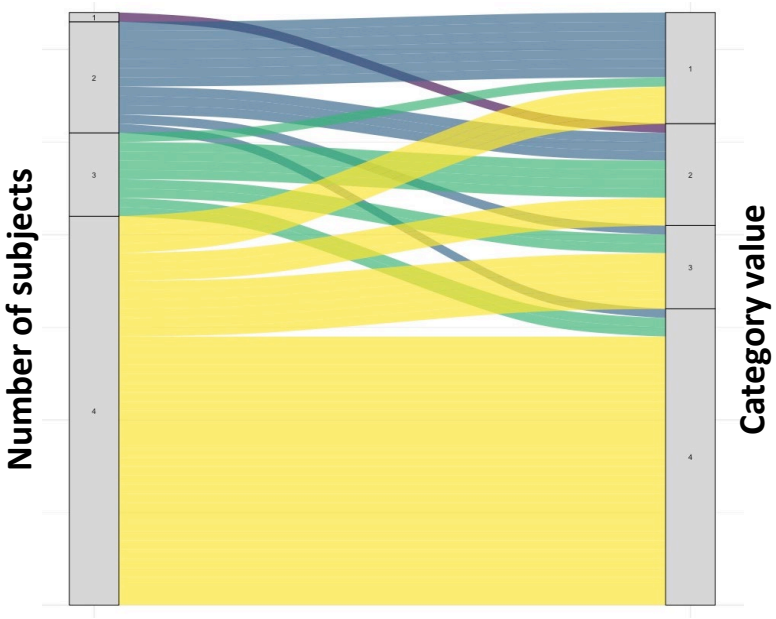
Item#6 Capillary sample collection preference



Questionnaires from the Fr1da Study (J Public Health 27:553-560, 2019), modified and adapted to D1Ce

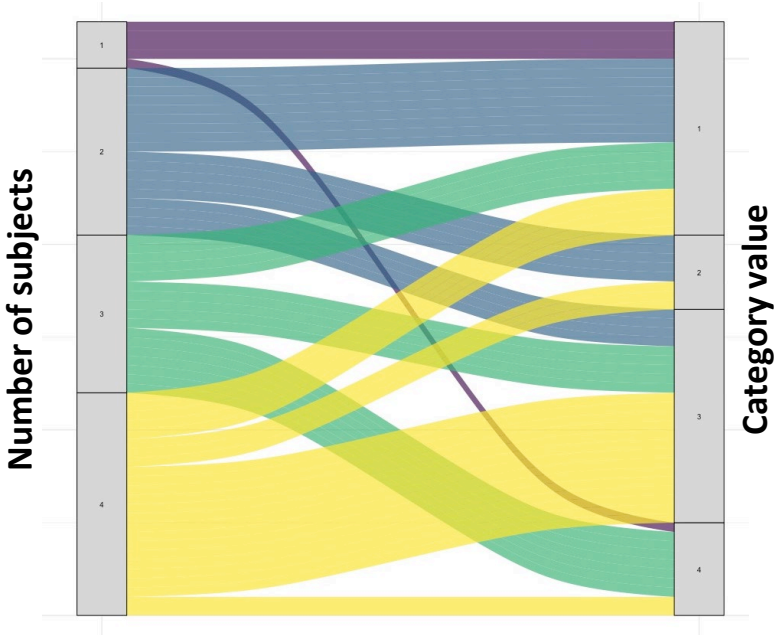
Questionnaire SAI-6 (EDENT1FI) – State Anxiety Inventory 6 items: When you think of your child's risk of developing diabetes do you feel? 6 items assessment on 4-point Likert scale: calm, worried, relaxed, tense, at ease, nervous. N=64 D1Ce Screen participating families

Calm



Baseline Median difference (T2-T1) = -0.5 **3 mos**
p=0.01

Nervous

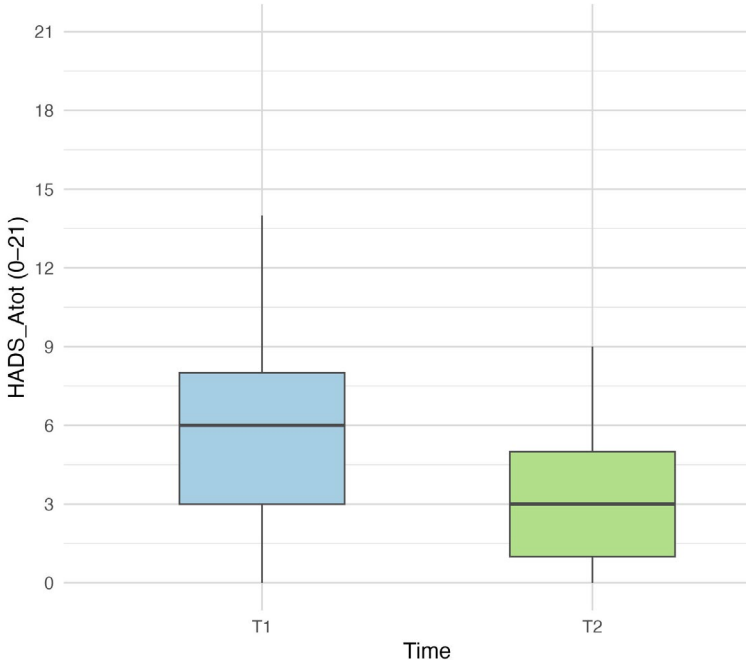


Baseline Median difference (T2-T1) = -1 **3 mos**
p=0.004

Questionnaire HADS (EDENT1FI) - Hospital Anxiety and Depression Scale

N=49 D1Ce Screen participating families (T1 baseline – T2 3 months)

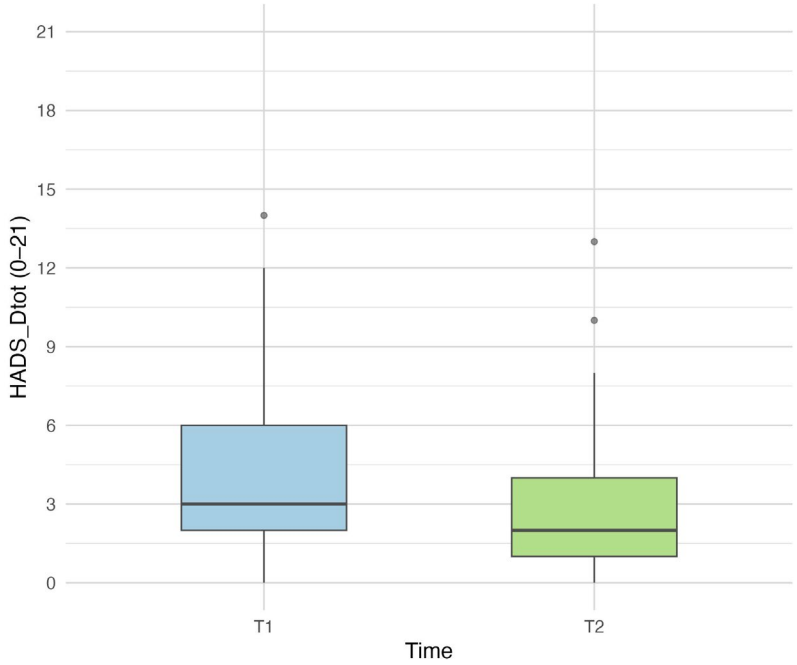
HADS - ANXIETY



Median difference (T2-T1) = -3

p<0.001

HADS - DEPRESSION



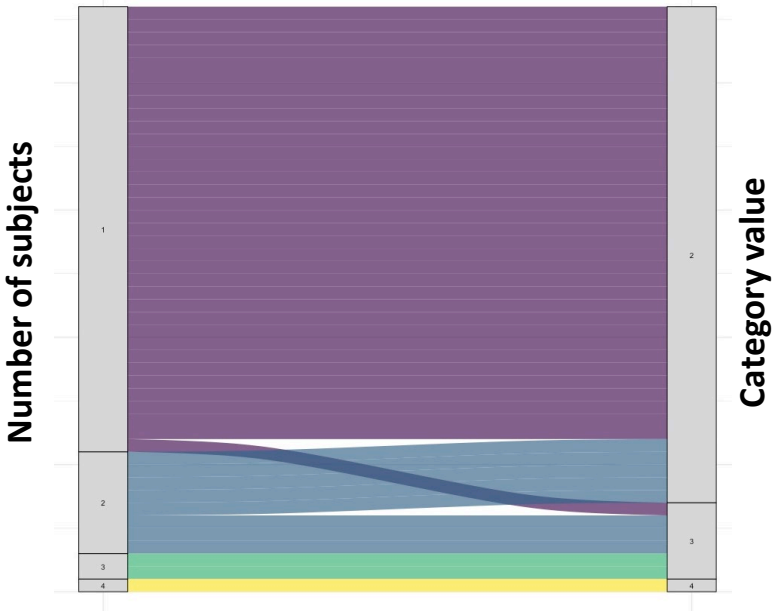
Median difference (T2-T1) = -1

p=0.01

Questionnaire EQ-5D-5L (EDENT1FI) – Assessment of quality of life self-reported as of 'today'

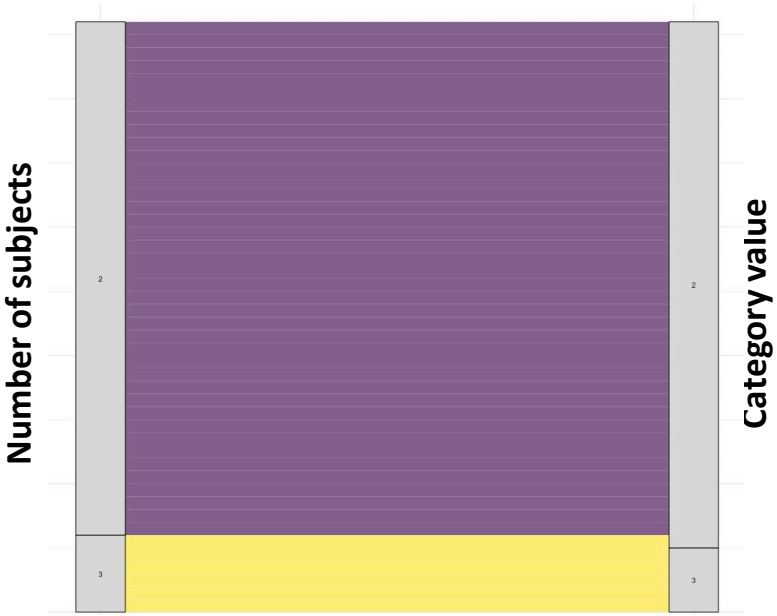
N=46 D1Ce Screen participating families (T1 baseline – T2 3 months)

ANXIETY-DEPRESSION



Baseline Median difference=0 p=0.5 **3 months**

PAIN-DISCONFORT



Baseline Median difference=0 p=1 **3 months**

National Law on type 1 diabetes and celiac disease screening in infants and adolescents in Italy: where are we now

Good

- Feasibility: the pilot D1Ce study in a sample of population from 4 Regions demonstrated feasibility and acceptability of screening in the general paediatric population. Pillars were: family paediatrician network, capillary blood sampling, centralized lab.
- Autoantibody prevalence: D1Ce showed a prevalence of autoantibodies similar to other Countries for type 1 diabetes (0.2%) and higher than expected for celiac disease (2.8%). Frequency of autoantibodies seems stable with ages in type 1 diabetes and decreasing in celiac.
- Genetics: very few transglutaminase antibodies outside HLA susceptibility types, especially when 2nd level confirmatory assays (ELISA + LIPS) are used
- Questionnaires on acceptability and impact: very good acceptability by participating paediatricians, overall reduction of anxiety and depression by families 3 months after screening

Pending

- The implementation of the Law nationwide requires the transfer of organizational and administrative responsibilities to the Italian Regional Health System. The specific implemental Ministerial Decree is still under revision. This is our main current political issue.

D1Ce Screen
Acknowledgments

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