

Celiachia: dalla epidemiologia allo screening

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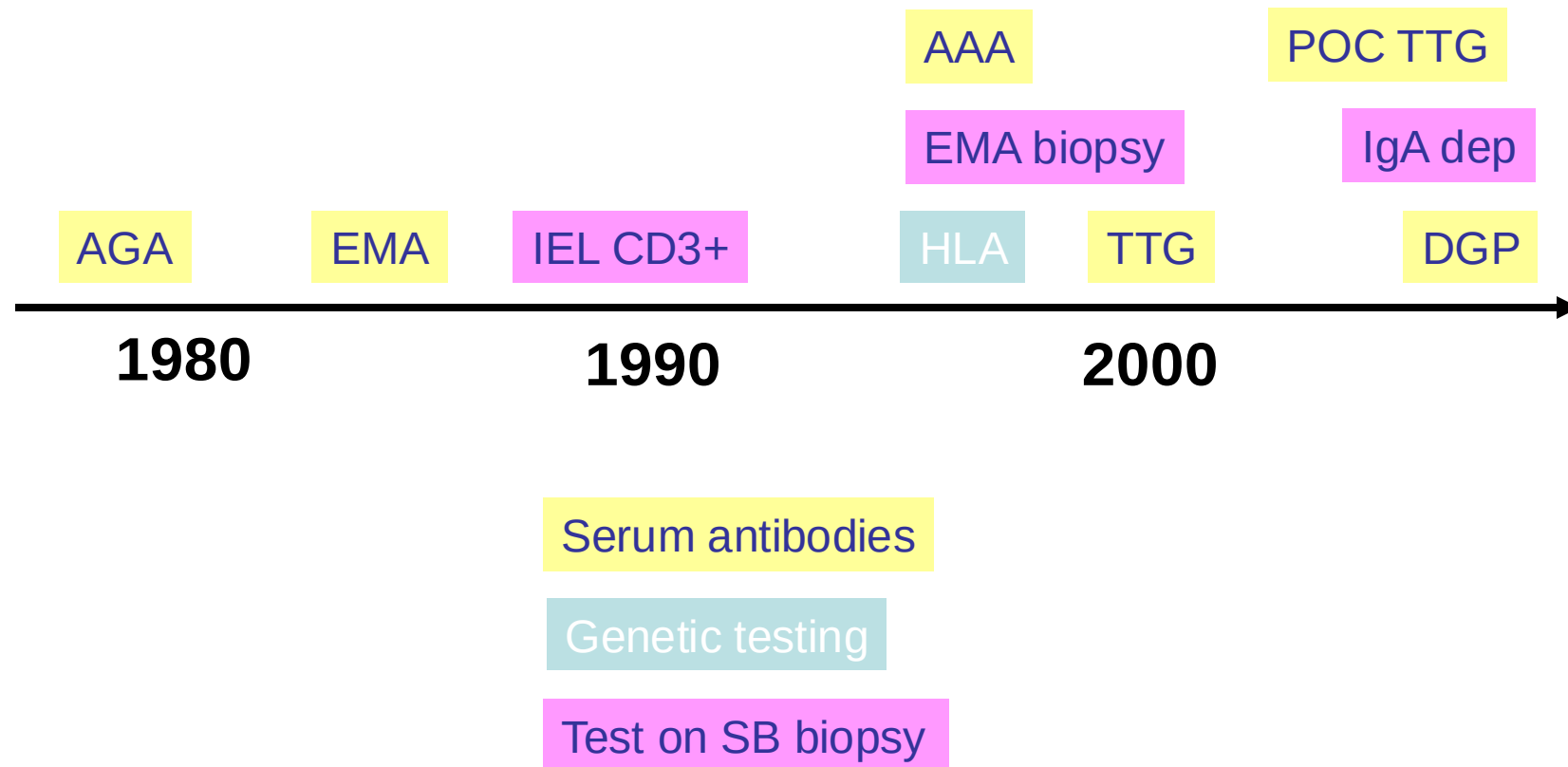
Epidemiologia della celiachia fino agli anni '80 del secolo scorso



Fig. 2.—Photograph of five cases of coeliac disease showing the general clinical feature

- Tipica s. da malassorbimento intestinale
- Malattia rara, tipica dell'età pediatrica
- Frequenza stimata in UK pari a 1:4000-8000
- + comune nell'Irlanda occidentale
- Fenotipo più comune: bambini bianchi e biondi

The «modern era” of CeD paralleled the development of powerful and simple diagnostic tools



Il primo screening della celiachia in Italia

THE LANCET

(MRD) in B lineage acute leukaemia using a simplified PCR strategy: evaluation of MRD rather than its detection is correlated with clinical outcome. *Br J Haematol* 1991; 78: 205-15.

28 Busch A, Yokota S, Hansen-Hagge TE, et al. Minimal residual disease in childhood acute lymphoblastic leukaemia: analysis of patients in continuous complete remission or with consecutive relapse. *Leukemia* 1992; 6: 282-88.

29 Foster MN, Howard CO, Oakley A. The significance of detection of

minimal residual disease in childhood acute lymphoblastic leukaemia.

Br J Haematol 1993; 85: 412-25.

30 Baskies A, Hahnen K, von Wiering ER, van Dongen JJM. Detection of minimal residual disease in childhood leukemia with the polymerase chain reaction. *N Engl J Med* 1991; 324: 772-73.

31 Wassenaar R, Vanzala M, Ito Y, et al. V_H gene rearrangement events can modify the immunoglobulin heavy chain during progression of B lineage acute lymphoblastic leukaemia. *Blood* 1992; 79: 223-28.

Coeliac disease in the year 2000: exploring the iceberg

C Catassi, I-M Raltch, E Fabiani, M Rossini, F Borolichia, F Candela, G V Coppa, P L Giorgi

Summary

It is now generally believed that subclinical coeliac disease is common in the general population. We have undertaken screening for this disorder in a school district in central Italy. Screening was divided into three levels: first, IgG and IgA anti-gluten antibody (AGA) assay on capillary blood obtained by finger prick; second, AGA plus IgA anti-endomysium antibody (AEA) test and measurement of serum immunoglobulins in venous blood; and third, intestinal biopsy.

3351 students (66% of the eligible population) aged 11-15 years attended first-level screening. 71 (2%) were recalled because of AGA positivity; 18 of these satisfied second-level criteria and underwent intestinal biopsy. Coeliac disease was diagnosed in 11 subjects, most of whom had no serious symptoms. Selective IgA deficiency was found in 4 subjects, 1 of whom also had coeliac disease. The prevalence of subclinical coeliac disease in the study group was 3.28 per 1000.

Coeliac disease screening is feasible and involves only slight discomfort to the general population. Such screening can detect large numbers of cases of coeliac disease, which can be treated with a gluten-free diet. Many subclinical cases of coeliac disease would not be detected by screening only a selected group of at-risk patients.

Lancet 1994; **343**: 200-03

See Commentary page 288

Introduction

It has become apparent over the past few years that clinically manifest cases of coeliac disease represent only a small proportion of the total population with this disorder. There are many patients who are free of major symptoms but who have typical damage to the jejunal mucosa on intestinal biopsy (subclinical or "silent" coeliac disease).¹ If such patients are not treated, they risk complications such as anaemia, infertility, and malignant disorders; they may die prematurely.²⁻⁴ Early dietary management of gluten enteropathy seems to protect coeliac disease patients from the development of malignant disorders.⁵

The serum anti-gluten antibody (AGA) assay is a widespread and simple screening test for coeliac disease and is especially informative when AGA of both IgG and IgA classes is measured.⁶ We undertook a pilot study on subclinical coeliac disease screening in a general school population; the first step was IgG-AGA and IgA-AGA assays on blood obtained from a finger prick. Our aims were to characterise and quantify the prevalence of subclinical coeliac disease and to assess the feasibility of such screening in the general population.

Patients and methods

Subjects

Our project was carried out in the school district of Pesaro-Urbino in central Italy, which has an area of 2893 km² and a population of 334 842, who live in scattered towns and villages. The immigration rate here has been low for the past few decades and the standard of living is medium-high on the national scale.

Between March, 1992, and April, 1993, 5061 students aged 11-15 years attending compulsory secondary schools were invited to take part in coeliac disease screening. There were 3 cases of known (biopsy-proven) coeliac disease in this population. The 3 patients were on gluten-free diet and did not take part in the screening. Informed consent was given by the families of 3351 students (1652 boys, 1699 girls), 68% of the eligible population. The study group had a mean age of 12.8 (SD 1.0, range 11-15) years.

Design

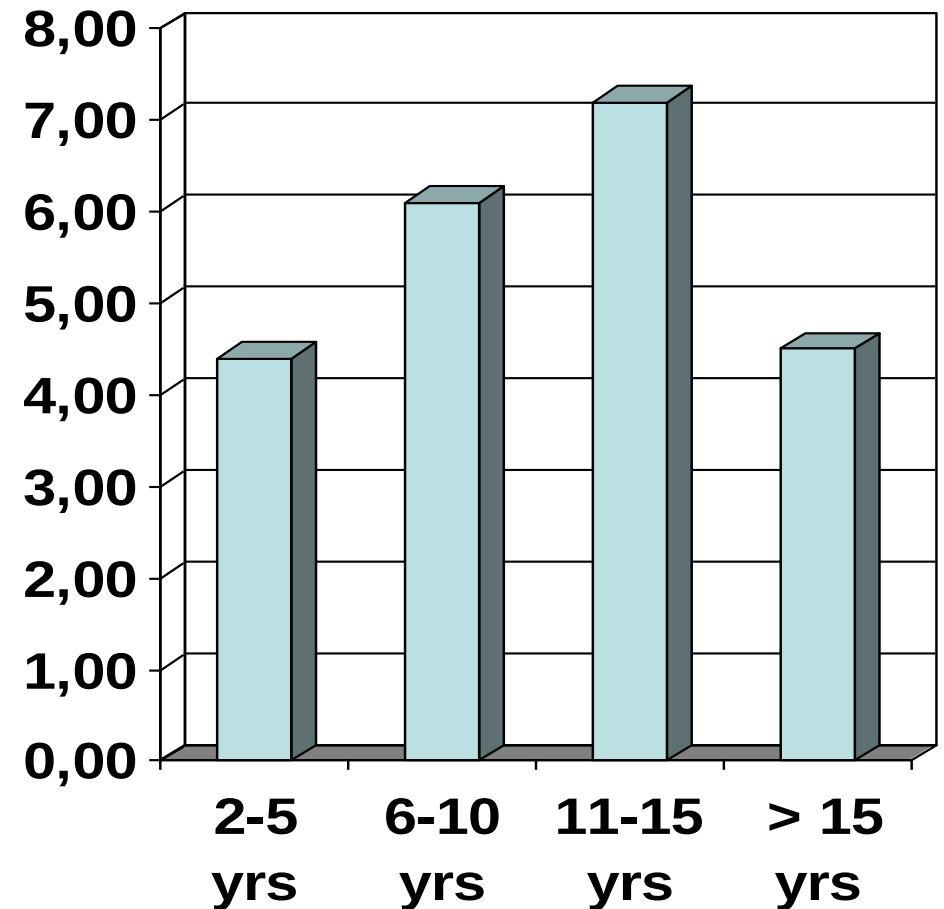
Samples of whole blood (at least 100 μ L) were taken from a finger prick of each subject during school time (the subjects were not fasting). After centrifugation, serum samples were stored at -20°C. Subjects with normal IgG-AGA and IgA-AGA values were taken not to have coeliac disease; those with either or both classes of AGA higher than the cut-off were recalled.

At the second-level investigation, venous blood was sampled during school time, after overnight fasting. AGA assays were repeated and we also measured IgA anti-endomysium antibody

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CeD prevalence (%) in 989 unselected Saharawi children



Perspectives on Coeliac Disease
Volume II



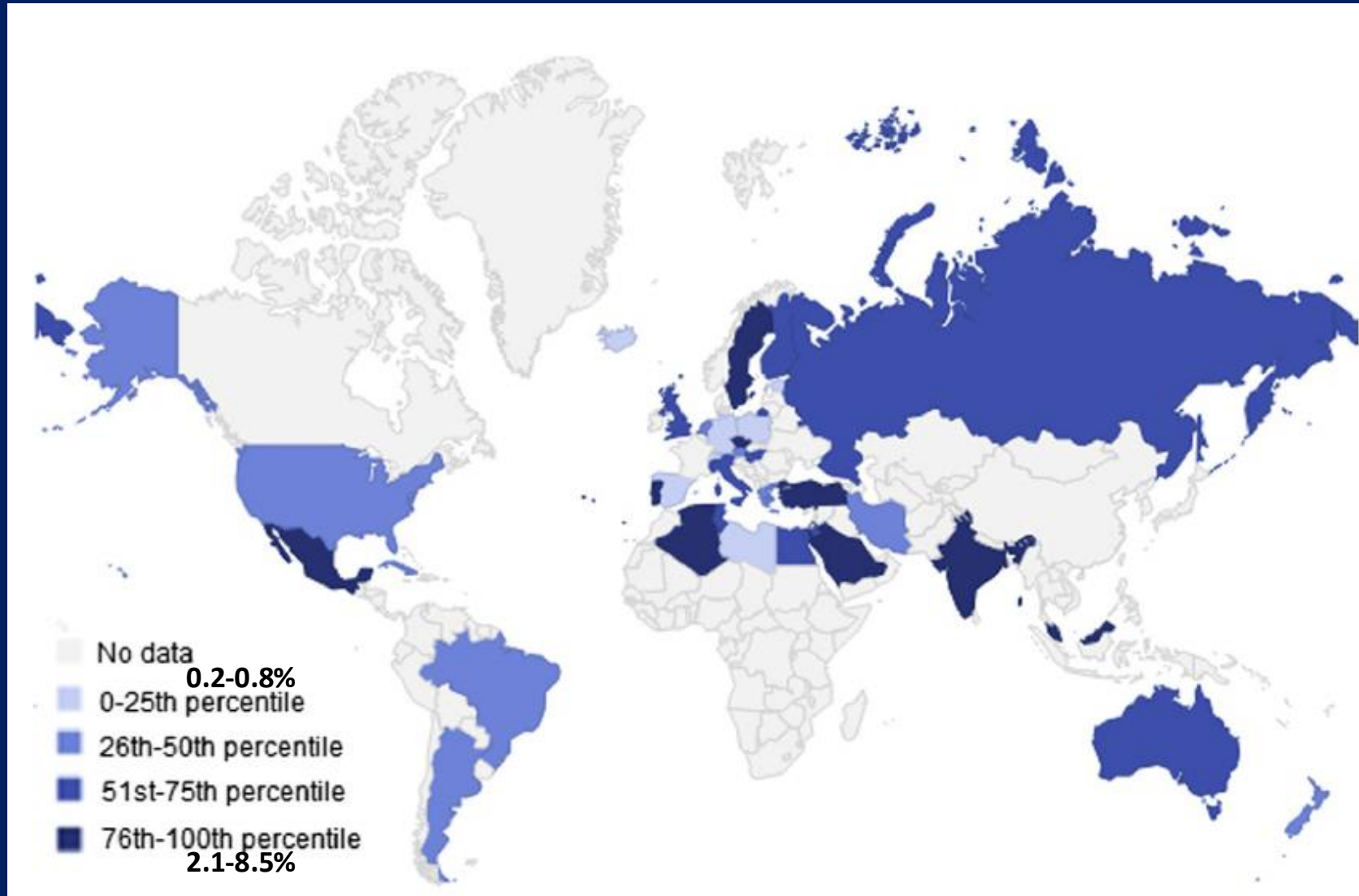
**THE GLOBAL
VILLAGE
OF COELIAC DISEASE**

EDITED BY

CARLO CATASSI
ALESSIO FASANO
GINO ROBERTO CORAZZA

AIC Press

Prevalence of CeD autoimmunity worldwide



Screening CeD in Italia: i dati più recenti

THE LANCET

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30. Baskies A, Baskies K, van Wiering ER, van Dongen JJM. Detection of minimal residual disease in childhood leukaemia with the polymerase chain reaction. *N Engl J Med* 1991; 324: 772-73.
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Alimentary Tract

Prevalence and detection rate of coeliac disease in Italy: Results of a SIGENP multicenter screening in school-age children

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ABSTRACT

Background: Coeliac disease is a common lifelong disorder. Recent studies indicate that the number of clinically detected cases has increased over the last decades, however little is known about changes in the prevalence and the detection rate of coeliac disease.

Aim: To evaluate the current prevalence and detection rate of coeliac disease in Italy by a multicenter, mass screening study on a large sample of school-age children.

Methods: children aged 5-11 years were screened at school by HLA-DQ2 and -DQ8 determination on a drop of blood in six Italian cities; total serum IgA and IgA anti-transglutaminase were determined in children showing HLA-DQ2 and/or -DQ8 positivity. Diagnosis of coeliac disease was confirmed according to the European guidelines.

Results: 5094 children were eligible, 4438 participated and 1873 showed predisposing haplotypes (42.2%, 95% CI 40.7-43.7). The overall prevalence of coeliac disease was 1.65% (95% CI 1.48-1.82). Only 40% of coeliac children had been diagnosed prior to the school screening. Symptoms evoking coeliac disease were as common in coeliac children as in controls.

Conclusion: In this multicenter study the prevalence of coeliac disease in school-age Italian children was one of the highest in the world. Determination of HLA predisposing genotypes is an easy and fast first-level screening test for coeliac disease. Without a mass screening strategy, 60% of coeliac patients remain currently undiagnosed in Italy.

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1. Introduction

Coeliac disease (CeD) is a chronic immune-mediated enteropathy triggered by gluten ingestion in genetically susceptible individuals [1]. Well identified haplotypes in the human leukocyte antigen (HLA) class II region (DQ2 [DQA*0501-DQB*0201] and DQ8 [DQA*0301-DQB*0302]) confer a large part of the genetic suscep-

Abbreviations: CeD, coeliac disease.

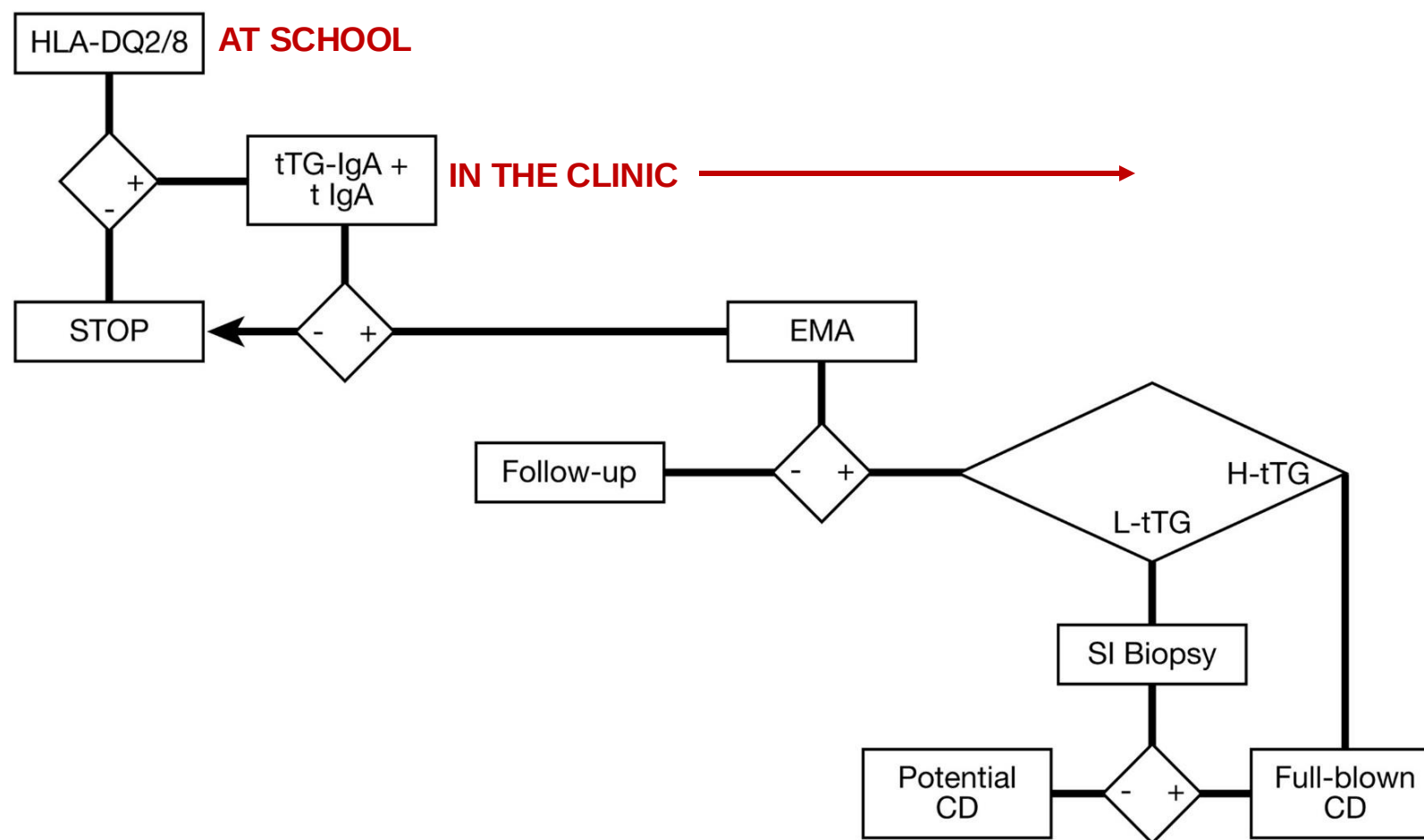
* Corresponding author at: Division of Pediatrics and Center for Coeliac Research, DSD Department, Marche Polytechnic University, via F. Corridoni 60123 Ancona, Italy.

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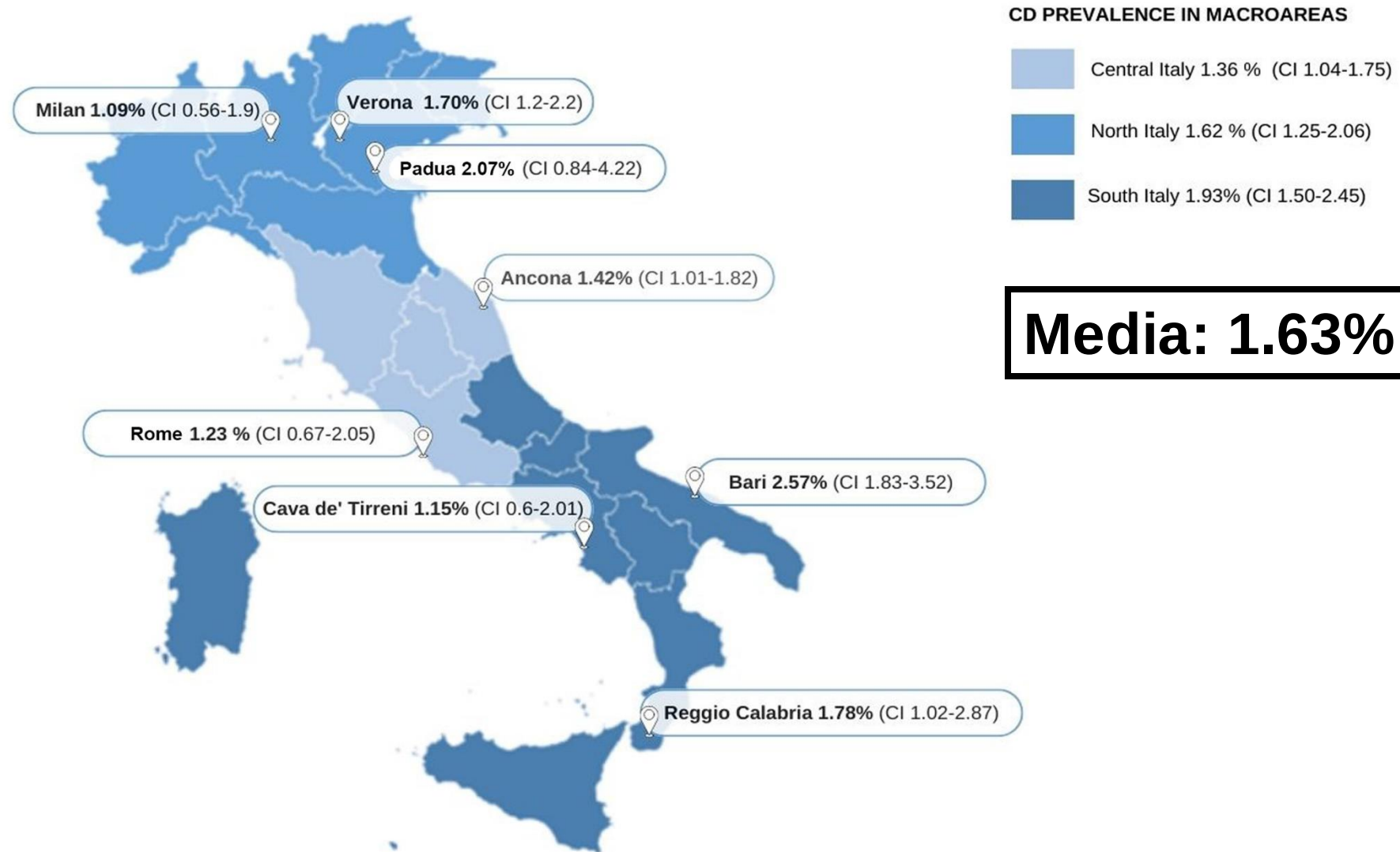
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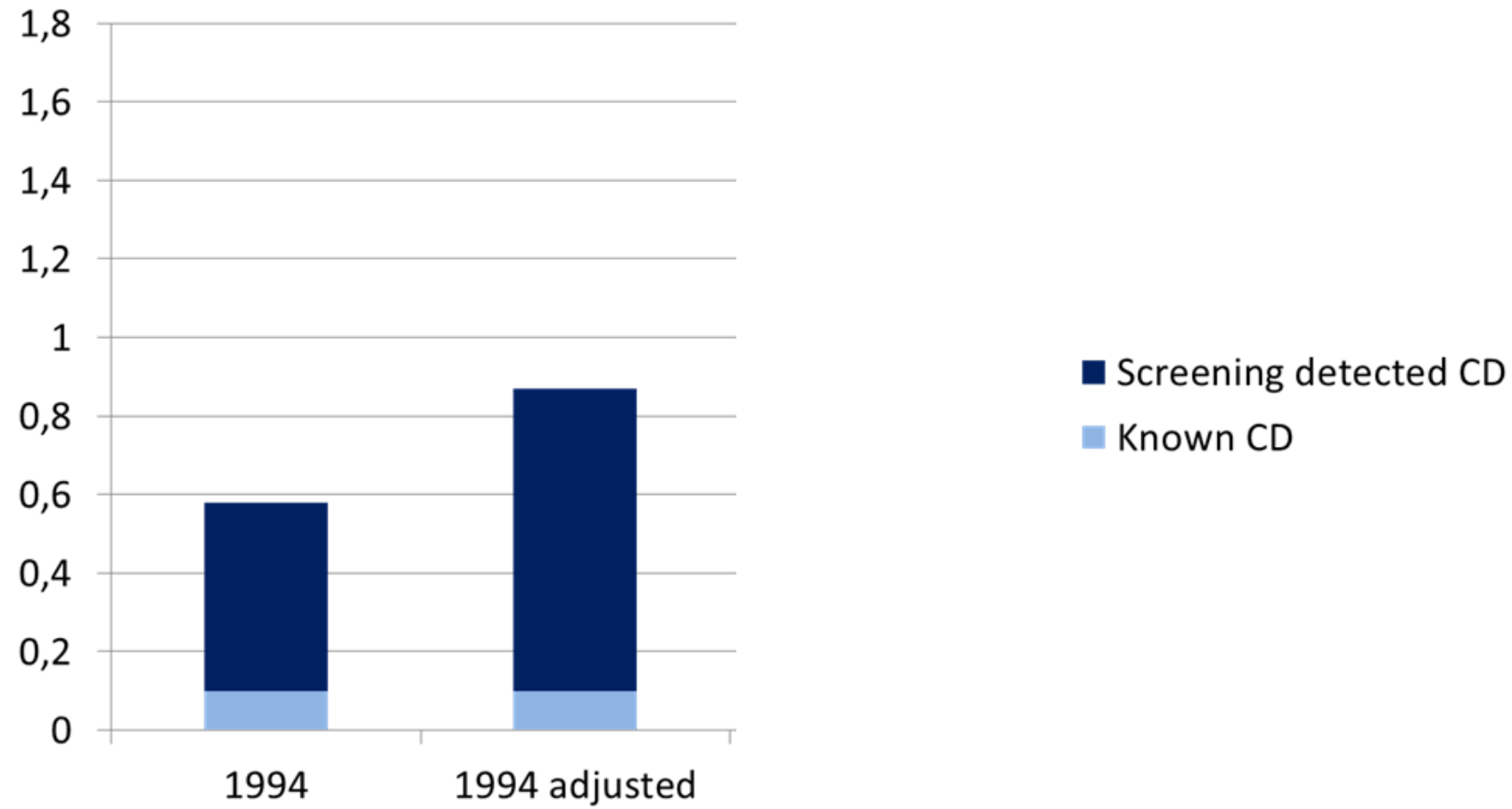
Multicenter Italian screening of celiac disease in school-age children (n=9006)



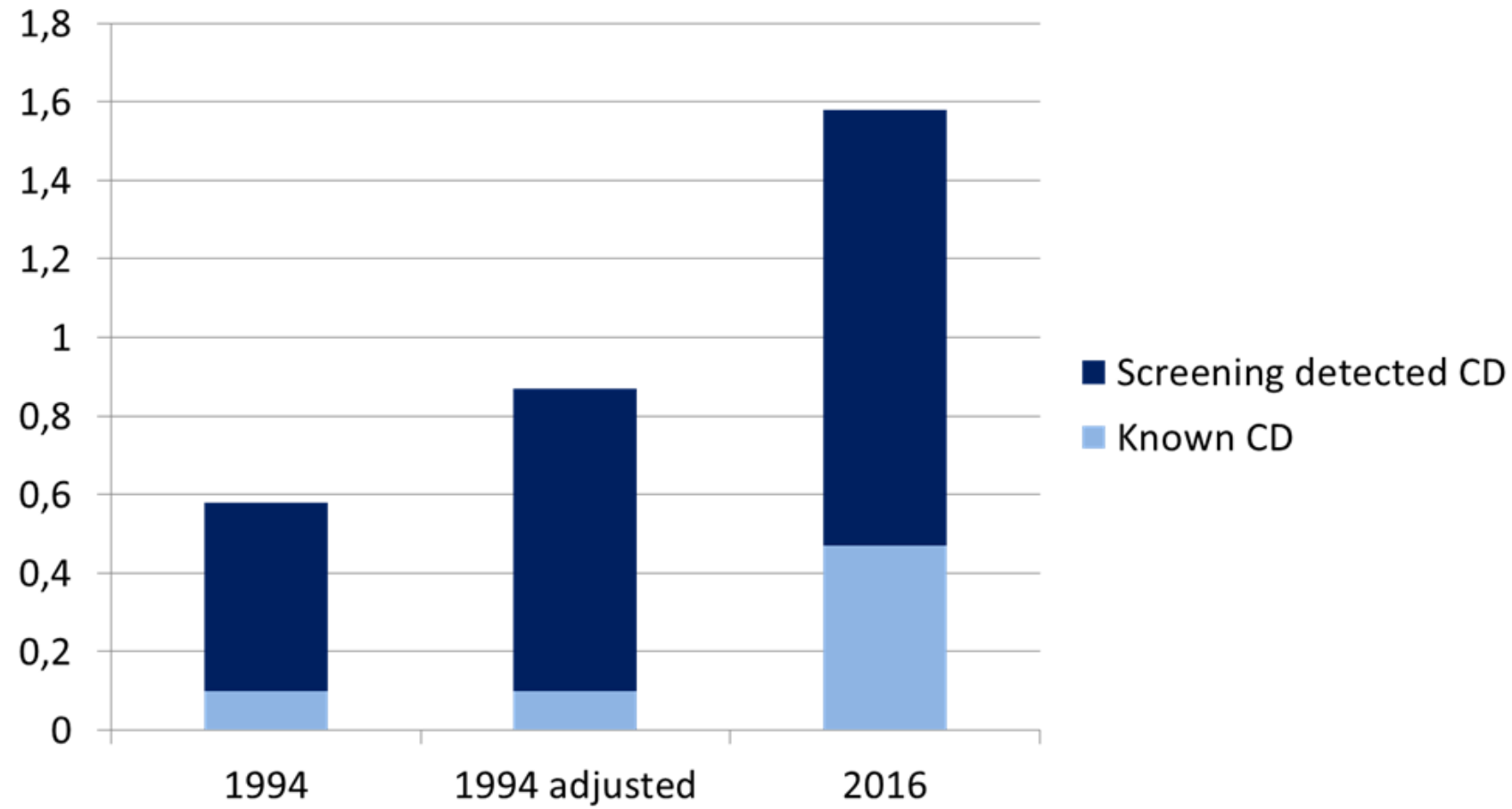
Prevalence of CeD in Italian school children



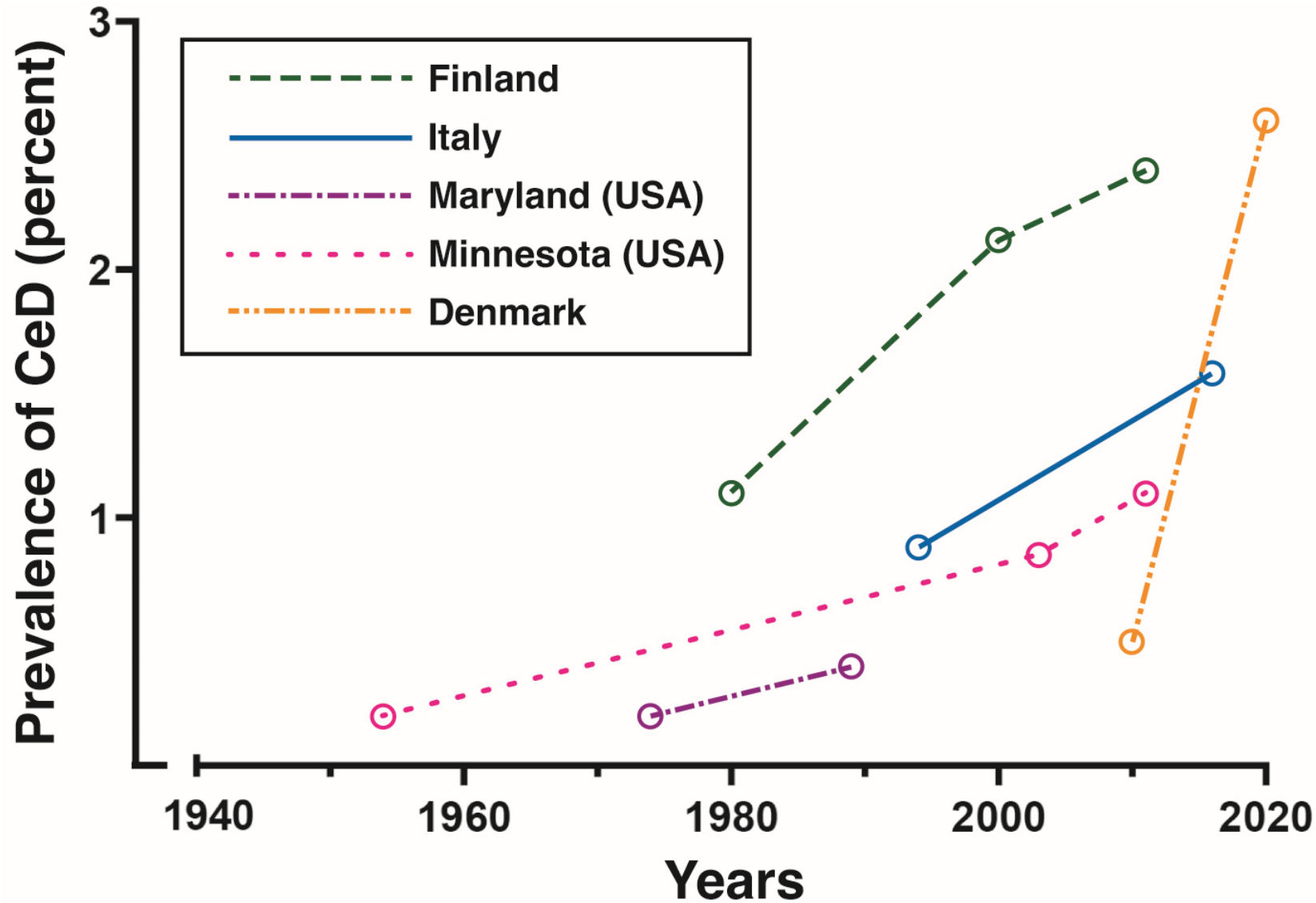
Increasing CeD prevalence in Italy over time



Increasing CeD prevalence in Italy over time

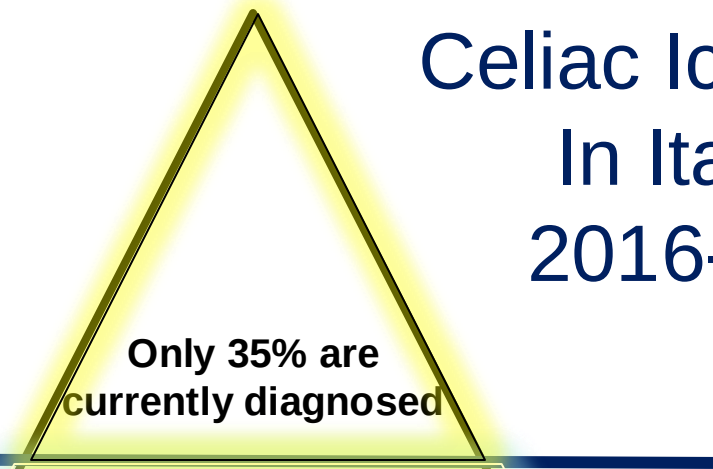


Increasing prevalence of CeD in many countries





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Celiac Iceberg In Italy 2016-20

Catassi G et al, Am J Gastroenterol 2023



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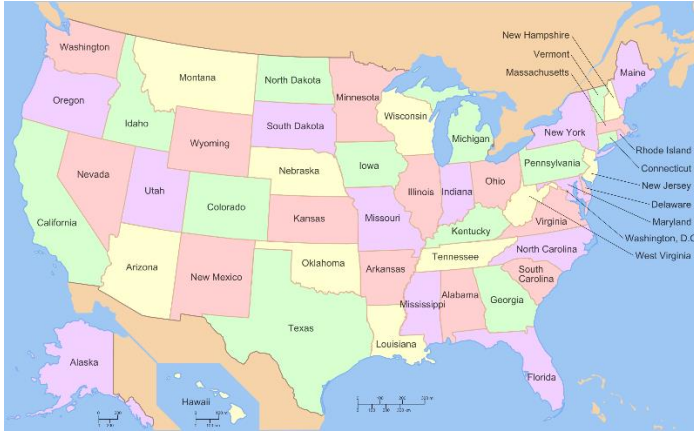
Celiac Iceberg In Italy 2016-20

**Only 35% are
currently diagnosed**

**The remaining 65% can
be diagnosed only by
mass screening. If not
recognized they remain
exposed to the risk of
complications**

Catassi G et al, Am J Gastroenterol 2023

The prevalence of undiagnosed CeD is high



Minnesota, USA

1.1% in 30,425 adults

Choung RS et al,

Gastroenterology 2017

Colorado, USA

1.5% confirmed CeD
autoimmunity in 9,973
children + **0.57%** known
CeD

*Stahl M et al, Am J Gastroenterol
2021*



Tromsø, Norway

1.1% in 12,981 adults

+ 0.37% known CeD

Kvamme JM et al,

Sci Rep 2022



Multicenter, Italy

0.95% in 9,008 children

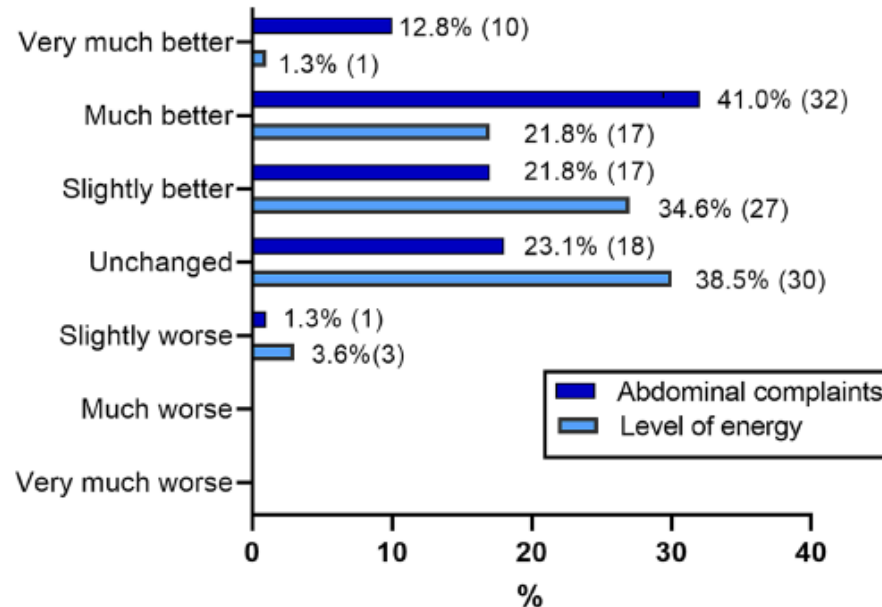
+ 0.63% known CeD

Lionetti E et al,

Dig Liver Dis 2023

Undiagnosed CeD is not silent disease

Population-based screening for CeD reveals that the majority of patients are undiagnosed and improve on a GFD



Kvamme JM et al, Sci Rep 2022

Long-term risks associated with undiagnosed CeD

Systemic consequence	Evidence
Impaired bone health and increased risk for fractures	Confirmed
Non-Hodgkin lymphoma and intestinal adenocarcinoma	Confirmed
Neurological complaints	Probable
Psychiatric symptoms	Probable
Impaired reproductive health	Probable
Decreased cardiovascular health	Controversial

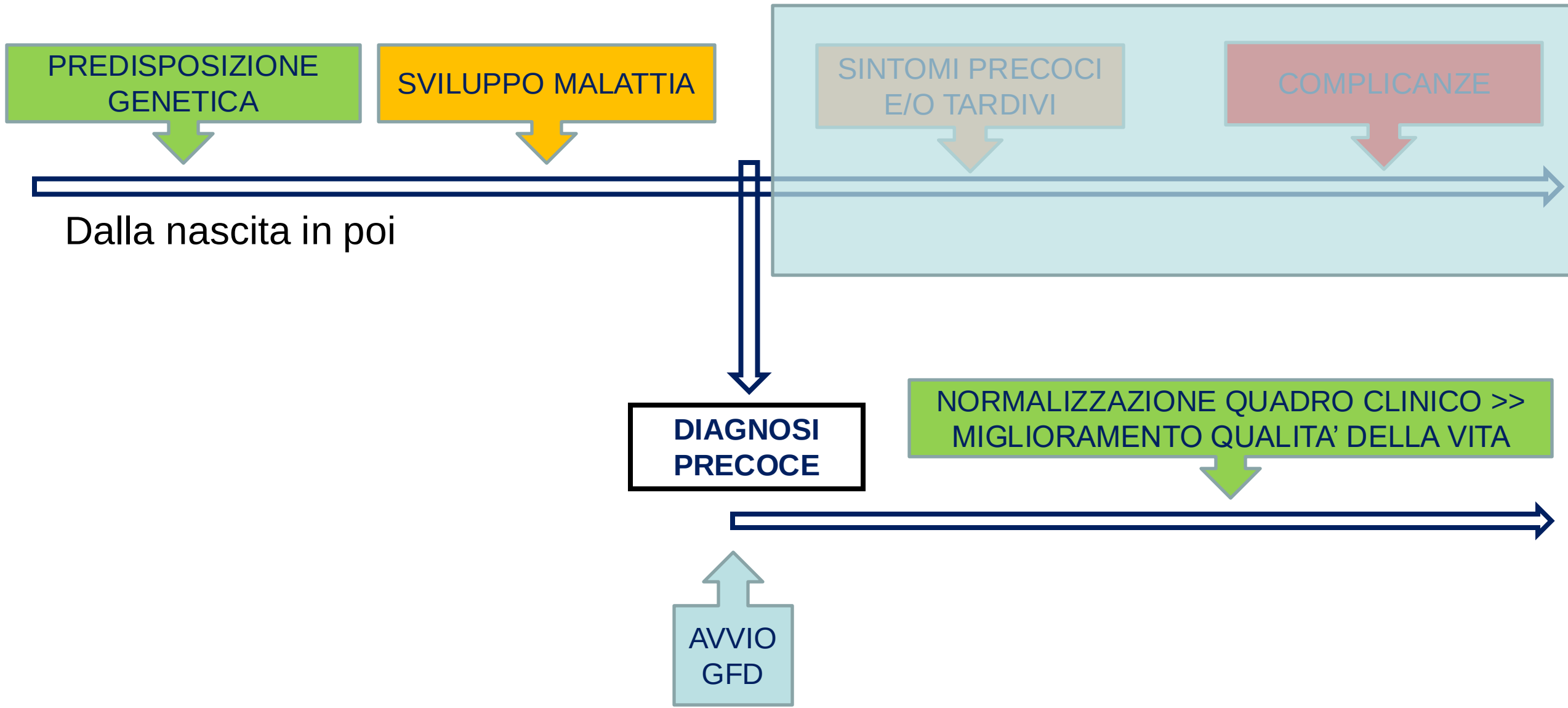
Laurikka P et al, Alim Pharm Ther 2022

La celiachia soddisfa I criteri delle malattie per le quali è opportuno lo screening

1. The condition sought should be an important health problem ✓
2. The natural history of the condition, including development from latent to declared disease, should be adequately understood ✓
3. There should be a recognizable latent or early symptomatic stage ✓
4. There should be a suitable test or examination ✓
5. The test should be acceptable to the population ✓
6. There should be an agreed policy on whom to treat as patients ✓
7. There should be an accepted treatment for patients with recognized disease ✓
8. Facilities for diagnosis and treatment should be available ✓
9. The cost of case detection (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole ✓
10. Case detection should be a continuing process and not a “once and for all” project ✓

Wilson and Jungner, 1968

Il significato dello screening: modificare la storia naturale dei tanti casi di celiachia che sfuggono alla diagnosi



Prima legge al mondo sullo screening pediatrico del diabete tipo 1 e celiachia. Roma, 19 Maggio 2023

Primo screening per m. infettive praticato agli emigranti Italiani in arrivo Ellis Island (NYC), 1882



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

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



Lancet Diabetes Endocrinol 2023

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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>

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Screening of celiac disease in Italy

- Celiac disease is a very common disorder affecting 1-2% of the general pediatric population in Italy
- The prevalence of undetected CeD is still higher than 50%
- Early diagnosis of CeD prevents immediate morbidity and long-term complications
- The present/future of CeD detection: moving from case-finding to mass screening (coupled with T1D screening)

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Pricci (D1Ce project, Istituto Superiore di Sanità, Roma)

GRAZIE DELL'ATTENZIONE!