Diagnostic Yield of 2 Strategies for Adult Celiac Disease Identification in Primary Care

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Goals: To compare the diagnostic yield and cost-consequences of 2 strategies, screening regardless of symptoms versus case finding (CF), using a point-of-care test (POCT), for the detection of celiac disease (CD) in primary care, to bridge the diagnostic gap of CD in adults.

Materials and Methods: All subjects under 75 years of age who consecutively went to their general practitioners' offices were offered POCT for anti-transglutaminase immunoglobulin A antibodies. The POCT was performed on all subjects who agreed, and then a systematic search for symptoms or conditions associated with higher risk for CD was performed, immediately after the test but before knowing the test results. The 2 resulting groups were: (a) POCT positive and (b) symptomatic subject at CF. Subjects were defined as symptomatic at CF in the presence of 1 or more symptoms. All POCT-positive or symptomatic subjects at CF were referred to the CD Centers for confirmation of CD. Data on resource consumption were gathered from patients' charts. Cost of examinations, and diagnostic and laboratory tests were estimated with regional outpatient tariffs (Sicily), and a price of €2.5 was used for each POCT.

Results: Of a total of 2197 subjects who agreed to participate in the study, 36 (1.6%) and 671 (30.5%) were POCT positive and symptomatic at CF, respectively. The yield from the screening and CF was 5 new celiac patients. The total cost and mean cost for each new CD case were €7497.35 and €1499.47 for the POCT screening strategy, and €9855.14 and €1971.03 for the CF strategy, respectively. Assuming consecutive use of both strategies, performing POCT only in symptomatic subjects at CF, the calculated yield would be 4 new diagnoses with a total cost of €2345.84 and a mean cost of €586.46 for each newly diagnosed patient. Only 1 patient was celiac despite a negative POCT.

Conclusions: Testing symptomatic subjects at CF only by POCT seems the most cost-effective strategy to bridge the diagnostic gap of adult CD in primary care.

Key Words: celiac disease, primary care, point-of-care test, screening, case finding

(*J Clin Gastroenterol* 2017;00:000–000)

Celiac disease (CD) is an autoimmune condition resulting from an abnormal reaction to dietary gluten leading to small bowel villous atrophy. It is a lifelong disorder presenting with a variety of gastrointestinal and extraintestinal symptoms[1–3] and affects approximately 1% of the population worldwide.[4–8] Owing to the variable manifestations of CD, clinical suspicion is not obvious, and, as a consequence, this disorder is underdiagnosed, as revealed by screening studies.[3,9] Screen-detected patients, with clinically silent disease but manifest small intestinal mucosal lesions, seem to benefit from a gluten-free diet;[10,11] therefore, it has been claimed that CD detected by screening is not clinically silent but simply unrecognized.[12]

Many asymptomatic patients are at risk of developing a number of gluten exposure-related complications, such as micronutrient malabsorption, that are associated with osteoporosis and iron-deficiency anemia, autoimmune disorders,[13,14] and increased risk for non-Hodgkin lymphoma.[15] As such, the importance of early recognition of CD has been underlined.

Received for publication April 30, 2017; accepted October 9, 2017.

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Supported by Assessorato della Salute Regione Siciliana—Piano Sanitario Nazionale (PSN) 2012. The Sicilian Celiac Disease Study Group: Catania—General Practitioners: Maria Lombardo, Salvatore Piro, Antonino Sidoti. Messina—General Practitioners: Umberto Alecci, Andrea Alvaro, Angelo Crescenti, Francesco Crescenti, Luciana Di Geronimo, Santi Inferrera, Luigi Lipari, Sebastiano Marino, Isabella Palmieri, Giuseppe Saija, Gaetano Scarso. Sciacca—General Practitioners: Antonio Curreri, Giuseppa Saieva, Angelica Guida, Antonino La Rocca, Antonino Randazzo, Vito Sclafani, Angela Perrone. Vittoria—General Practitioners: Anna Maria Cucuzzella, Giovanni Dezio, Giuseppe Ferro, Massimo Giarretto, Giorgia Virgadaula, Roberto Zelante. University of Messina, Celiac Disease Regional Center Residents: Giuliana Del Campo, Cristina Mignosa, Simona Nigro, Enzo Pintabona, Simona Santucci, Jessica Trombatore, Simona Valenti.

The authors declare that they have nothing to disclose.

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DOI: 10.1097/MCG.0000000000000962

Although population screening has been suggested as a possible strategy for detecting undiagnosed CD, many doubts remain on the usefulness and cost-effectiveness of such a strategy, primarily because of low compliance to a gluten-free diet in asymptomatic cases and the difficulty of defining the best age to screen to reduce false-positive and false-negative results.[16,17] An alternative approach is the case-finding (CF) strategy in both adult and pediatric populations. This approach relies on an active role played by primary care physicians in selecting the individuals to be tested for CD, in the presence of conditions known to be associated with CD.[18]

One method of increasing detection rates would be to introduce a quick screening test in the form of a finger-prick blood test in subjects suspected of having CD. Rapid methods of antibody detection at the point-of-care using blood from finger pricks[19] have recently become available, and point-of-care detection of immunoglobulin (Ig) A antibodies in CD has already been validated for clinical CFs in gastroenterology settings.[20,21] An easy to use on-site whole blood self-TG2-based fingertip point-of-care test (POCT) has been shown to be effective in CD CF in school children, at a population-based level and in children with type 1 diabetes.[22,23]

At present, there are no comparative studies of diagnostic accuracy of the CF approach versus screening in the same population, utilizing POCT, to determine which is the costliest strategy.

The main aim of this study was to compare diagnostic yield of a POCT-based screening for CD versus a CF strategy in the same general population not yet diagnosed as having CD, in a primary care setting, using conventional serology and histology as gold standard. In addition, the study evaluated the cost-consequences of the different screening strategies according to resource consumption and to the perspective of the Sicilian Regional Healthcare System.

MATERIALS AND METHODS

Study Design

Observational cross-sectional study.

Setting

Seven Sicilian regional referral centers for diagnosis and management of CD and a regional research network of 34 general practitioners (GP) with previous experience in clinical research.

Study Population

A total of 45,921 subjects throughout Sicily in the care of 34 GPs.

Data Collection

After thorough practical training, each participating GP proposed the administration of a POCT for CD diagnosis to all subjects below 18 and above 75 years of age who consecutively accessed their office from March to April 2014, until they had each enrolled 70 subjects. POCTs were administered to the subjects only after receiving oral informed consent in accordance with recommendations from the local ethics committee at the University Hospital of Messina, which had approved the study.

Exclusion Criteria

Age below 18 years, subjects already diagnosed with CD, subjects tested for CD in the last 12 months, patients with fever or under treatment with immunosuppressive or corticosteroids drugs.

POCT

The Biocard Celiac Test, AniBiotech, Vantaa, Finland, was selected as the point-of-care biomarker test for CD CF.[24–27]

This rapid whole blood self-TG2-based IgA-class fingertip test uses the patient's own endogenous TG2 found in the erythrocytes of a whole blood sample. When the fingertip blood is hemolyzed, the liberated TG2 forms a complex with circulating autoantibodies, if present in the same sample. Blood erythrocyte self-TG2-autoantibody complexes are captured from the hemolyzed sample by TG2-binding proteins onto a solid phase and the presence of autoantibodies is measured by labeled antihuman IgA.[20] The results of the POCT were evaluated visually on site after 5 minutes, but no later than 10 minutes, according to the manufacturer's recommendations. A positive test result shows 2 lines on the strip within 10 minutes of collection of a drop of blood from the finger, while only 1 line appears if the test is negative. If there is no line, IgA deficiency should be suspected.

CF

Relevant demographic and clinical data of the persons enrolled in the study were collected using an electronic case report form. In particular, information on signs, symptoms, and conditions associated with higher risk for CD was collected according to an already utilized, published questionnaire[18] (Table 1), and, if present, subjects were defined as symptomatic at CF. These clinical data were recorded before performing the POCT; consequently, both patients and GPs were unaware of POCT results.

Following the study design, all subjects with a positive or no line POCT, as well as those with a negative POCT but symptomatic at CF, were offered further investigations at the referral centers. All centralized laboratory serologic determinations were made in blinded manner without knowledge of the on-site fingertip POCT results.

TABLE 1. List of Signs, Symptoms, and Conditions Associated With Higher Risk for Celiac Disease

Irritable bowel syndrome
Dyspepsia (requiring endoscopy)
Hashimoto thyroiditis, type 1 diabetes or other autoimmune endocrinopathies
Anemia
Family history of celiac disease
Stomatitis (> 3 episodes/y)
Dermatitis herpetiformis, vitiligo, alopecia, or psoriasis
Weight loss associated with gastrointestinal symptoms
Short stature
Chronic urticaria
Tooth enamel alterations
Infertility or repeated miscarriages (2 or more)
Rheumatic disease
Hypertransaminasemia sine causa
Epilepsy/ataxia

Adapted from Berti et al.[18] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

CD Diagnosis

All POCT positive and no line subjects, and patients symptomatic at CF were referred to one of the Regional Referral Centers of the corresponding enrollment area for a routine CD diagnostic work-up. This was based on detection of IgA anti-transglutaminase antibodies (tTG IgA) for POCT-positive subjects and on IgG deamidated gliadin peptide antibodies (DGP IgG) plus serum total IgA for subjects with no-line POCT who were suspected of having IgA deficiency. For all subjects with positive serology, a histologic examination of 4 endoscopic duodenal biopsies, including a bulb sample, taken by upper gastrointestinal endoscopy, was carried out.

The biopsy specimens were fixed in formalin, embedded in paraffin, cut, stained with hematoxylin-eosin and scored by pathologists according to the Marsh-Oberhuber classification.[28,29] According to current criteria,[30] patients were diagnosed as having CD if they had a positive serum tTG IgA test result (or DGP IgG for "no line POCT") that was associated with a typical celiac enteropathy at the small bowel biopsy (partial or subtotal villous atrophy with an increase in the intraepithelial lymphocyte count).

Serum tTG IgA were determined using an enzyme-linked immunosorbent assay. DGP IgG were assayed with a commercial kit according to manufacturer's instructions and cut-off.

To define GP and patient compliance to the study we evaluated the performed POCT and completed CF reports by the number of tests assigned. Moreover, to assess confidence in POCT and awareness of CD, the percentage of positive POCT and symptomatic subjects at CF sent to the reference center, respectively, was also arbitrarily assessed.

Statistical Analysis

For sample size calculation, we considered the prevalence of CD in CF, 1:1073 (0.1%), about10 times lower than the prevalence expected in the screening, that is 1%, as primary outcome. Thus, assuming a population prevalence of 0.1%, according to a previous study,[18] an expected prevalence in the study of about 0.35%, a statistical power of 80% and a 2-sided significance level of 0.05, the minimum number of subjects for adequate study power was 1995 patients. The sample size was increased by a further 220 patients (for a whole sample of 2215 eligible patients) to factor in potential refusals or drop-outs.

Sensitivities, specificities, negative predictive values (NPV), and positive predictive values (PPV) with relative 95% confidence interval (CI), diagnostic accuracy, positive and negative likelihood ratio (LR) were calculated for the POCT, utilizing histology as the gold standard and comparing it to the tTG.

Cost Analysis

To assess the cost-consequences of the different strategies, data on resource consumption were gathered through patients' charts. Costs of examinations, and diagnostic and laboratory tests were estimated with regional outpatient tariffs (Sicily) and for each POCT a price of €2.5 was used. The study was performed from the Sicilian Regional Health System perspective, therefore, indirect and intangible costs were not taken into account.

To evaluate the strength of the results, 2 sensitivity analyses were developed. In the first analysis, a cost of ±10% for POCT was used, whereas in the second, to compare POCT screening strategy versus CF a cost for each GP's visit of €15.31 was added to every patient in the CF. This cost for an Italian GP's visit was retrieved from a previously published study inflated to Euro 2016 according to the Italian National Institute of Statistics.[31]

RESULTS

Of the 45,921 subjects who are cared for by 34 GPs (mean age 50.2 ± 19.6 y, 44.9% males), 133 were already diagnosed with CD (prevalence = 1:345). Of the 2215 eligible subjects, older than 18, who were consecutively examined at the GPs' office during the observation period (average 1 wk), 2197 (99.2%) agreed to participate to the study, and underwent the POCT for CD (Fig. 1). The mean age of the population tested was 50.1 ± 16.7 (range, 18 to 89), and 801 (36.5%) patients referred were male. Of these, 8 (0.36%) showed a positive test and 28 (1.27%) a no line test, thus requiring further investigation for CD.

Of the 8 subjects with a positive POCT, only 6 completed the routine diagnostic work-up, which confirmed CD diagnosis in 3 of them. Two positive POCT subjects (1 of them CF positive) refused to undergo further investigations. Among the 28 subjects with no line at POCT, 16 accepted to undergo further investigations at the referral celiac center, and in 2 cases serology and histology confirmed the presence of CD. No case of selective IgA deficiency was confirmed.

Of the 2197 who underwent POCT, 671 (30.5%) met criteria of suspected CD when applying the CF approach. The distribution of different conditions/symptoms suggestive of CD is shown in Figure 2.

Of the 671 symptomatic subjects at CF, 639 (95.2%) turned out negative at POCT. Of these, 351 (52.3%) agreed to undergo tTG IgA determination at the referral celiac center: 350 were negative and only 1 had positive serological markers of CD, and histology of duodenal biopsies confirmed the diagnosis of CD.

As can be seen from Table 2, sensitivity of POCT is 75% (95% CI, 30.1-95.4), specificity is 99.2% (95% CI, 97.5-99.7), NPV estimated on subjects who agreed to be referred to the Celiac Center is 99.7% (95% CI, 98.4-99.9), PPV 50% (95% CI, 18.8-81.2). LR+ and LR− are 88.2% (95% CI, 23.1-280.3) and 0.25% (95% CI, 0.046-0.705), respectively. Compared with tTG, sensitivity of POCT is 75% (95% CI, 30-95), specificity 99% (95% CI, 97-99), NPV 100% (95% CI, 98-100), PPV 38% (95% CI, 14-69).

When the yield of the different strategies was calculated, that of screening was 5 celiac patients out of a total of 2197 tested subjects (1:439), 4 of whom would anyway have been recognized by means of CF; the yield of CF was 5 new CD diagnoses applying this strategy to 371 symptomatic subjects at CF who accepted to be referred to Centers, one of whom was missed at screening. By using both strategies the calculated yield was 6 new diagnoses out of a total of 2197 tested subjects.

In the base case, taking into account a cost of POCT of €2.5 and the regional tariffs for examinations, diagnostic, and laboratory tests a total cost for screening strategy with POCT of €7497.35 and a mean cost for each CD patient of €1499.47 were estimated. Instead, for CF strategy a total cost of €9855.14 and a mean cost of €1971.03 per CD patient were assessed (Table 3).

Considering the protocol with consecutive use of both strategies, thus performing the POCT only in symptomatic subjects at CF, a total cost of €2345.84 and a mean cost of €586.46 for each newly diagnosed patient can be assumed (Table 3).

In the first sensitivity analysis, considering an increase of +10% of POCT price (€2.75), total cost and the mean cost

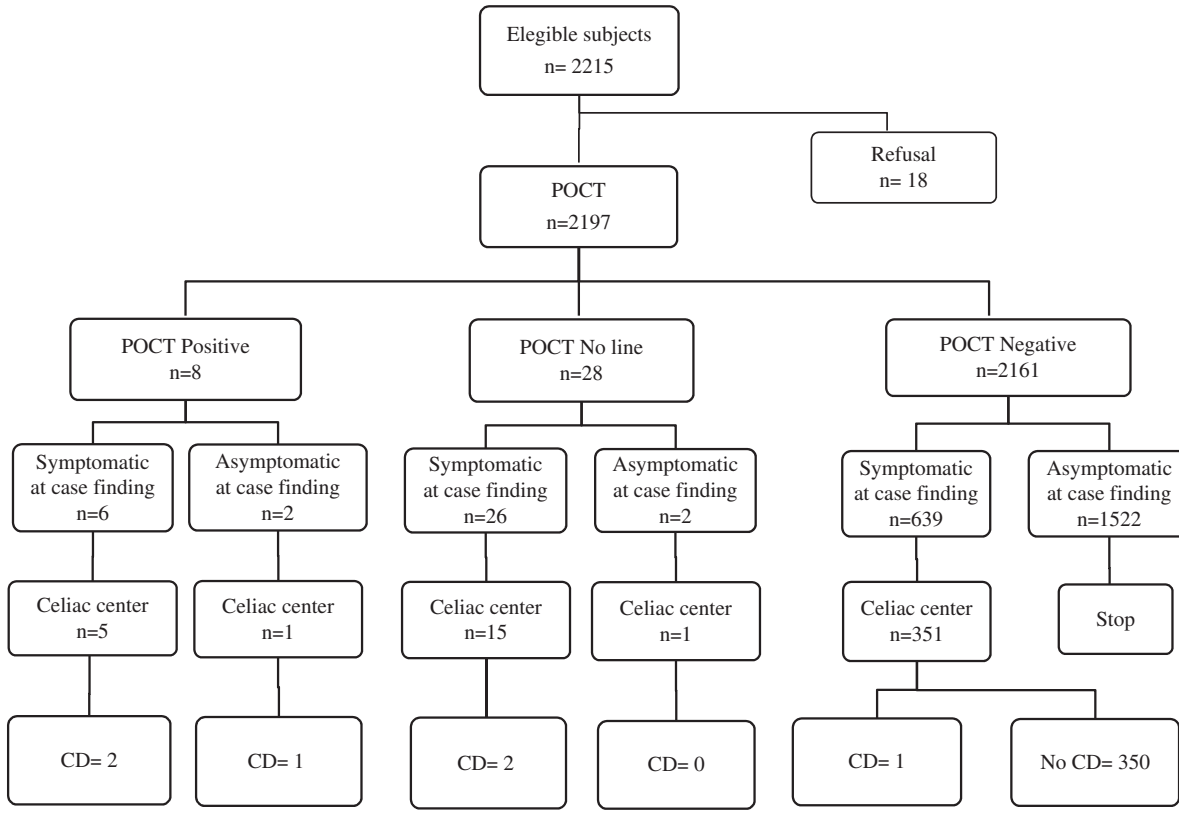

FIGURE 1. Flowchart of study patient enrollment. POCT indicates point-of-care test.

per CD patient were €8046.60 and €1609.32 for the POCT strategy, and €2438.59 and €609.65 for the combined strategy, respectively, with no difference in CF. Instead, considering a reduction of −10% of POCT price (€2.25), the total cost and the mean cost per CD patient with POCT strategy were €6948.10 and €1389.62 for POCT strategy, whereas they were €2253.09 and €563.27 for the combined strategy, respectively. Also in the first sensitivity analysis, the protocols including POCT were less costly than CF.

Considering the mean CD patient cost, the POCT strategy is equal to CF with a price per POCT of €3.57, whereas the combined strategy is equal to CF with a POCT price of €17.43.

In the second sensitivity analysis, considering an additional cost of GP visit of €15.31 in Italy, the CF strategy showed a dramatic increase in both total (€43,491.21 of which 33,636.07 for GPs' visits) and mean CD patient cost (€8698.24).

Finally, we calculated compliance, evaluating the performed POCT, the completed CF reports compared with the assigned ones, and the percentage of POCT and/or symptomatic subjects at CF sent to the reference center. Compliance of physicians and patients to achieve the planned objectives of the study are shown in Figure 3.

DISCUSSION

We performed CF based on detecting at least 1 symptom or clinical condition recognized as high risk for CD in previous studies that widely recommended this strategy as the best approach to increase the number of CD diagnoses in the community.[18,32] In fact, a CF approach can be a feasible, successful strategy for detecting undiagnosed CD in general practice, thus reducing the risk of developing gluten-related complications.

Nevertheless, such a strategy is not likely to significantly increase the number of CD diagnoses up to achieving the expected prevalence of 1% in the general population, with almost 60% of CD patients still remaining undiagnosed.[33]

In contrast, a mass screening program for CD would have excessive costs. Therefore, in this respect, a quick, low cost, easy to perform test, carried out at the point-of-care could be an effective policy.

Our data confirmed that POCT is easy to use in general practice and is well accepted by patients, as confirmed by the low rate of refusal in our study.

As regards the effectiveness of the 2 different screening approaches, it should be noted that only 1 of 351 symptomatic subjects at CF, who had a negative POCT, was diagnosed with CD. This observation is somewhat weak as only half of the symptomatic subjects at CF agreed to continue the study when they turned out negative at POCT. This low rate of acceptance may be explained by the reassurance induced by a negative POCT, which they trusted in. However, according to these data, we must underline that POCT showed an excellent NPV (99.2%); this is even more relevant if we consider the settings where the POCT was performed by personnel who were not completely dedicated to performing diagnostic

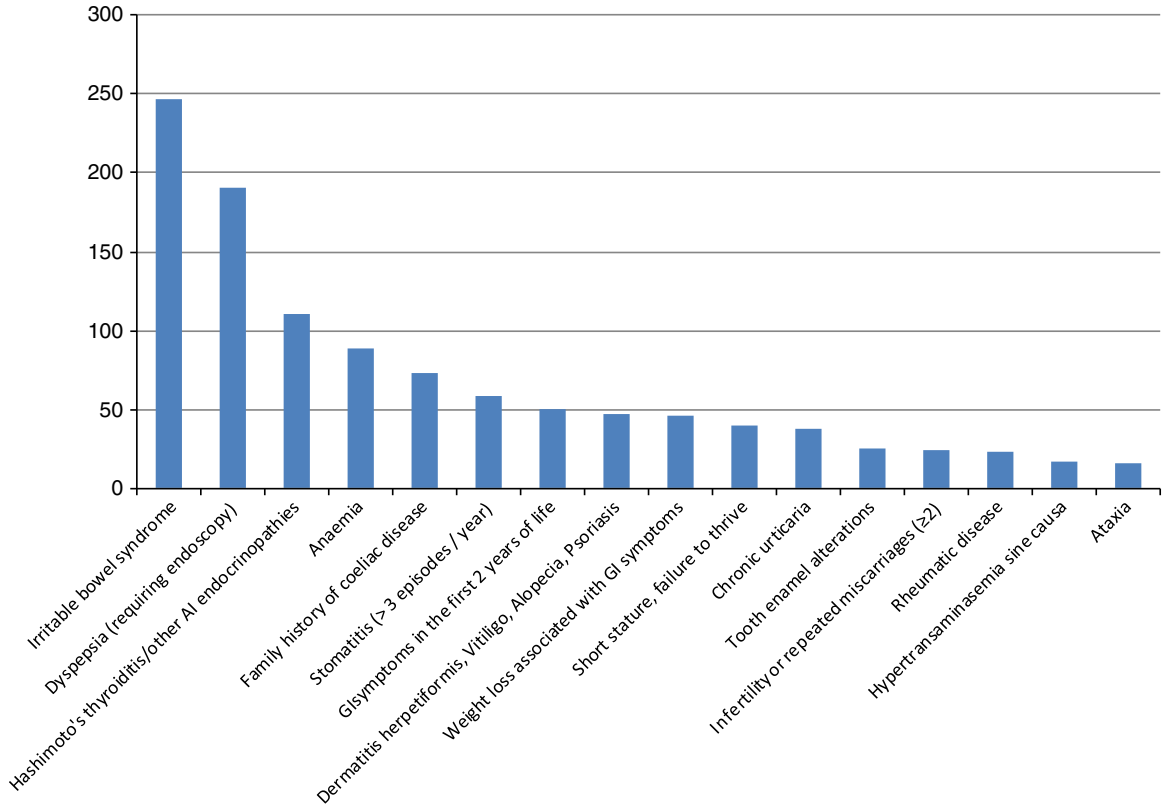

FIGURE 2. Distribution of major conditions/symptoms suggestive of celiac disease in case finding positive patients. full color online

procedures, such as GPs in their office. In this respect, our study has 2 further limitations that may overestimate the NPV of POCT in that, even though we assessed symptoms in all subjects before knowing the result, among subjects with POCT negative only those with symptoms were invited to undergo further investigation and those who were positive at conventional serology underwent intestinal biopsy. This may introduce a "double standard bias" that might be more relevant considering that some celiac patients can have negative serology.[34] Ethical reasons considered in the design study and approved by the ethics committee did not allow to eliminate this bias. However, in clinical practice, upper digestive endoscopy with duodenal biopsy should be offered to a subject with strong suspicion of CD due to gastrointestinal symptoms.

The PPV of POCT found in this study was not satisfying (50%), but the very low cost and high NPV of POCT make it useful and cost-effective for a population study, in our opinion.

In our study, 16 patients were referred to the Celiac Center as no line appeared at the POCT thus suggesting IgA deficiency according to the manufacturer's instructions; none of them showed IgA deficiency but 2 were diagnosed as suffering from CD as they tested positive for DGP IgG and showed intestinal villi atrophy at duodenal histology. These data suggested that "no line POCT" did not indicate an IgA deficiency, but more probably a possible "false negative" assay for tTG IgA. Furthermore, they underline the usefulness of DGP IgG assay in the serologic work-up of the CD diagnosis, as demonstrated also by another study which showed that performing serum tTG IgA plus DGP IgG had a higher diagnostic accuracy than tTG IgA assay alone.[35] On this basis, we must underline another limitation of our study as we did not perform serum DP IgG assay for all the patients referred to the Celiac Center. Consequently, other POCT-positive or POCT-negative/symptomatic patients could have been missed for CD diagnosis. However, in our study we stressed the estimation of the cost-effectiveness of the 2 screening strategies; in this respect, to consider a routine assay of serum DGP IgG would have greatly increased the costs.

In comparison with results of previous studies of CF[18,32] and of population screening,[36] it is of note that the prevalence of CD at the beginning of our study (1:345) was higher than that reported by Berti et al[18] and thus, the difference of prevalence at the end of the study (1:330) was less remarkable than that found in another region. This may depend on the

TABLE 2. Accuracy of POCT for Celiac Disease Identification

POCT	%	95% CI
Sensitivity	75.0	30.1-95.4
Specificity	99.2	97.5-99.7
Positive predictive value	50.0	18.8-81.2
Negative predictive value	99.7	98.4-99.9
Diagnostic accuracy	98.9	97.7-99.9
LR+	88.2	23.1-280.3
LR−	0.252	0.046-0.705

CI indicates confidence interval; LR, likelihood ratio; POCT, point-of-care test.

TABLE 3. Yield and Direct Costs of POCT Screening Versus a Case Finding Versus Combined Strategy—Base Case Scenario

Patients	Test/Visit	Test Cost (€)	No. Tested Patients (%)	Estimated Cost (€)
POCT screening (no. CD diagnosed = 5)				
All	POCT	2.50	2197 (100.00)	5492.50
Positive POCT	tTG IgA	19.00	6 (0.27)	114.00
	Gastroenterology visit	20.66	6 (0.27)	123.96
	EGD	56.81	5 (0.23)	284.05
	Biopsy	99.40	5 (0.23)	497.00
	Histologic exam	14.10	5 (0.23)	70.50
No line POCT	DGP IgG	10.27	16 (0.73)	164.32
	Total IgA	4.99	16 (0.73)	79.84
	Gastroenterology visit	20.66	16 (0.73)	330.56
	EGD	56.81	2 (0.09)	113.62
	Biopsy	99.40	2 (0.09)	198.80
	Histologic exam	14.10	2 (0.09)	28.20
Total cost (€)				7497.35
Mean cost for each cd diagnosis (€)				1499.47
Case finding (no. CD diagnosed = 5)				
All	GP visit	0.00	2197 (100.00)	0.00
Symptomatic	tTG IgA	19.00	371 (16.89)	7049.00
	Total IgA	4.99	371 (16.89)	1851.29
	Gastroenterology visit	20.66	5 (0.23)	103.30
	EGD	56.81	5 (0.23)	284.05
	Biopsy	99.40	5 (0.23)	497.00
	Histologic exam	14.10	5 (0.23)	70.50
Total cost (€)				9855.14
Mean cost for each CD diagnosis (€)				1971.03
POCT carried out after case finding search (no. CD diagnosed = 4)				
All	GP visit	0.00	2197 (100.00)	0.00
Symptomatic	POCT	2.50	371 (16.89)	927.50
Positive POCT	tTG IgA	19.00	5 (0.23)	95.00
	Gastroenterology visit	20.66	5 (0.23)	103.30
	EGD	56.81	2 (0.09)	113.62
	Biopsy	99.40	2 (0.09)	198.80
	Histologic exam	14.10	2 (0.09)	28.20
No line POCT	DGP IgG	10.27	15 (0.68)	154.05
	Total IgA	4.99	15 (0.68)	74.85
	Gastroenterology visit	20.66	15 (0.68)	309.90
	EGD	56.81	2 (0.09)	113.62
	Biopsy	99.40	2 (0.09)	198.80
	Histologic exam	14.10	2 (0.09)	28.20
Total cost (€)				2345.84
Mean cost for each CD diagnosis (€)				586.46

CD indicates celiac disease; DGP IgG, immunoglobulin G deamidated gliadin peptide antibodies; EGD, esophagogastroduodenoscopy; GP, general practitioner; POCT, point-of-care test; tTG IgA, IgA anti-transglutaminase antibodies.

different awareness of GPs in our region that explains the prevalence of celiac patients already known.

In contrast, the prevalence of CD found by means of the POCT screening in our study (1:439) is higher than that reported by Corazza et al[36] (1:559) on a similar number of subjects utilizing conventional celiac serology.

When the costs of the 2 different screening strategies were compared, POCT showed a 24% lower cost than CF. However, our results suggest that an integrated program, performing POCT only in symptomatic subjects at CF is considerably more cost-effective. In fact, this proposed integrated strategy involves a planned expenditure of €586.46 for each newly diagnosed patient, thus allowing a considerable money saving.

Sensitivity analyses have confirmed the results, but have also shown that the cost of POCT test affects them.

Despite Italian GPs being paid a capitation fee based on the number of people (adults or children) registered on

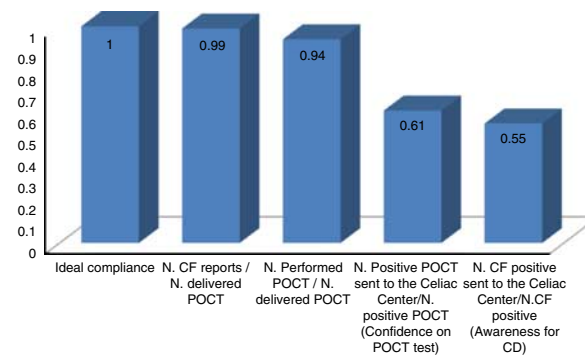

FIGURE 3. Compliance of general practitioners and patients to study design. CD indicates celiac disease; CF, case finding; POCT, point-of-care test. full color online

their list, when we considered the cost for a GP visit, as in countries with a largely fee-for-service system such as France and Germany[37] the health care expenditure for the CF strategy was dramatically increased.

According to current data, we believe that the integrated diagnostic pathway may be the most cost-effective one in the search for new celiac patients, but more pharmaco-economic evidence, such as cost-effectiveness and cost-utility analyses developed in Italy (with our specific national/regional health care settings) are required to better evaluate this assumption due to a relatively less transferability of evidence between countries.

In the Maki et al 2003 study,[5] it was estimated that each case was diagnosed at a cost of €1400, whereas in the Berti et al 2006 experience, the CF approach had a cost of €923.25 per case.[18]

Finally, regarding GP and patient compliance to the study, we found an excellent percentage of tests performed (94%) by the number of tests assigned. This indicated the awareness of GPs regarding CD diagnosis, although we must underline that they had been involved in a thorough practical training which surely increased attention to CD. In contrast, only 61% of POCT positives and 55% of the symptomatic subjects underwent further evaluation for CD diagnosis. Both these data indicate the need for improved educational strategies.

In conclusion, we showed that an accurate POCT may increase the rates of diagnosis of CD if used effectively as part of a CF approach in primary care and can save money in comparison with a simple CF strategy. Results to date are encouraging but further research in this area is required as recently suggested,[38] comparing the cost-effectiveness or cost-utility, in an Italian setting, of POCT detecting tTG IgA or anti-DGP IgG and their combination.

ACKNOWLEDGMENT

The authors thank Trays Macdonnell for the English language revision of the article.

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