Long-term cost-effectiveness of case finding and mass screening for celiac disease in children

Suasnabar, J.H.; Meijer, C.R.; Smit, L.; Overveld, F. van; Thom, H.; Keeney, E.; ... ; Akker-van Marle, M.E. van den

Long-Term Cost-Effectiveness of Case Finding and Mass Screening for Celiac Disease in Children

Jan Heijdra Suasnabar,[1] Caroline R. Meijer,[2] Lucy Smit,[3] Floris van Overveld,[4] Howard Thom,[5] Edna Keeney,[5] M. Luisa Mearin,[2] and M. Elske van den Akker-van Marle[1]

[1]Department of Biomedical Data Science, Leiden University Medical Centre, Leiden, the Netherlands; [2]Department of Pediatric Gastroenterology, Willem-Alexander Children's Hospital, Leiden University Medical Center, the Netherlands; [3]Youth Health Care Centre, Kennemerland, the Netherlands; [4]Dutch Celiac Patients Society, Naarden, the Netherlands; and [5]Department of Population Health Sciences, Bristol Medical School, Bristol, United Kingdom

BACKGROUND & AIMS: Celiac disease (CD) is a common yet underdiagnosed autoimmune disease with substantial long-term consequences. High-accuracy point-of-care tests for CD antibodies conducted at youth primary health care centers may enable earlier identification of CD, but evidence about the cost-effectiveness of such strategies is lacking. We estimated the long-term cost-effectiveness of active case finding and mass screening compared with clinical detection in the Netherlands. **METHODS:** A decision tree and Markov model were used to simulate a cohort of 3-year-old children with CD according to each strategy, taking into account their impact on long-term costs (from a societal perspective) and quality-adjusted life-years (QALYs). Model parameters incorporated data from the GLUTENSCREEN project, the Dutch Celiac Society, the Dutch Pediatric Surveillance Unit, and published sources. The primary outcome was the incremental cost-effectiveness ratio (ICER) between strategies. **RESULTS:** Mass screening produced 7.46 more QALYs and was €28,635 more costly compared with current care (ICER: €3841 per QALY), and case finding produced 4.33 more QALYs and was €15,585 more costly compared with current care (ICER: €3603 per QALY). At a willingness to pay of €20,000 per QALY, both strategies were highly cost-effective compared with current care. Scenario analyses indicated that mass screening is likely the optimal strategy, unless no benefit in detecting asymptomatic cases is assumed. **CONCLUSIONS:** An earlier identification of CD through screening or case finding in children using a point-of-care tests leads to improved health outcomes and is cost-effective in the long-term compared with current care. If the feasibility and acceptability of the proposed strategies are successful, implementation in Dutch regular care is needed.

Keywords: Celiac Disease; Screening; Case Finding; Point-of-Care Test; Children.

Celiac disease (CD) is a common yet underdiagnosed autoimmune disease triggered by gluten consumption, for which the only known effective treatment is adherence to a gluten-free diet (GFD). Although the prevalence of CD varies internationally, it is usually estimated at ∼1%.[1–3] Cohort studies have shown that CD likely develops early in life[4,5] and can be easily diagnosed by detection of CD-specific antibodies against the enzyme tissue transglutaminase type 2 (IgA-TG2).[6] Nonetheless, population-based studies have shown that only ∼20% to 60% of CD cases are clinically detected in the current standard of care and that diagnoses usually occur years after the onset of symptoms.[7–10] Such high rates of missed/delayed diagnoses have been attributed to CD's varied and non-specific symptoms, lack of awareness, and the resource-intensive process necessary to establish the diagnosis.[11,12]

CD has a lifelong impact on quality of life (QoL), affecting physical and social aspects.[7,13] Before their diagnosis and treatment, patients experience a wide range of gastrointestinal and extraintestinal symptoms[12] that can impair daily activities and affect psychosocial well-being.[7,14] Additionally, CD is a risk factor for long-term complications (LTCs), including osteoporosis and certain types of cancer,[7,15] which further contribute to the burden of CD.

From an economic perspective, the burden of CD translates into substantial excess health care and societal costs.[7] Health care costs arise due to the numerous tests and specialist visits that occur before the diagnosis.[14] After diagnosis, health care costs arise due to treatment and medical follow-up visits. Furthermore, 2 important non-health care costs associated with CD are productivity losses (due to CD-related absenteeism from work or school)[16] and the costs of following a GFD (ie, purchasing gluten-free products, dining out).[7,17]

Advancements in diagnostic tools, such as high-accuracy point-of-care tests (POCTs), have the potential to enable earlier detection of CD[18] by facilitating screening and case finding strategies at the primary care level. By identifying individuals with CD earlier, treatment can be initiated promptly, leading to improved health outcomes, reduced disease burden, and potential cost savings.[19]

In the Netherlands, the GLUTENSCREEN project was recently conducted to evaluate the feasibility, acceptability, and cost-effectiveness of active case finding for CD in

Abbreviations used in this paper: **aCD, asymptomatic celiac disease; CD, celiac disease; CEAC, cost-effectiveness acceptability curve; GFD, gluten-free diet; ICER, Incremental cost-effectiveness ratio; IDA, iron-deficiency anemia; LTC, long-term consequence; NCV, Nederlandse Coeliakie Vereniging; POCT, point of care test; QALY, quality-adjusted life-year; QoL, quality of life; TG2, transglutaminase type 2; WTP, willingness to pay; YHCC, youth health care center.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2024.07.024

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Primary care level screening or case finding for celiac disease using a point-of-care test enables an early identification of the disease and leads to improved outcomes, but little is known about the long-term health economic justification for such strategies.

NEW FINDINGS

Mass screening and case finding using tissue transglutaminase IgA point-of-care testing among young children attending preventive youth health care centers are highly cost-effective compared with clinical detection in the Netherlands.

LIMITATIONS

This was a model-based analysis to estimate long-term cost-effectiveness. Empirical data about the long-term costs and outcomes of the strategies are needed to validate the results.

CLINICAL RESEARCH RELEVANCE

These findings suggest that it makes economic sense to introduce screening or case finding strategies for celiac disease at youth health care centers. If these strategies are shown to be feasible and acceptable by patients and clinicians in further research, they should be implemented in regular care.

BASIC RESEARCH RELEVANCE

Our analyses highlight the need for more evidence about the progression and impact of asymptomatic celiac disease to inform the potential benefits of early detection in this subgroup.

children.[20] Parents of all children aged 1 to 4 years attending youth health care centers (YHCCs) were asked whether their child had ≥1 CD-related symptoms from a standardized list (Supplementary Appendix 1).[20] If so, they were invited to participate in the case finding study. After informed consent, a POCT to assess IgA-TG2 was performed at the YHCC.

Screening and case finding strategies, such as that of GLUTENSCREEN, have not yet been widely implemented, partly because of limited evidence about whether their long-term costs are justified relative to decision makers' willingness to pay (WTP) for the benefits they present. Addressing this gap, we evaluated the long-term cost-effectiveness of case finding and mass screening for CD at YHCCs using a POCT compared with current care in the Netherlands.

Methods

Study Design

This was a model-based cost-effectiveness analysis.[21] A hypothetical cohort representing all children with CD in the Netherlands was simulated throughout their lifetime according to each strategy, taking into account the impact of earlier/greater detection on long-term costs and outcomes. Outcomes were expressed in quality-adjusted life-years (QALYs), which incorporate length of life and QoL (ie, utility) into 1 metric.[22] Incremental cost-effectiveness ratios (ICERs), representing the additional costs per QALY between any 2 strategies, are reported.[21]

To inform key input parameters, the model incorporates primary data collected during the GLUTENSCREEN project, data collected from 2702 members (2338 adults and 364 children) of the Dutch Celiac Society (Nederlandse Coeliakie Vereniging [NCV]), and data from the national Dutch Pediatric Surveillance Unit, which records all clinically detected CD pediatric cases in the Netherlands. Other model parameters were informed by secondary sources and expert opinion. To account for the statistical uncertainty surrounding parameter estimates, the main analysis was probabilistic, whereby parameter estimates were resampled 1000 times based on their standard errors and distributions.[23] This enabled the calculation of 95% Bayesian credible intervals of results and the construction of cost-effectiveness acceptability curves (CEACs) representing the probability of each strategy being cost-effective for a given WTP threshold.[23]

The economic model is openly accessible (github.com/jmheij/Glutenscreen-CUA). The code used to computerize the model is an adaptation of a previously developed model for the United Kingdom, where the cost-effectiveness of various laboratory-based testing strategies for CD was investigated from a health care perspective.[24]

Study Population and Setting

The simulated patient cohort represents all 3-year-old children with CD in the Netherlands assuming a lifetime prevalence of 1.06% with a 95% credible interval of 0.8% to 1.4%.[1–3] In line with the process followed during GLUTENSCREEN, the POCT was assumed to take place at routine visits to YHCCs.[20] In the Netherlands, >95% of children aged 0 to 4 years old routinely visit YHCCs.[25]

Interventions

The current practice in the Netherlands, known as (delayed) clinical detection, involves no active efforts to identify individuals at risk of CD before they present with related symptoms. This strategy is consistent with the current situation in most countries, and it is assumed that ∼1 in 3 cases eventually becomes clinically detected based on findings from population-based studies.[7–10] In the Netherlands, nearly all new pediatric diagnoses of CD are recorded in the Dutch Pediatric Surveillance Unit along with data about patients' trajectory leading up to the diagnosis (eg, visits, tests, biopsies).

Two POC testing strategies were explored: active case finding and mass screening using an IgA-TG2 POCT with sensitivity and specificity of 0.94 and 0.944,[18] respectively.

The active case finding strategy was consistent with the process followed during the GLUTENSCREEN project.[20] Children experiencing at least 1 CD-related symptom (Supplementary Appendix 1) are tested using a POCT during routine visits at YHCCs. Children with positive POCT results subsequently undergo confirmatory diagnostics, which consist of a laboratory test battery (ie, HLA, endomysium IgA, IgA–anti-tTG, ferritin, iron, thyroid peroxidase antibodies, vitamin B_{12}, folic acid), and biopsy specimens when laboratory IgA-tTG is <10 times the upper limit of normal.

Mass screening involved testing all children during routine visits at YHCCs regardless of symptoms. Positive POCTs are followed-up with the same confirmatory diagnostic process as in case finding.

Model Structure

A decision tree and a discrete-time Markov model were used to simulate the patient cohorts according to each competing strategy.[21] The decision tree (Figure 1) shows the percentage of CD cases detected and missed according to each strategy. These differing proportions of detected and missed CD cases then enter the Markov model (Figure 2) as diagnosed and undiagnosed CD cases. Although the POCT eligibility criteria (with case finding) of having at least one CD-related symptom increased the background prevalence of CD among symptomatic children, it also resulted in ∼42% of individuals with CD being missed and therefore entering the model as undiagnosed CD (Figure 2). That percentage would include asymptomatic individuals or those with non-specific symptoms and was calculated based on the number of cases detected in GLUTENSCREEN compared with the number of expected cases, assuming a prevalence of 1.06%.

The Markov model diagram (Figure 2) shows the health states and transitions that patients can experience throughout their lifetime according to our model. In line with a lifetime time horizon, patients enter the model at 3 years old and exit after 97 model cycles of 1 year.[21]

The model assumes that individuals with diagnosed and undiagnosed CD may develop 3 CD-related LTCs, namely osteoporosis, non-Hodgkin lymphoma (NHL), and gastrointestinal cancer. These LTCs were included in consultation with clinical experts and based on evidence indicating that the risk of developing them is higher among individuals with undiagnosed CD compared with diagnosed individuals adhering to a GFD; that is, that the risk of developing these LTCs may be influenced by earlier detection.[7,15,26–28] Additionally, the prevalence of iron-deficiency anemia (IDA) in the cohort (ie, across all health states) was accounted for using age-stratified prevalence estimates from Elwenspoek et al.[24]

Input Parameters

The model's input parameters with corresponding data sources are presented in Table 1.[1–3,18,26–46] For parameters that are not fixed, standard errors and statistical distributions used for the 1000 resampling iterations are reported. An extended version of Table 1 with further details and justifications is presented in Supplementary Table 1.

Transition Probabilities

As a discrete-time Markov model,[47] the natural history of CD was simulated through probabilities assigned to the possible transitions between health states (ie, the arrows in Figure 2). The proportions of patients entering, remaining in, and leaving each health state at a given cycle were thus determined by a matrix of transition probabilities. The model was time inhomogeneous, in that some transition probabilities varied over time. Specifically, the baseline risks of mortality[40] and developing LTCs[34,37] varied according to age-stratified general population rates in the Netherlands (Supplementary Table 1).

To capture the differential risk of developing LTCs by diagnosis status, measures of relative risk sourced from literature were combined with population incidence rates on the log scale.[21] Additionally, people developing LTCs carried an excess risk of death, which was calculated based on public registry data or literature.

Finally, the main analysis assumes that ∼1 in 3 patients in the undiagnosed health states eventually become clinically detected during their lifetime (in sensitivity analyses, we assume 2 in 3) and that 40% of these delayed diagnoses occur during childhood. These assumptions were informed by findings from previous studies[7–9,41] and in consultation with clinical experts.

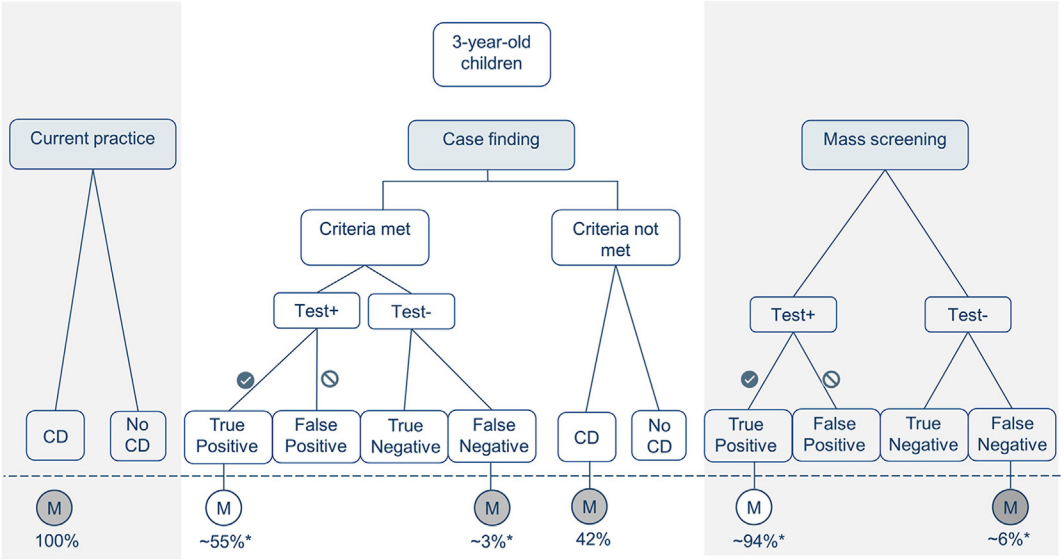

Figure 1. Decision tree for strategies in the main analysis. (M) Percentage of CD cases entering model as undiagnosed; (M) Percentage of CD cases entering model as diagnosed; ✓ Positive result confirmed (further diagnostics); ⊘ Positive result rejected (further diagnostics). *Approximate because the prevalence of CD and POCT accuracy are variable. Note that percentages for non-CD cases (ie, "false positive," "true negative," and "no CD") are not shown because only CD cases enter the model.

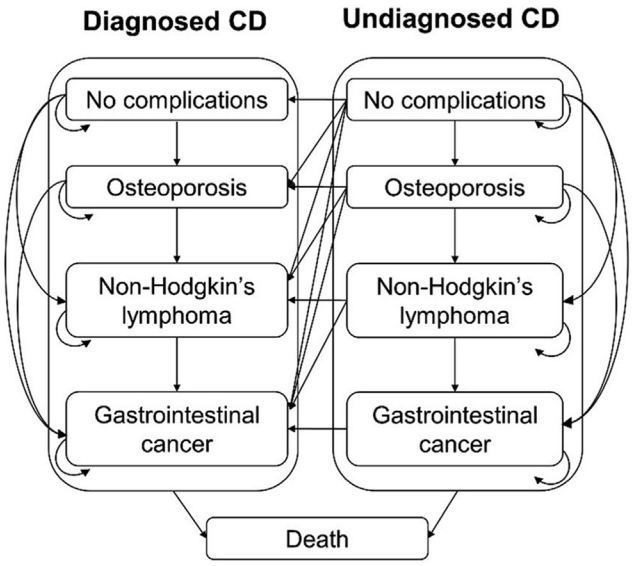

Figure 2. Markov model structure.

Costs

Following a societal perspective, health care and non-health care costs associated with each competing strategy were included.[21] All cost parameters presented in Table 1 are per CD case in 2021 euros (when necessary, converted using the national consumer price index).[48] Additional cost information and calculations are presented in Supplementary Table 1.

Health care costs were those incurred by the health care system and included costs of the POCT (including personnel time), conducting further diagnostics after a positive POCT, treating/managing LTCs, IDA medication, cost of diagnosis when clinically detected, and CD-related visits to health care professionals before and after the diagnosis. When sufficient data were available, different cost estimates were used before and after the cohort reaches adulthood. Supplementary Table 1 describes the breakdown and source of several cost parameters.

Non-health care costs included productivity losses due to absenteeism and costs of a GFD. Productivity losses were calculated using the friction cost method[49,50] on data from NCV members who self-reported their annual number of workdays missed due to CD before and after their diagnosis (details in Supplementary Table 1). The costs associated with following a GFD, estimated at €1506 annually, were also based on self-reported data from NCV members who were asked to estimate their weekly extra expenses due to following a GFD.

In line with Dutch guidelines for economic evaluations, an annual discount rate of 4% was applied to all costs.[49]

Outcomes

To capture the long-term outcomes according to each strategy, QALYs were estimated using QoL data (ie, utilities and disutilities) sourced from primary or secondary sources (Table 1). Utilities are an index score representing the value of health based on population preferences, where 1 corresponds with full health and 0 with death.[51] The total QALYs for each strategy was calculated as the sum of utilities over all model cycles, applying a discount rate of 1.5% per cycle.[21,49] The utilities for diagnosed and undiagnosed CD patients without any LTCs were estimated using data from NCV members, who completed the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) twice: once retrospectively for the period before their CD diagnosis and once reporting their current QoL when diagnosed and after a GFD.

The impact of developing LTCs on QoL was accounted for using disutilities obtained from the literature (Table 1). Finally, the disutility associated with undergoing a biopsy was assumed to equal 2 quality-adjusted life days for children and 1 quality-adjusted life day for adults, in line with assumptions from previous analyses.[24,33]

Assumptions

Our main analysis is subject to several assumptions, namely:

- The disease is detectable at the point of testing.
- The process of confirmatory diagnostics after a positive POCT is perfectly accurate, leaving no false-positive diagnoses.
- The only costs related to children without CD are the costs of conducting the POCT and (in case of false-positive POCT results) confirmatory diagnostics.
- The disutility of osteoporosis depends on the rates and impact of osteoporosis-related fractures (Supplementary Table 1).
- The disutility of IDA is captured in the utility values reported by members of the NCV.
- The costs of diagnosis depend on whether it occurs after a positive POCT or delayed clinical detection, and the costs of the latter further depend on whether the diagnosis occurs in childhood vs adulthood (see Supplementary Table 1).
- Costs associated with following a GFD apply to all individuals diagnosed with CD in the model.

Deterministic Sensitivity Analyses

Deterministic sensitivity analyses are useful to describe the influence of individual parameters (ie, 1-way sensitivity analysis) or sets of parameters (ie, 2-way sensitivity analysis) on estimated ICERs. We performed 1-way sensitivity analyses on 28 model parameters. For example, data on the utilities for diagnosed and undiagnosed CD came from NCV members who may have experienced an especially poor QoL before their diagnosis or especially benefited from treatment. We therefore assumed utilities that were 0.1 higher for undiagnosed CD and 0.1 lower for diagnosed CD in the 1-way sensitivity analyses. Results are presented using tornado diagrams, including which upper/lower values were assumed for each parameter.

Additionally, we conducted a 2-way sensitivity analysis on the sensitivity and specificity of the case finding strategy. In our main analysis, the criteria to prompt testing corresponds with a sensitivity and specificity of 0.58 and 0.63, respectively, calculated based on data from GLUTENSCREEN and the assumed prevalence. A different list of symptoms or criteria, or both, for testing (eg, having CD-affected family) would

Table 1. Model Input Parameters

Parameter	Mean	Standard error	Sampling distribution	Source
Utilities				
Diagnosed CD (children)	0.900	0.050	Beta	NCV[a,b]
Undiagnosed CD (children)	0.590	0.050	Beta	NCV[a,b]
Diagnosed CD (adults)	0.840	0.050	Beta	NCV[a,b]
Undiagnosed CD (adults)	0.650	0.050	Beta	NCV[a,b]
Disutility osteoporosis	0.001	6.3e-05	Beta	[29,30]
Disutility NHL	0.104	0.025	Beta	[31]
Disutility GIC	0.129	0.017	Uniform	[32,b]
Disutility biopsy (children)	0.005	0.002	Triangular	[24,33,b]
Disutility biopsy (adults)	0.003	0.001	Triangular	[24,33,b]
Costs[c]				
POCT (including personnel time)	25.38	…	Fixed	GLUTENSCREEN[a,b]
Diagnosis if positive POCT	604.62	…	Fixed	GLUTENSCREEN[a,b]
Delayed diagnosis (children)	633.07	7.9	Fixed and beta	GLUTENSCREEN and expert opinion[a,b]
Delayed diagnosis (adults)	828.98	2.7	Fixed and beta	GLUTENSCREEN and expert opinion[a,b]
Symptom screening questionnaire	2	…	Fixed	Assumed
Osteoporosis annual	227.33	22.7	Gamma	[34,35,b]
NHL annual	7584.43	758.4	Gamma	[36,37,b]
IDA annual	26.08	…	Fixed	[38,b]
GIC annual	5348.68	534.9	Gamma	[37,39,b]
Diagnosed/treated CD, annual health care (children)	205.65	20.6	Gamma	NCV[a,b]
Undiagnosed CD, annual health care (children)	24.33	2.4	Gamma	DPSU[a,b]
Diagnosed/treated CD, annual health care (adults)	172.85	17.3	Gamma	NCV[a,b]
Undiagnosed CD, annual health care (adults)	51.2	5.1	Gamma	NCV[a,b]
GFD (annual)	1506	16.93	Gamma	NCV[a,b]
Undiagnosed CD, annual absenteeism costs	1674.54	76.83	Gamma	NCV[a,b]
Diagnosed CD, annual absenteeism costs	332.12	33.09	Gamma	NCV[a,b]
Probabilities				
Prevalence of CD (%)	1.06	0.16	Triangular	[1–3,9,b]
POCT sensitivity	0.940	0.017	Lognormal	[18]
POCT specificity	0.944	0.014	Lognormal	[18]
Probability biopsy with delayed diagnosis (adults)	0.860	0.007	Beta	NCV[a,b]
Probability biopsy with delayed diagnosis (children)	0.310	0.020	Beta	DPSU[a,b]
Probability biopsy after positive POCT	0.082	…	Fixed	GLUTENSCREEN[a,b]
Baseline (population) mortality	Age dependent	…	Fixed	[40,b]
Probability of (delayed) clinical detection if initially missed	1/3	…	Fixed	Assumed based on:[7–9,41] and expert opinion[b]
Probability delayed clinical detection occurs during childhood	0.400	…	Fixed	Assumed based on[42,b]
Osteoporosis excess mortality	HR: 2.8	1.043	Lognormal	[43,b]
NHL annual probability of death	0.659	…	Fixed	[37,b]
GIC annual probability of death	0.767	…	Fixed	[37,b]
Prevalence IDA	Age dependent	Age dependent	Beta	[24,b]
Developing consequences				
Osteoporosis population rate	Age dependent	1/10th of mean	Lognormal	[34,b]
NHL population rate	Age dependent	1/10th of mean	Lognormal	[37,b]
GIC population rate	Age dependent	1/10th of mean	Lognormal	[37,b]
Relative/increased risks[b]				
Osteoporosis, diagnosed CD	OR: 1.43	1.112	Lognormal	[44,b]
Osteoporosis, undiagnosed CD	OR: 1.77	1.229	Lognormal	[45,b]
NHL, diagnosed CD	RR: 3.28	1.443	Lognormal	[46,b]
NHL, undiagnosed CD	RR: 4.70	1.266	Lognormal	[28,b]
GIC, diagnosed CD	RR: 1.32	1.041	Lognormal	[27,b]
GIC, undiagnosed CD	RR: 2.33	1.323	Lognormal	[26,b]

DPSU, Dutch Pediatric Surveillance Unit; GIC, gastrointestinal cancer; NCV, Dutch Celiac Association; NHL, non-Hodgkin's lymphoma; HR, hazard ratio; OR, odds ratio; POCT, point-of-care test; RR, rate ratio.
[a]Primary data source.
[b]Relevant additional information provided in Supplementary Table 1.
[c]All costs are in 2021 euros.

correspond with different sensitivities and specificities, which may influence cost-effectiveness. We therefore explored 25 other hypothetical case finding strategies, each corresponding to different combinations of sensitivities and specificities (ie, all combinations in 0.2, 0.4, 0.6, 0.8, and 1.0).

Scenario Analyses Accounting for Asymptomatic Celiac Disease

Owing to the inherent challenges with studying asymptomatic CD (aCD) populations, most model parameters were based on data from symptomatic cohorts. However, the degree to which aCD impacts patients' long-term costs and outcomes likely influences the cost-effectiveness of the proposed strategies relative to current practice or may determine which strategy is optimal.

To test whether accounting for aCD could lead to different conclusions about cost-effectiveness, we conducted 2 scenario analyses whereby 42% of all individuals with CD were assumed asymptomatic (in line with the proportion of cases missed by case finding in the main analysis). To provide a "lower limit" of the cost-effectiveness of both strategies, scenario 1 conservatively assumed no benefit in identifying and treating aCD, whereas scenario 2 still assumed a modest benefit.

Scenario 1 (conservative) assumptions:

- aCD individuals do not eventually get clinically detected (if initially missed),
- experience a QoL (utility) equal to that of the Dutch general population,[52,53]
- do not run an excess risk of developing LTCs compared with the general population,
- make no costs in terms of productivity losses or CD-related health care use before diagnosis, and
- if detected (note this only occurs with mass screening), all asymptomatic individuals incur the costs of following a GFD and have the same annual CD-related health care costs as symptomatic individuals after diagnosis.

Scenario 2 (modest) assumptions:

- individuals with aCD experience a lower utility than the general population, but higher than symptomatic individuals (specifically, at the midpoint between the two). This reflects that even individuals with aCD may experience negative health outcomes or may experience symptoms that were not captured in the case finding questionnaire,
- individuals with aCD run 50% of the increased risk of developing LTCs as symptomatic individuals, reflecting that they may not be risk-free due to enteropathy,
- they make 50% of the costs due to productivity losses and CD-related health care before diagnosis, and
- if detected, 50% of individuals with aCD adopt a GFD and have the same annual CD-related health care costs as symptomatic individuals after diagnosis.

Model Validation

The Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool was used to evaluate and report on the validity of our cost-effectiveness model.[54] The AdViSHE tool consists of 13 items comprising conceptual validation, data validation, computerized model validation, and operational validation.[54] Members of the research team and external clinical experts were consulted to inform the validation process. This was done by presenting the model and its assumptions at internal/external meetings or via email, or both.

Results

Mass screening and case finding both resulted in higher QALYs per CD case compared to current care (7.46 and 4.33 more QALYs, respectively), but were also more costly (Table 2). The greater health care costs of mass screening and case finding were attributable to the costs for POC testing, confirmatory diagnostics, and subsequent CD-related health care costs (eg, regular checkups). Although the 2 strategies did result in slight savings in costs due to LTCs compared with current care (ie, due to less patients developing LTCs), the costs of LTCs were low in general due to the low overall rates of LTCs.

Including non-health care costs, the greater societal costs of mass screening and case finding compared with current care were primarily driven by the costs of following a GFD, which were accrued for longer due to the earlier detection. This was especially the case with mass screening, where the most cases were detected. At the same time, the earlier detection also resulted in substantial savings due to productivity losses, again especially with mass screening.

Because most patients did not develop LTCs, the total QALY gains with mass screening and case finding compared with current care were attributable to the higher utility (ie, QoL) accrued by diagnosed patients (ie, more patients became diagnosed earlier).

Summarizing the results from Table 2, the ICERs for mass screening and case finding compared with current care were €3841 and €3603 per QALY gained, respectively. At a WTP threshold of €20,000 per QALY, these results indicate that either strategy would be cost-effective compared with current care.

Figure 3 presents the CEACs for all strategies compared simultaneously. The CEAC plots the probability of each strategy being the optimum strategy (y-axis) for a given WTP threshold (x-axis). In this joint comparison, mass screening was the preferred strategy at WTP thresholds above €5000 per QALY.

Deterministic Sensitivity Analyses

The 10 most influential parameters are presented in Figure 4. Higher utilities for undiagnosed CD or lower utilities for diagnosed CD had the most influence on the estimated ICERs, but not to the point where it would lead to different conclusions about cost-effectiveness (ie, ICERs remained below €10,000/QALY). Other influential parameters included the annual costs of a GFD, specificity of the POCT, annual absenteeism costs, and the lifetime probability of a delayed clinical detection if initially missed (Figure 4). The rest of the model parameters explored had a low-to-negligible influence on the estimated ICERs (Supplementary Figure 1).

Table 2. Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Ratios (ICERs) vs No Screening For Case Finding Mass Screening

Variable	Current practice	Case finding	Mass screening
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Health care costs			
Questionnaire costs, €[a]	0	189	0
Test costs, €[a]	0 (0–0)	913 (674–1237)	2452 (1807–3330)
Diagnosis costs, €[a]	0 (0–0)	1568 (996–2411)	3916 (2376–6202)
CD-related healthcare, €	1632 (1485–1792)	3313 (2912–3726)	4532 (3918–5186)
Long-term consequences, €	208 (164–259)	184 (149–229)	166 (130–218)
Total healthcare costs, €	1840 (1690–2014)	6167 (5366–7315)	11,066 (9050–14,048)
Non-health care costs, €			
Productivity losses, €	14,266 (13,112–15,455)	8393 (7681–9171)	4143 (3388–4926)
GFD costs, €	5329 (5214–5452)	22,460 (21,550–23,217)	34,861 (33,350–36,105)
Total societal costs, €	21,435 (20,240–22,606)	37,020 (35,738–38,463)	50,070 (47,449–53,243)
QALYs	27.19 (24.78–29.54)	31.52 (29.07–33.57)	34.65 (31.36–37.29)
Incremental societal costs vs current practice, €	0 (0–0)	15,585 (14,201–17,161)	28,635 (25,802–32,230)
Incremental QALYs vs current practice	0 (0–0)	4.33 (2.38–6.22)	7.46 (4.11–10.72)
ICER vs no screening (healthcare perspective)	NA	1000/QALY	1237/QALY
ICER vs no screening (societal perspective)	NA	3603/QALY	3841/QALY

NOTE. Costs and QALYs are per CD patient in the population.
CI, credible interval; NA, not applicable.
[a]One-time cost (other costs are lifetime costs).

In our 2-way sensitivity analysis looking at 25 hypothetical case finding strategies with different sensitivities/specificities (depending on the symptom checklist used or criteria for receiving a POCT, or both), all ICERs relative to current practice remained under €10,000 per QALY gained (Supplementary Table 2).

Scenario Analyses

The estimated costs and QALYs in the scenario analyses resulted in higher ICERs for mass screening and case finding compared with current care (Table 3), but these still remained below commonly applied WTP thresholds for prevention interventions. In the first scenario, which assumed no benefit in identifying asymptomatic children, case finding was the preferred strategy (Supplementary Figure 2) due to its nearly equivalent QALYs but lower costs compared with mass screening (Table 3). In contrast, assuming a modest benefit to identifying and treating asymptomatic individuals (scenario 2) resulted in mass screening being the preferred strategy (Supplementary Figure 3), consistent with our main analysis results. Independent of the scenario, mass screening and case finding were both preferable over current practice.

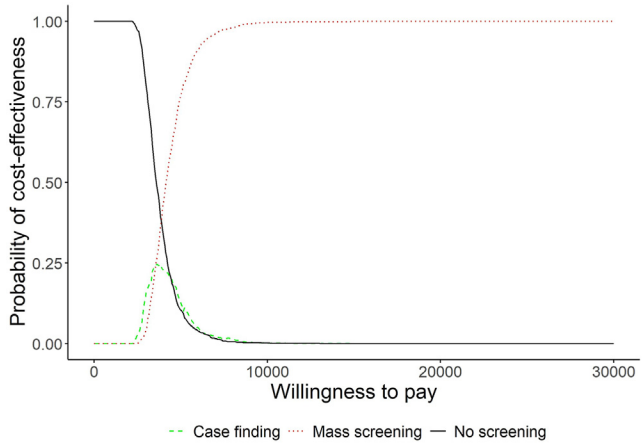

Figure 3. Cost-effectiveness acceptability curves for main analysis.

Validation Results

The report of the model validation using the AdViSHE tool is presented in Supplementary Appendix 2. On the basis of input from internal (ie, research team members) and external clinical experts, the conceptual validity of the model was considered adequate and in line with the research aims. The computerized model code underwent various tests (Part C, Supplementary Appendix 2), and no issues were identified. In terms of operational validity, model outcomes were consistent with outcomes from other models and empirical data sources. The validity of the model input parameters was considered adequate, with a strength being the use of primary or representative data sources for most key parameters.

Discussion

In this economic evaluation, we found that testing for CD in children using an IgA-TG2 POCT during routine visits at

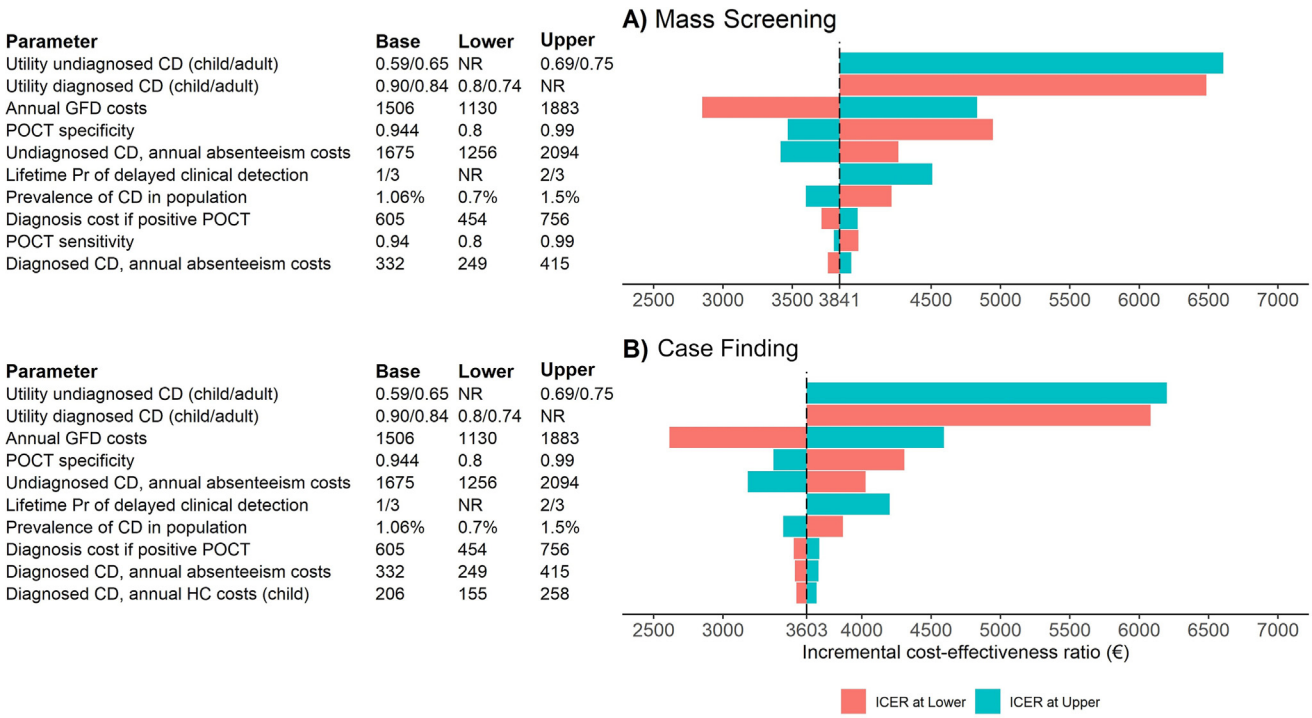

Figure 4. One-way sensitivity analysis results for the top 10 influential parameters.

YHCCs is highly cost-effective compared with current practice in the Netherlands. This conclusion was robust to extensive sensitivity analyses, including 1-way sensitivity analyses on 28 model parameters (Figure 4), a 2-way sensitivity analysis assuming different hypothetical case finding strategies (Supplementary Table 2), and scenario analyses making different assumptions about the impact of aCD (Table 3).

As a commonly undiagnosed disease with considerable long-term health and economic consequences, there is a motivation to improve the identification of CD among children.[7,19] However, our ability to do so has thus far been limited by various factors, including limited evidence about the long-term economic benefit of screening and case finding strategies, especially POCT strategies that may be substantially cheaper and easier to implement at the primary care level. Addressing these gaps, we evaluated the long-term cost-effectiveness of mass screening and active case finding for CD among children visiting the preventive YHCCs.[20] Incorporating a diverse set of parameters, our model-based approach enabled a comprehensive estimation of each strategy's impact on the lifetime costs and outcomes of young individuals with CD.

Another strength of this study is its societal perspective, including health care and non-health care costs (ie, productivity losses and costs of following a GFD). Non-health care costs are often overlooked in economic evaluations of CD testing strategies, yet they represent substantial cost categories in the context of CD.[7]

Our results illustrate how an earlier detection of CD through screening or case finding, although more costly, leads to improved health outcomes and a reduction in disease burden compared with current care. By identifying and diagnosing CD at an early age, individuals can initiate a GFD sooner, leading to the alleviation of symptoms, increased QoL, and a lower risk of developing LTCs. Our modeling of the natural history of CD using evidence-based parameters enabled the quantification of these improvements in QALYs. On average, mass screening and case finding produced 7.46 and 4.33 more QALYs per individual with CD compared with the current situation. These additional QALYs are not due to a gain in life years but rather to more years lived with better QoL due to an earlier initiation of treatment.

Our findings further reflect the complexities of cost-effectiveness in the context of CD. Mass screening and case finding both incurred higher costs compared with the current practice (Table 2). These higher costs were primarily driven by expenses related to the implementation of the POCT, confirmatory diagnostics, the costs of a GFD once diagnosed, and higher CD-related health care visits after the diagnosis. Naturally, these costs were highest with mass screening, where most cases are detected at the point of testing. Simultaneously, mass screening and case finding also resulted in substantial savings in productivity losses, offsetting some of the aforementioned costs.

The ICERs reported in Tables 2 and 3 indicate the additional cost per QALY gained for each strategy relative to the current practice. This joint analysis of costs and benefits indicated that the additional costs incurred by these strategies are justified by the QALY gains they offer, even when adopting a conservative WTP threshold of €10,000 per QALY gained (in the Netherlands, the WTP for screening/prevention interventions is up to €20,000 per QALY).[55] These conclusions are also in line with recent studies, although to our knowledge, ours is the first economic evaluation of POCT strategies in youth primary care

Table 3. Scenario Analysis Results

Variable	Current practice Mean (95% CI)	Case finding Mean (95% CI)	Mass screening Mean (95% CI)
Health care costs			
Questionnaire costs, €[a]	N/A	189	N/A
Test costs, €[a]	0 (0–0)	913 (674–1237)	2452 (1807–3330)
Diagnosis costs, €[a]	0 (0–0)	1568 (996–2411)	3916 (2376–6202)
CD-related health care			
Scenario 1, €	1249 (1135–1374)	2650 (2315–2983)	4494 (3901–5118)
Scenario 2, €	1459 (1328–1608)	2862 (2525–3200)	3602 (3268–3977)
Long-term consequences			
Scenario 1, €	163 (137–195)	139 (113–171)	138 (116–165)
Scenario 2, €	184 (155–217)	166 (139–199)	151 (127–182)
Total health care costs			
Scenario 1, €	1412 (1295–1543)	5459 (4639–6556)	11,000 (8963–13,961)
Scenario 2, €	1643 (1503–1801)	5698 (4879–6816)	10,121 (8072–12,896)
Non-health care costs			
Productivity losses			
Scenario 1, €	7208 (6605–7820)	2436 (2096–2832)	2337 (1930–2759)
Scenario 2, €	10,743 (10,140–11,336)	6142 (5785–6541)	3245 (2799–3728)
GFD costs			
Scenario 1, €	5338 (5214–5461)	20,112 (19,157–20,865)	34,902 (33,365–36,066)
Scenario 2, €	5334 (5216–5449)	20,110 (19,189–20,883)	27,632 (26,493–28,484)
Total societal costs			
Scenario 1, €	13,958 (13,343–14,589)	28,007 (26,652–29,405)	48,239 (45,632–51,266)
Scenario 2, €	17,720 (17,118–18,343)	31,950 (30,658–33,407)	40,999 (38,751–43,948)
QALYs			
Scenario 1	32.18 (31.00–33.33)	35.66 (33.88–37.21)	35.72 (34.03–37.4)
Scenario 2	29.72 (28.52–30.93)	33.22 (31.43–34.77)	35.21 (33.44–36.88)
ICER vs no screening (health care perspective)			
Scenario 1, €	N/A	1162/QALY	2709/QALY
Scenario 2, €	N/A	1159/QALY	1546/QALY
ICER vs no screening (societal perspective)			
Scenario 1, €	N/A	4033/QALY	9688/QALY
Scenario 2, €	N/A	4068/QALY	4245/QALY

NOTE. Lifetime costs and QALYs are per CD patient in the population. Scenario 1 conservatively assumes no benefit in detecting aCD, whereas scenario 2 assumes a modest benefit.
CI, credible interval.
[a]One-time cost (other costs are lifetime costs) which are equal in both scenarios.

adopting a societal perspective. Elwenspoek et al,[24] who developed the economic model we adapted, found that mass screening using a laboratory IgA-tTG (with or without combination with HLA) was cost-effective compared with no screening (from a health care/payer perspective) among 10-year-old children in the United Kingdom at a WTP of £20,000 per QALY gained. Looking at a school-based screening program in Sweden, Norström et al[56] concluded that CD screening (using laboratory serologies and biopsy specimens) among 12-year-old children was cost-effective from a societal perspective at a WTP of €50,000 per QALY gained, although their model was conceptually different and omitted GFD costs.

Findings from our analyses of 2 scenarios reflect the robustness of our results and provide additional insights into the potential impact of aCD on the study's conclusions. These scenario analyses were relevant given the current lack of evidence about aCD to inform key model parameters. Our findings from scenario 1 provide supporting evidence that even under pessimistic assumptions about the benefits of detecting asymptomatic individuals, mass screening and case finding would be cost-effective over current care. However, the exaggerated assumptions of scenario 1 suggested case finding as the optimal strategy, which is contrary to our main analysis results and may not be a justifiable conclusion under less conservative assumptions. Indeed, under more modest assumptions about the benefits of detecting asymptomatic individuals (scenario 2), mass screening would again be the preferred strategy. Taken together, the results of our scenario analyses point to an important conclusion: although case finding and mass screening are likely cost-effective over current care, the

relative merit of mass screening over case finding depends on the (currently uncertain) extent to which aCD impacts long-term costs and outcomes.

Limitations

As with all model-based analyses, the validity of our results depends on the appropriateness of the model structure, the assumptions made, and the input data. Our validity assessment using the AdViSHE tool (Supplementary Appendix 2) explicitly addresses these aspects and highlights this study's strengths and limitations. Although no significant concerns/issues were raised to us by external experts (ie, pediatric gastroenterologists, dietitians), we note several potential limitations.

First, although most parameter estimates are based on primary or secondary data from Dutch patient populations, we could not identify nationally representative estimates for several parameters (eg, relative risk for LTCs and prevalence of IDA among individuals with CD). In such cases, we relied on sources/data from international populations. The use of international sources is common in economic evaluations but may limit the generalizability of our findings to the Dutch context. Additionally, the unavailability of evidence/literature also prevented the inclusion of poor growth as a model health state. Although poor growth is considered a LTC of untreated CD, we were unable to identify information/literature on its rate of development and attributable costs and utilities to appropriately parametrize it in the model. Of note, including poor growth as a LTC would only increase the cost-effectiveness of the strategies.

Second, the main analysis assumes that all CD cases are detectable at the point of testing. In practice, a proportion of children would probably not yet meet the diagnostic criteria for CD before age 4. This raises 2 considerations that were not within the scope of this study, the possibility of repeat testing, which would influence cost-effectiveness, and the presence of "potential/suspected CD" cases, which are a very small subgroup of patients that usually incur higher health care costs in the years before diagnosis due to increased monitoring.[6] Our chosen age for testing was informed by recent experience with GLUTENSCREEN, where as many as 2% (ie, twice the generally accepted prevalence of CD) of children from the general population with at least 1 CD-related symptom had detectable CD at ages 1 to 4 years. Nonetheless, recent evidence indicates that a single-test approach may miss some children and that testing at least twice before age 10 may be preferable.[57] Conducting an additional POCT is likely still cost-effective given the low ICERs in our study, but future models should assess this empirically.

Third, our assumption that the confirmatory diagnostic process leaves no false-positive diagnoses is a simplification. In practice, some biopsy specimens may be misread as abnormal or laboratory errors may occur. Nonetheless, the comprehensive confirmatory diagnostic process (ie, which took place after every positive POCT and included laboratory HLA, endomysium IgA, IgA-tTG, ferritin, Iron, thyroid peroxidase antibodies, vitamin B_{12}, folic acid, and biopsy specimens when IgA-tTG was $<$10 times the upper limit of normal) would likely result in an extremely low false-positive diagnosis rate. Accounting for such a minute cohort of falsely diagnosed children who actually do not have CD would have had a negligible impact on results.

Finally, despite being a commonly stated figure among clinicians, the assumption that 1 in 3 individuals with CD become diagnosed in the current care situation, is debatable. In practice, the percentage of individuals with CD that become diagnosed has been reported to range between 20% and 60% and appears to be increasing due to greater awareness about the disease.[7–9,11] We addressed this in our 1-way sensitivity analyses by assuming that 2 in 3 individuals would become clinically detected and found it did not influence the estimated ICERs considerably (Figure 4). In fact, according to our model, all undiagnosed cases would need to become clinically detected at a very young age (ie, before age 11) for the ICERs of mass screening and case finding to cross €20,000 per QALY relative to current practice.

Conclusion

This study has shown that secondary prevention by case finding and mass screening for CD in young children is cost-effective compared with the regular clinical standard of care. These results contribute valuable insights about the economic benefits of CD screening and case finding strategies using a POCT in the Netherlands. The findings demonstrate how an earlier identification of CD may lead to improved health outcomes, reduced disease burden, and long-term savings in certain cost categories. The study's robust methodology, including a conservative scenario analysis and our critical appraisal of the model's validity, make it a useful resource for informing decision making regarding the adoption of CD testing strategies. If found to be feasible and acceptable by clinicians and patients, these strategies should be implemented in the Netherlands.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2024.07.024.

References

1. Dubé C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology 2005;128(Suppl 1):S57–S67.
2. Roberts SE, Morrison-Rees S, Thapar N, et al. Systematic review and meta-analysis: the incidence and prevalence of paediatric coeliac disease across Europe. Aliment Pharmacol Ther 2021;54:109–128.
3. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:823–836.e2.
4. **Meijer CR, Auricchio R**, Putter H, et al. Prediction models for celiac disease development in children from

high-risk families: data from the PreventCD Cohort. Gastroenterology 2022;163:426–436.
5. Vriezinga SL, Auricchio R, Bravi E, et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med 2014;371:1304–1315.
6. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–156.
7. **Makharia GK, Singh P**, Catassi C, et al. The global burden of coeliac disease: opportunities and challenges. Nat Rev Gastroenterol Hepatol 2022;19:313–327.
8. Choung RS, Unalp-Arida A, Ruhl CE, et al. Less hidden celiac disease but increased gluten avoidance without a diagnosis in the United States: findings From the National Health and Nutrition Examination Surveys from 2009 to 2014. Mayo Clin Proc 2017;92:30–38.
9. Kvamme JM, Sørbye S, Florholmen J, et al. Population-based screening for celiac disease reveals that the majority of patients are undiagnosed and improve on a gluten-free diet. Sci Rep 2022;12:12647.
10. Choung RS, Larson SA, Khaleghi S, et al. Prevalence and morbidity of undiagnosed celiac disease from a community-based study. Gastroenterology 2017;152:830–839.e5.
11. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet 2018;391:70–81.
12. Catassi C, Verdu EF, Bai JC, et al. Coeliac disease. Lancet 2022;399:2413–2426.
13. Möller SP, Hayes B, Wilding H, et al. Systematic review: exploration of the impact of psychosocial factors on quality of life in adults living with coeliac disease. J Psychosom Res 2021;147:110537.
14. Majsiak E, Choina M, Golicki D, et al. The impact of symptoms on quality of life before and after diagnosis of coeliac disease: the results from a Polish population survey and comparison with the results from the United Kingdom. BMC Gastroenterol 2021;21:99.
15. Kaukinen K. Updates on systemic consequences of coeliac disease. Nat Rev Gastroenterol Hepatol 2021;18:87–88.
16. Bozorg SR, Söderling J, Everhov ÅH, et al. Work loss in patients with celiac disease: a population-based longitudinal study. Clin Gastroenterol Hepatol 2022;20:1068–1076.e6.
17. Lee AR, Ng DL, Zivin J, et al. Economic burden of a gluten-free diet. J Hum Nutr Diet 2007;20:423–430.
18. Singh P, Arora A, Strand TA, et al. Diagnostic accuracy of point of care tests for diagnosing celiac disease: a systematic review and meta-analysis. J Clin Gastroenterol 2019;53:535–542.
19. Meijer C, Shamir R, Szajewska H, et al. Celiac disease prevention. Front Pediatr 2018;6:368.
20. Meijer-Boekel C, Van Den Akker ME, Van Bodegom L, et al. Early diagnosis of coeliac disease in the Preventive Youth Health Care Centres in the Netherlands: study protocol of a case finding study (GLUTENSCREEN). BMJ Paediatr Open 2021;5:e001152.
21. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press, 2006.
22. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health Policy Plan 2006;21:402–408.
23. Briggs AH, Claxton K, Sculpher M. Making decision models probabilistic. In: Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press, 2006:77–120.
24. Elwenspoek MM, Thom H, Sheppard AL, et al. Identifying the optimum strategy for identifying adults and children with coeliac disease: systematic review and economic modelling. Health Technol Assess 2022;26:1–310.
25. Inspectie voor de Gezondheidszorg. De jeugdgezondheidszorg beter in positie, 2014 [in Dutch]. Available at: www.ncj.nl/inspiratie/rapport-igz-de-jeugdgezondheidszorg-beter-in-positie-gepubliceerd/. Accessed June 1, 2022.
26. Kårhus LL, Skaaby T, Petersen J, et al. Long-term consequences of undiagnosed celiac seropositivity. Am J Gastroenterol 2020;115:1681–1688.
27. Lebwohl B, Green PHR, Emilsson L, et al. Cancer risk in 47,241 individuals with celiac disease: a nationwide cohort study. Clin Gastroenterol Hepatol 2022;20:e111–e131.
28. Silano M, Volta U, Mecchia A, et al. Delayed diagnosis of coeliac disease increases cancer risk. BMC Gastroenterol 2007;7:8.
29. Si L, Winzenberg TM, De Graaff B, et al. A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. Osteoporos Int 2014;25:1987–1997.
30. Lötters FJB, van den Bergh JP, de Vries F, et al. Current and future incidence and costs of osteoporosis-related fractures in the Netherlands: combining claims data with BMD measurements. Calcif Tissue Int 2016;98:235–243.
31. Versteegh MM, Leunis A, Luime JJ, et al. Mapping QLQ-C30, HAQ, and MSIS-29 on EQ-5D. Med Decis Making 2012;32:554–568.
32. Djalalov S, Rabeneck L, Tomlinson G, et al. A review and meta-analysis of colorectal cancer utilities. Med Decis Making 2014;34:809–818.
33. National Institute for Health and Care Excellence (NICE). Coeliac Disease: Appendix G, Full Health Economics Report. London, UK, 2015.
34. National [Netherlands] Institute for Public Health and the Environment. Osteoporose, Zorguitgaven, 2019 [in Dutch]. Available at: www.vzinfo.nl/osteoporose/zorguitgaven. Accessed June 1, 2022.
35. Nederlands Instituut voor Onderzoek van de Gezondheidszorg (NIVEL). Cijfers over ziekten op jaarbasis—hoe gezond is Nederland? Uit de registraties van Nivel Zorgregistraties Eerste Lijn, 2019 [in Dutch]. Available at: www.nivel.nl/nl/zorg-en-ziekte-in-cijfers/cijfers-ziekten-op-jaarbasis. Accessed June 1, 2022.
36. National [Netherlands] Institute for Public Health and Environment. Zorguitgaven voor non-hodgkinlymfomen, 2019 [in Dutch]. Available at: www.vzinfo.nl/non-hodgkin-lymfomen-nhl/zorguitgaven. Accessed June 1, 2022.
37. Netherlands Comprehensive Cancer Organisation. Cijfers Nederlandse Kankerregistratie: Netherlands Cancer Registry Figures, 2023 [in Dutch]. Available at: https://iknl.nl/nkr/nkr-cijfers. Accessed June 1, 2022.
38. Bouma M, Burgers J, Drost B, et al. NHG-Standaard Anemie (M76), 2021 [in Dutch]. Available at:

https://richtlijnen.nhg.org/standaarden/anemie. Accessed January 29, 2024.
39. National [Netherlands] Institute for Public Health and Environment. Zorguitgaven dikkedarmkanker, 2019 [in Dutch]. Available at: www.vzinfo.nl/dikkedarmkanker/zorguitgaven. Accessed June 1, 2022.
40. Netherlands Bureau of Statistics (CBS). StatLine: Levensverwachting; geslacht, leeftijd (per jaar en periode van vijf jaren), 2022 [in Dutch]. Available at: https://opendata.cbs.nl/#/CBS/nl/dataset/37360ned/table?ts=1725522293888. Accessed June 1, 2022.
41. Collin P, Vilppula A, Luostarinen L, et al. Review article: coeliac disease in later life must not be missed. Aliment Pharmacol Ther 2018;47:563–572.
42. Bergman D, King J, Lebwohl B, et al. Two waves of coeliac disease incidence in Sweden: a nationwide population-based cohort study from 1990 to 2015. Gut 2022;71:1088–1094.
43. Klop C, Welsing PMJ, Cooper C, et al. Mortality in British hip fracture patients, 2000-2010: a population-based retrospective cohort study. Bone 2014;66:171–177.
44. Olmos M, Antelo M, Vazquez H, et al. Systematic review and meta-analysis of observational studies on the prevalence of fractures in coeliac disease. Dig Liver Dis 2008;40:46–53.
45. Hujoel IA, Van Dyke CT, Brantner T, et al. Natural history and clinical detection of undiagnosed coeliac disease in a North American community. Aliment Pharmacol Ther 2018;47:1358–1366.
46. Goldacre M, Wotton C, Yeates D, et al. Cancer in patients with ulcerative colitis, Crohn's disease and coeliac disease: record linkage study. Gastroenterol Hepatol 2008;20:297–304.
47. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. In: Mallarkey G, ed. Economic Evaluation in Healthcare. Auckland: Adis International, 1999:131–143.
48. Centraal Bureau voor de Statistiek [Central Bureau of Statistics]. Dutch consumer price index, 2019 [in Dutch]. Available at: www.cbs.nl/nl-nl/cijfers/detail/83131NED. Accessed June 1, 2022.
49. Dutch Institute National Health Care (Zorginstituut Nederland). Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidzorg (Protocol for the execution of economic evaluation in healthcare), 2016 [in Dutch]. Available at: www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed June 1, 2022.
50. Netherlands Bureau of Statistics. Werkzame beroepsbevolking; arbeidsduur, 2003-2022 [in Dutch]. Available at: https://opendata.cbs.nl/#/CBS/nl/dataset/85275NED/table?ts=1725522424615. Accessed June 1, 2022.
51. Eisen GM, Locke GR, Provenzale D. Health-related quality of life: a primer for gastroenterologists. Am J Gastroenterol 1999;94:2017–2021.
52. Versteegh MM, Vermeulen KM, Evers SMAA, et al. Dutch tariff for the five-level version of EQ-5D. Value Health 2016;19:343–352.
53. Van Koppen EJ, Schweizer JJ, Csizmadia CGDS, et al. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. Pediatrics 2009;123:e582–e588.
54. Vemer P, Corro Ramos I, van Voorn GAK, et al. AdViSHE: A Validation-Assessment Tool of Health-Economic models for decision makers and model users. Pharmacoeconomics 2016;34:349–361.
55. van den Berg M, de Wit G, Vijgen S, et al. Kosteneffectiviteit van preventie: kansen voor het Nederlandse volsgezonheidsbeleid. Ned Tijdschr Geneeskd 2008;152:1329–1334.
56. Norström F, Myléus A, Nordyke K, et al. Is mass screening for coeliac disease a wise use of resources? A health economic evaluation. BMC Gastroenterol 2021;21:159.
57. Boström M, Brundin C, Björck S, et al. Longitudinal screening of HLA-risk and HLA-nonrisk children for celiac disease to age 15 years: CiPiS study. J Pediatr Gastroenterol Nutr 2024;78:1143–1148.

Author names in bold designate shared co-first authorship.

Received January 29, 2024. Accepted July 22, 2024.

Correspondence
Address correspondence to: J.M. Heijdra Suasnabar, MSc, Department of Biomedical Data Science, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, Netherlands. e-mail: j.m.heijdra_suasnabar@lumc.nl.

Acknowledgments
The authors thank the Nederlandse Coeliakie Vereniging (Dutch Celiac Association) for their participation in the survey about their life before and after their diagnosis.

CRediT Authorship Contributions
Jan Heijdra Suasnabar, MSc (Conceptualization: Equal; Formal analysis: Lead; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Lead)
Caroline R. Meijer, PhD (Conceptualization: Equal; Funding acquisition: Equal; Methodology: Supporting; Writing – review & editing: Equal)
Lucy Smit, MD (Conceptualization: Supporting; Funding acquisition: Supporting; Writing – review & editing: Equal)
Floris van Overveld, MSc (Conceptualization: Supporting; Funding acquisition: Supporting; Resources: Supporting; Writing – review & editing: Equal)
Howard Thom, PhD (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Validation: Supporting; Writing – review & editing: Equal)
Edna Keeney, PhD (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Validation: Equal; Writing – review & editing: Equal)
M. Luisa Mearin, PhD (Conceptualization: Equal; Funding acquisition: Lead; Methodology: Supporting; Writing – review & editing: Equal)
M. Elske van den Akker-van Marle, PhD (Conceptualization: Lead; Formal analysis: Supporting; Funding acquisition: Equal; Methodology: Equal; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Equal)

Conflicts of interest
The authors disclose no conflicts.

Funding
This research was performed as part of the GLUTENSCREEN project, with funding from the Netherlands Organization for Health Research and Development (ZonMw, Netherlands). The funding body had no role in the analysis or writing of the manuscript.

Data Availability
The full code used to run the analyses is publicly accessible at github.com/jmheij/Glutenscreen-CUA. Primary patient-level data used to estimate model parameters are confidential and will not be made publicly available.