Cost-effectiveness of Universal Serologic Screening to Prevent Nontraumatic Hip and Vertebral Fractures in Patients With Celiac Disease

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BACKGROUND & AIMS: **Patients with asymptomatic or poorly managed celiac disease can experience bone loss, placing them at risk for hip and vertebral fractures. We analyzed the cost-effectiveness of universal serologic screening (USS) vs symptomatic at-risk screening (SAS) strategies for celiac disease because of the risk of nontraumatic hip and vertebral fractures if untreated or undiagnosed.**

METHODS: **We developed a lifetime Markov model of the screening strategies, each with male or female cohorts of 1000 patients who were 12 years old when screening began. We screened serum samples for levels of immunoglobulin A, compared with tissue transglutaminase and total immunoglobulin A, and findings were confirmed by mucosal biopsy. Transition probabilities and quality of life estimates were obtained from the literature. We used generalizable cost estimates and Medicare reimbursement rates and ran deterministic and probabilistic sensitivity analyses.**

RESULTS: **For men, the average lifetime costs were $8532 and $8472 for USS and SAS strategies, respectively, corresponding to average quality-adjusted life year gains of 25.511 and 25.515. Similarly for women, costs were $11,383 and $11,328 for USS and SAS strategies, respectively, corresponding to quality-adjusted life year gains of 25.74 and 25.75. Compared with the current standard of care (SAS), USS produced higher average lifetime costs and lower quality of life for each sex. Deterministic and probabilistic sensitivity analyses showed that the model was robust to realistic changes in all the variables, making USS cost-ineffective on the basis of these outcomes.**

CONCLUSIONS: **USS and SAS are similar in lifetime costs and quality of life, although the current SAS strategy was overall more cost-effective in preventing bone loss and fractures among patients with undiagnosed or subclinical disease. On the basis of best available supportive evidence, it is more cost-effective to maintain the standard celiac screening practices, although future robust population-based evidence in other health outcomes could be leveraged to reevaluate current screening guidelines.**

Keywords: tTG IgA; Cost-benefit; Cost-utility; Bone Health; Detection; Diagnosis.

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing products, including wheat, barley, rye, and possibly oats. Ingestion of gluten can cause inflammation of the small bowel, leading to intestinal and extraintestinal symptoms.[1,2] Classic CD is characterized by gastrointestinal symptoms such as abdominal pain, diarrhea, bloating, and failure to thrive in children. However, manifestations of CD are diverse and can present in various ways from an asymptomatic presentation (silent CD)[3] to exclusively extraintestinal manifestations.[4,5] The prevalence of CD has been increasing over time[6] and has been shown to be as high as 0.8%–1.5% in the North American and European populations.[7,8] The latest consensus among gastroenterologists is that CD is currently underdiagnosed because of the frequency of silent or latent disease.[9] The prevalence in at-risk groups has been shown to be as high as 1:56 in symptomatic patients, 1:22 in first-degree relatives, and significantly increased in various autoimmune conditions.[10]

Undiagnosed and untreated CD can lead to significant complications, including poor intestinal absorption of macronutrients and micronutrients, potentially leading to poor growth in

Abbreviations used in this paper: CD, celiac disease; GFD, gluten-free diet; ICER, incremental cost-effectiveness ratio; IgA, immunoglobulin A; QALY, quality-adjusted life year; QOL, quality of life; SAS, symptomatic and at-risk screening; tTG, tissue transglutaminase; USS, universal serologic screening; WTP, willingness-to-pay.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2012.12.037

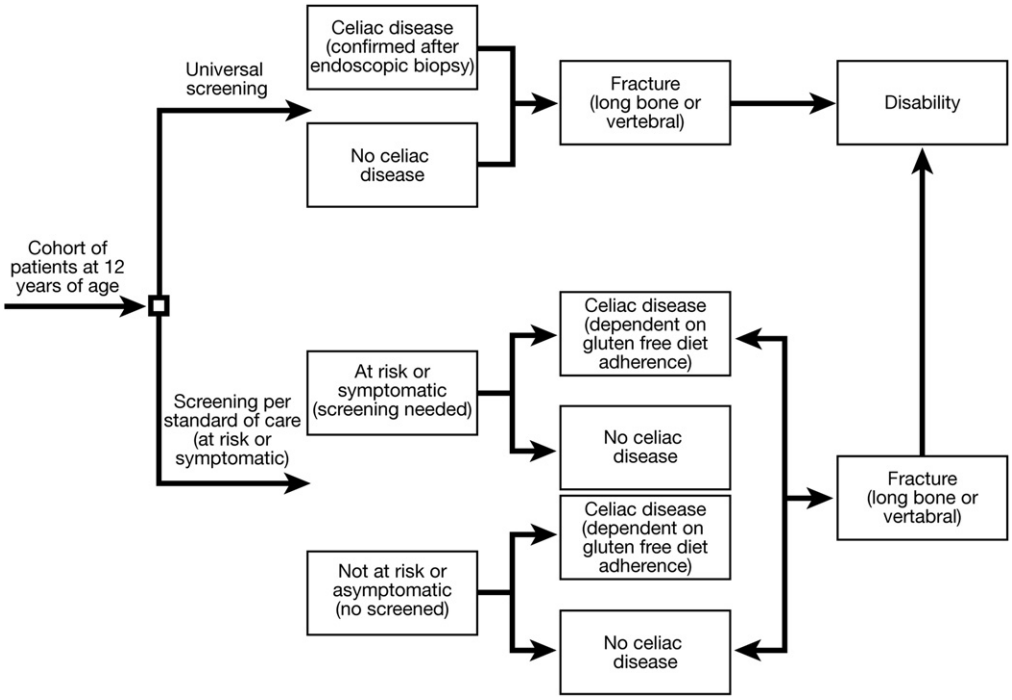

Figure 1. Simplified schematic of Markov model with major health states.

children and chronic nutritional deficiencies. In particular, evidence supports that untreated CD universally leads to progressive bone loss and derangements,[11] increasing the risk for early osteoporosis and nontraumatic fractures. Although the etiology of bone derangements in CD is thought to be multifactorial,[12,13] almost all longstanding disability from nontraumatic fractures occurs from 2 primary sites, hip and vertebrae.[14] Furthermore, these 2 sites are used as the standard of care locations to measure osteoporosis on the basis of bone mineral density criteria.[15,16]

Standard practice screening for CD involves screening symptomatic individuals as well as some high-risk groups.[4,17] Diagnosis of CD involves serologic screening, followed by confirmation of characteristic biopsy findings from upper endoscopy. Although serologic screening tests are relatively inexpensive and have excellent sensitivity and specificity,[18,19] the role of universal screening for CD continues to be a difficult decision because of multiple factors including the utility of serologic screening, low adherence to gluten-free diet (GFD) when CD is accurately diagnosed, and unclear long-term patient benefits in reducing potential morbidity and mortality among treated CD patients, especially if asymptomatic.[20,21]

On the basis of a comprehensive review of relevant literature supporting the various rationales behind universal screening, we found that bone disease—specifically nontraumatic fractures at the hip and vertebrae—is currently the most quantifiable and analyzable outcome measure validated by robust literature findings. We hypothesized that universal serologic screening (USS) during early adolescence may represent an optimal clinical strategy to detect subclinical CD patients and prevent future health consequences from bone disease. The aim of our investigation was to determine the cost-effectiveness of USS with serum tissue transglutaminase (tTG) immunoglobulin A (IgA) and total IgA compared with the standard diagnostic screening that is limited to at-risk and symptomatic patients because of the increased risk of nontraumatic fractures among undiagnosed or untreated CD patients.

Methods

Decision Analytic Model

We constructed a decision analytic Markov model of 12-year-old cohorts with population-based prevalence of CD in North America. A natural history and progression toward hip bone and vertebral fractures were used as clinical end points to assess the cost-effectiveness of providing universal CD serologic screening. A base case age of 12 years was determined clinically relevant for serologic CD testing because dietary habits are more likely shaped by peers, and primary physicians are screening for baseline anemia and dyslipidemia as per standard of care during preadolescence.[22,23] Because the natural age progression to osteoporosis and bone loss is different for male and female subjects, our model is categorized in 2 groups that are based on male or female gender. We considered 2 strategies for comparison, as shown in Figure 1, USS vs standard of care screening.

Our model followed the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine in the development and the analysis of results by using a societal perspective, considering costs and benefits over a lifetime horizon and discounting at 3% annually.[24] Base case parameter estimates and ranges and distributions used in the sensitivity analysis are presented in Table 1. We constructed and implemented the model in TreeAge Pro 2012 Suite (TreeAge Software Inc, Williamstown, MA) and Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA). The 2 cohorts progressed through the model in 1-year time steps until death or 100 years of age. Within each health state, patients could die at a rate that is based on the average age-specific mortality tables, as estimated by the Centers for Disease Control and Prevention.[25] The model analyzed the differences in lifetime discounted costs and ben-