# Genetic Testing Before Serologic Screening in Relatives of Patients With Celiac Disease as a Cost Containment Method

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**Goals and Background:** Relatives of patients with celiac disease have an increased lifetime risk of developing celiac disease. Repeat screening of relatives would improve diagnosis rates, but at significant cost. Genetic testing before screening would potentially reduce costs by eliminating HLA-DQ2 and DQ8 negative patients who are at extremely low risk for developing celiac disease.

**Study:** A decision tree was developed incorporating 3 diagnostic branches: initial screening with anti-tissue transglutaminase at time $t_0$, repeat screening at time $t_1$, and genetic testing before repeat screening. Costs were estimated using Medicare reimbursement fees. Modeling and sensitivity analyses were performed using Tree Age Pro 2006.

**Results:** The cost of an initial screening with anti-tissue transglutaminase is approximately $434 per person. Repeat screening would cost $683, but would diagnosis an additional 4.4% cases. Genetic testing before screening would cost $750, but would decrease the lower endoscopy workload by nearly 25%. Genetic testing would have to decrease from $301 to $234, a difference of $67, to justify its use before serologic testing. As the specificity of anti-tissue transglutaminase approaches 100%, the cost of genetic testing would have to continue to decrease to less than $200 in order for it to be an affordable option.

**Conclusions:** Repeat screening of relatives with celiac disease results in a significant increase in cost, but also an associated increase in cases diagnosed. Genetic testing would potentially eliminate up to 60% of the population to be screened and, if available at a lower cost, would partially offset costs of repeat serologic screening.

**Key Words:** decision analysis, anti-tissue transglutaminase, human leukocyte antigen (HLA) typing

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Celiac disease is a multigenic, chronic inflammatory disease that is triggered by the ingestion of gluten.[1] Classically, the disease manifests as a malabsorptive enteropathy; however, the disease more resembles a multisystem disorder than a primary intestinal disorder.[2] Overall, the disease is associated with an increased morbidity and mortality.[3] The increased mortality rate declines to that of the general population after 3 to 5 years on the gluten-free diet (GFD),[4] a finding which has significant implications for patients with celiac disease. Although previously thought to be a rare disorder, studies using serologic testing have found celiac disease to be common with an estimated prevalence of about $\sim$1%,[5,6] although celiac disease continues to be widely underdiagnosed.[7] While screening for celiac disease is not recommended in the general population, high-risk groups, such as family members of patients with celiac disease may benefit from screening.[8]

Prevalence of celiac disease in first-degree relatives has been estimated to be anywhere from 2.0% to 44.1%[6,9–15] and from 2.6% to 19.5% in second-degree relatives,[6,16] depending on the method used for diagnosis (biopsy vs. serology) and country of study. Celiac disease is also a dynamic process that may emerge much later in life than initially expected; an estimated 1.6% to 6.6% of first-degree relatives may seroconvert over a range of 0.5 to 20 years after an initial negative result, with an annual incidence ranging anywhere from 0.3% to 1.7%.[6,13–15,17,18] The incidence of celiac disease in second-degree relatives is even more uncertain, with 1 study demonstrating, on average, a 10% seroconversion rate over 1.7 years, but these data are limited by a small sample size of n = 20.[13] This makes it very difficult to determine appropriate screening recommendations, as their risk of developing celiac disease is spread over a lifetime. A single screening would most likely miss many cases of celiac disease that have yet to develop, but repeat screening at a set time interval would also be extremely costly and time consuming.

To reduce the burden of diagnostic testing, some have proposed the use of human leukocyte antigen (HLA) typing to exclude patients that lack the necessary phenotype, namely patients who are negative for HLA-DQ2 or DQ8,[19,20] which are necessary, but not sufficient, for the development of celiac disease.[21] An estimated 20% of first-degree family members could be excluded,[20] which would theoretically decrease costs of diagnostic workup. However, HLA typing is not a perfect solution: approximately 40% of the general population also carries either DQ2 or DQ8, of which the majority never develops celiac disease.[22]

In this study, we attempt to determine, using a decision analysis-based computer model, if HLA typing before screening relatives of celiac disease patients is able to reduce screening costs by eliminating HLA-DQ2 and DQ8 negative patients.

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## MATERIALS AND METHODS

### Decision Analysis Model

Decision analysis was used to compare the costs of screening family members of patients with celiac disease. Modeling and sensitivity analyses were performed using Tree Age Pro 2006 (Williamstown, MA). Detailed information about decision analysis and available software can be found elsewhere.[23–27]

The decision tree incorporates 3 diagnostic branches: (1) initial screening with anti-tissue transglutaminase (tTG) at time $t_0$, (2) repeat screening with tTG at time $t_1$ which in the literature ranges from 0.5 to 20 years, and (3) genetic testing using HLA typing before tTG at time $t_0$ followed by repeat tTG at time $t_1$ (Fig. 1). The annual incidence of celiac disease in relatives is unknown. The available studies are difficult to compare directly as they have different mean study population ages, use widely variable time intervals in which repeat testing is performed, and use different methods for diagnosing celiac disease. Given the inherent uncertainty, we chose to model the same methodology that all current studies have used, which is to perform only a single repeat testing as opposed to a yearly testing.

In the first branch, a relative of a patient with celiac disease is screened only once with tTG, which results in either a true positive, false positive, true negative, or false negative, with associated costs for the initial clinic visit, tTG testing, and subsequent esophagogastroduodenoscopy (EGD) with biopsy depending on whether the tTG demonstrated a positive result. In the second branch, a relative is tested initially with tTG as in the first branch, but differs in that all patients who were not biopsy-proven to have celiac disease are retested at time $t_1$, as they are at continued risk for developing celiac disease. In the third branch, relatives are screened twice, first at $t_0$ and then $t_1$, as in the second branch, but are also HLA-typed before initiating celiac disease screening to eliminate those who lack DQ2 or DQ8 from future screening.

Several assumptions were made to simplify the model: (1) time was not factored into the model, therefore patients in the model were not assigned ages and had no mortality rate, (2) there was no inflation rate, (3) EGD with biopsy was designated as the gold standard, (4) HLA typing would be 100% sensitive and specific for identifying HLA-DQ2, DQ8, and heterodimers, (5) cost of a GFD was not included in the model.

### Model Inputs

Celiac disease prevalence and incidence, and HLA-DQ2 and DQ8 prevalence data were derived from the literature, as depicted in Table 1. When applicable, base case inputs were based on data from Goldberg et al,[13] as the study population was located in the United States and the results are relatively conservative in comparison to the available literature.[6,10,14,15] Wide ranges were chosen during sensitivity analysis to account for variability in the literature.

The model uses anti-tTG as the serologic test for celiac disease screening because of its high sensitivity and specificity, wide availability, and reproducibility. Endomysial antibody also has a high sensitivity and specificity, but requires technical expertise to perform. Prior studies have found tTG and endomysial antibody to be equivalent.[28] Sensitivities and specificities for tTG were obtained from the literature and ranged widely to test the consistency of the model, as seen in Table 1.[28,29] Total serum IgA was included in the diagnostic workup as patients with celiac disease are at increased likelihood of being IgA deficient and would therefore be missed on tTG testing alone.

The direct healthcare costs of clinic visits (initial and follow-up), serologic testing, HLA typing, EGD, and biopsy interpretation were estimated using 2005 Medicare reimbursement fees, American Medical Association current procedural terminology billing codes, and vendor pricing information.[30–33] Values were ranged widely over 50% and are detailed in Table 2.

### Sensitivity Analysis

Sensitivity analysis is a method used to measure the influence of a variable on the model by changing the variable to encompass a wide range of real-world values and then examining the outcomes for any changes.[23] A multivariable sensitivity analysis was performed to determine the influences of each variable on the model and determine the robustness of the model. One-way sensitivity analyses were performed on the most influential variables. Costs were reported as a per-person dollar amount.

The prevalence and incidence data for first-degree and second-degree relatives are uncertain and have a great degree of overlap. For the purposes of the model, the prevalence and incidence inputs of first-degree and second-degree relatives were combined as an overall prevalence and incidence. The inputs were varied using sensitivity analysis to encompass the lower-limit and upper-limit values for both first-degree and second-degree relatives and then analyzed using the decision model.

## RESULTS

### Cost Analysis

The cost of an initial screening with tTG of first-degree and second-degree relatives of patients with celiac disease would be an estimated $434 per person. Repeat screening would cost $683 per person, which is an additional $249. HLA typing before screening relatives would be slightly more costly, at $750 per person (Fig. 2). In terms of cost per diagnosis of celiac disease, it would cost $2668 per case in the "tTG at $t_0$" branch, $4047 at the "tTG at $t_0$ and $t_1$" branch, and $4422 at the "HLA typing then tTG at $t_0$ and $t_1$" branch. The incremental cost per additional case of celiac disease diagnosed would be approximately $227,000 for "tTG at $t_0$ and $t_1$" and $449,000 for "HLA typing then tTG at $t_0$ and $t_1$" when compared with tTG alone. In other words, screening with "tTG at $t_0$" is the least costly, followed by "tTG at $t_0$ and $t_1$," and most costly is "HLA typing then tTG at $t_0$ and $t_1$." According to 1-way sensitivity analysis, the cost of genetic testing would have to decrease from $301 to $234, a difference of $67, to justify its use before serologic testing (Fig. 3A). Further reduction in the cost of HLA typing would continue to favor genetic testing before serologic screening.

One-way sensitivity analysis also indicates that HLA typing does not exclude a large enough proportion of patients from further celiac disease screening. On the basis of this model, the genetic test would have to exclude at least 54% of the patients before it would an affordable alternative (Fig. 3B). According to 2-way sensitivity analysis, as the specificity of tTG approaches 100%, the cost of genetic

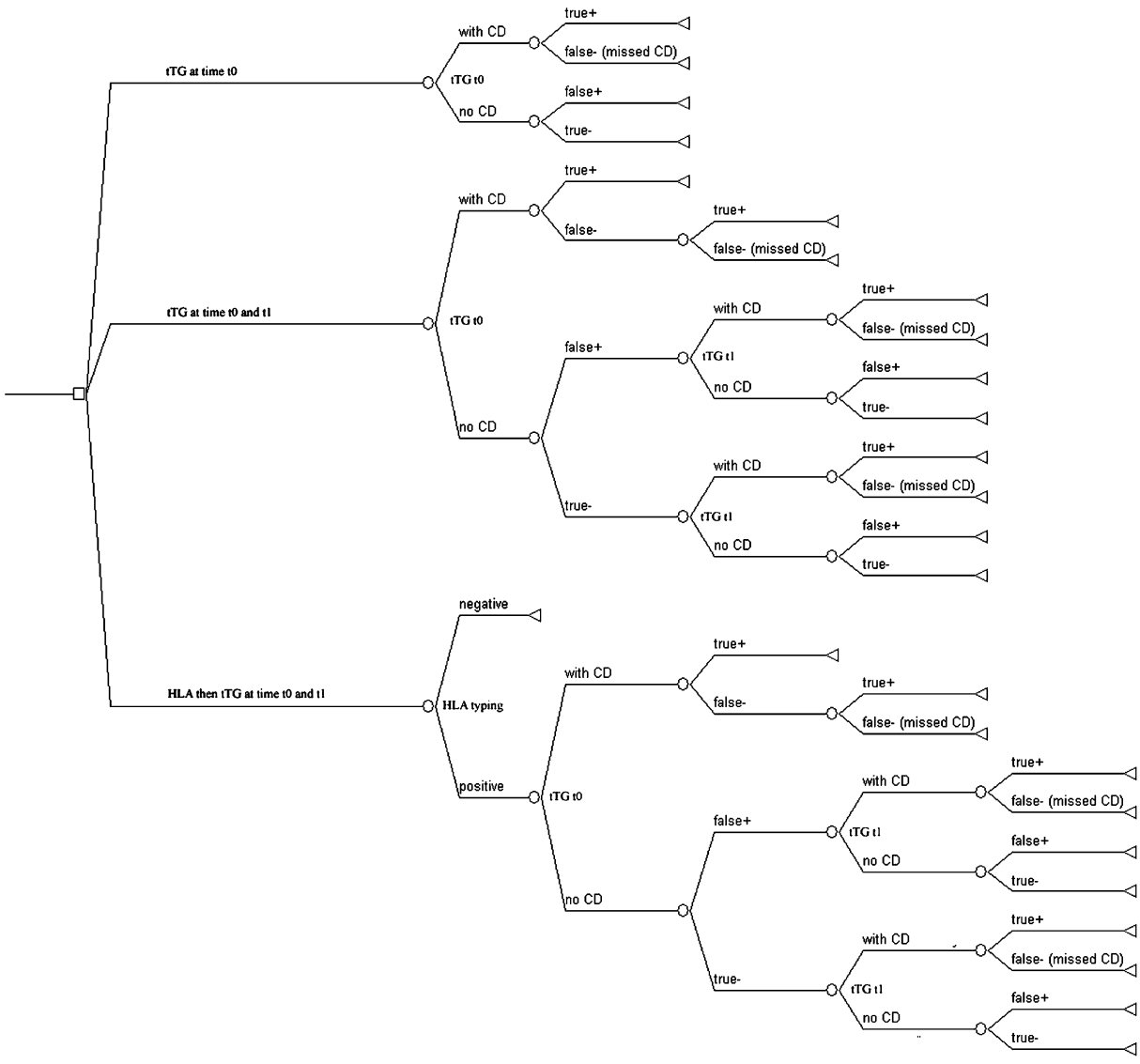


**FIGURE 1.** Decision tree: Open squares represent choice nodes. Open circles represent chance nodes. Open triangles represent end points. CD indicates celiac disease; tTG, anti-tissue transglutaminase.

testing would have to continue to decrease to less than $200 in order for it to be an affordable option (Fig. 3C). This is due to the improved ability to correctly identify patients without celiac disease, which would reduce the number of patients with false positive results and prevent further costly diagnostic testing. On the other hand, because celiac disease is infrequent even among relatives of celiac disease patients, improvements in the sensitivity of tTG would not substantially affect screening costs.

As the cost of tTG is increased, overall screening costs also increase as expected while maintaining the same relative cost relationship among the screening groups. Individual sensitivity analyses of tTG test specificity and sensitivity confirm that an improvement in specificity would reduce screening costs, but an improvement in sensitivity would only affect costs marginally.

Sensitivity analysis on celiac disease prevalence will raise overall cost, but will not result in greater savings with HLA typing (Fig. 4A). Only at very high incidence rates of 47% or greater would HLA typing demonstrate cost savings, but these are unrealistically high rates for either first-degree or second-degree relatives (Fig. 4B).

## Celiac Disease Cases Missed

A 1-time serologic screening would miss an estimated 1.4% of cases as false negatives, and another 3.5% that would seroconvert after the initial screening, for a total of 4.9% of celiac disease cases. Repeat screening would diagnosis an additional 4.4%, missing only 0.4% of celiac disease cases. The addition of HLA typing before screening would improve this only marginally, missing a total of 0.3% of celiac disease cases (Fig. 5).

## Endoscopy (EGD) Workload

Screening once with tTG would result in approximately 21% of patients having a positive result suggestive

 

**TABLE 1.** Input Variables and Ranges Found in the Literature

| Variable | Base-case Estimate (%) | Range in Literature (%) | Range Tested in Sensitivity Analysis (%) | References |
|---|---|---|---|---|
| Incidence rates | | | | |
| % of relatives with HLA-DQ2 and DQ8 | 64 | 63.5-83.1 | 40-100 | 10,20 |
| % of relatives (overall) with positive serologic test, initial | 13.6 | 4.1-13.6 | 0-50 | 6,13 |
| % of first-degree relatives with positive serologic test, initial | | 2.0-44.1 | | 6,10,12–19 |
| % of second-degree relatives with positive serologic test, initial | | 2.6-19.5 | | 6,12 |
| % of relatives (overall) with positive serologic test, repeat | 3.5 | 3.5 | 0-50 | 13 |
| % of first-degree relatives with positive serologic test, repeat | | 1.6-6.6 | | 13–15,17,18 |
| % of second-degree relatives with positive serologic test, repeat | | 10.0 | | 13 |
| Time interval between repeat serologic testing | | 0.5-20 y | | 13–15,17,18 |
| Annual incidence of celiac disease (overall) | | 1.7 | | 13 |
| Annual incidence of celiac disease (first-degree relatives) | | 0.3-1.6 | | 14,15,17,18 |
| Annual incidence of celiac disease (second-degree relatives) | | 5.9 | | 13 |
| Test variables | | | | |
| tTG sensitivity | 90 | 54-100 | 85-99 | 22,23 |
| tTG specificity | 90 | 79-100 | 85-99 | 22,23 |

HLA indicates human leukocyte antigen; tTG, tissue transglutaminase.

of celiac disease, which would therefore require an EGD with biopsy for confirmation. Repeat screening with tTG would increase the number of patients requiring EGD to approximately 31%, in the form of actual cases of celiac disease, but also false positives. Additionally, another 1% of patients who were initially tTG false positive but went to EGD and were subsequently biopsy negative would potentially seroconvert later and require a second EGD. HLA typing before tTG screening would reduce the number of patients requiring EGD, with approximately 24% of patients undergoing EGD once and 0.6% twice. On the basis of these estimates, endoscopy workload would be decreased by nearly 25% with the use of HLA typing before screening when compared with repeat screening with tTG alone.

**TABLE 2.** Estimated Costs of Testing and Services

| | Cost Variables | | |
|---|---|---|---|
| Item | Base Cost | Range | References |
| HLA typing | $301.40 | $150.7-452.1 | 31,32 |
| tTG | $54.27 | $27.13-81.41 | 31,32 |
| Total serum IgA | $12.99 | $6.49-19.49 | 31,32 |
| Initial clinic visit | $254.57 | $127.28-381.86 | 29,30 |
| Follow-up clinic visit | $153.96 | $76.98-230.94 | 29,30 |
| EGD and biopsy | $538.46 | $269.23-807.69 | 29 |

EGD indicates esophagogastroduodenoscopy; human leukocyte antigen; tTG, tissue transglutaminase.

## DISCUSSION

Celiac disease is a genetically determined disease that requires the presence of the alleles that encode for HLA-DQ2 or DQ8.[34] The disease occurs in relatives of those with

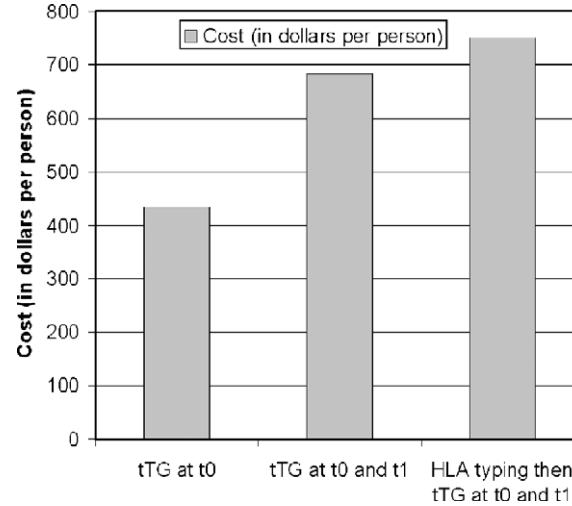


**FIGURE 2.** Cost of screening relatives of patients with celiac disease.

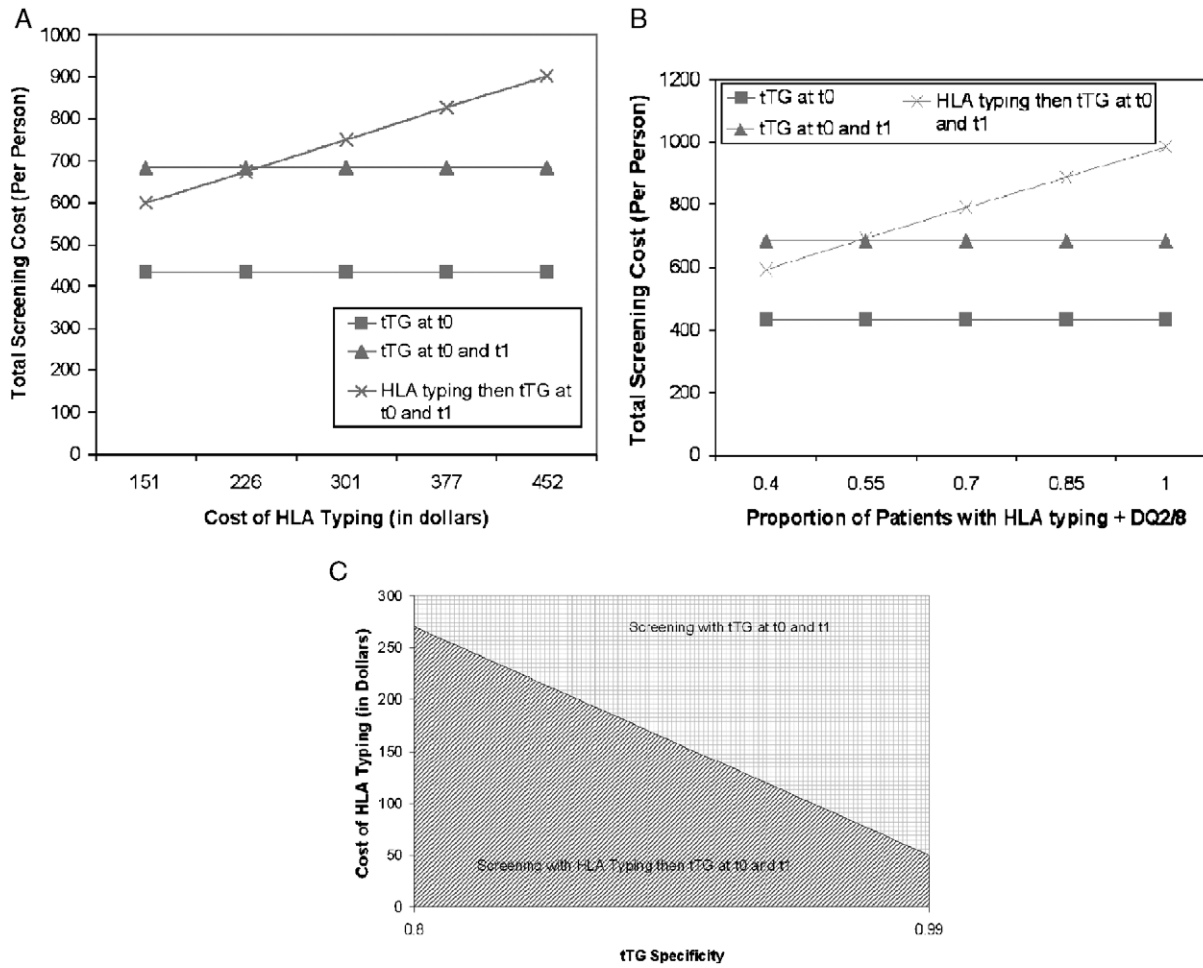


**FIGURE 3.** Sensitivity analysis on HLA typing inputs: (A) the cost of HLA typing, where the 2 lines intersect indicates the cost at which HLA typing would result in equal screening costs for screening with HLA typing and screening with tTG at $t_0$ and $t_1$, (B) the proportion of HLA-DQ2 or DQ8 positive patients where the 2 lines intersect indicates the proportion of patients who would need to be HLA-DQ2 or DQ8 positive to result in equal screening costs for screening with HLA typing before tTG at $t_0$ and tTG at $t_1$, (C) both the cost of HLA typing and tTG specificity. HLA indicates human leukocyte antigen; tTG, anti-tissue transglutaminase

the disease, both first and second degree.[6] The screening of relatives provides about 10% of newly diagnosed patients with celiac disease.[35] Previous studies have demonstrated that a single serologic screening will not pick up all those that have or will develop celiac disease. Although the frequency of testing has not been determined, our recent study demonstrated that 3.7% of those family members at a mean of 1.7 years seroconverted, applying to both adults and children.[13] Other studies have found a lower incidence,[14,15,17,18] but have smaller study populations of assorted ages, use varying methods of diagnosis, and different follow-up periods, which makes it difficult to interpret and compare directly.[36] In view of the requirement for DQ2 or DQ8, we studied the cost-effectiveness of a model that incorporated HLA testing as part of the screening for celiac disease among relatives of those with celiac disease. On the basis of our model, the use of HLA typing before screening for celiac disease, at its current cost, would not reduce screening costs. A substantial reduction in the cost of HLA typing ( > 22%) would be required before it could become an affordable option.

Current serologic tests are too sensitive and specific for HLA typing to make much of an impact from a cost containment standpoint. HLA typing is also a poor genetic screen for celiac disease as positivity does not equal a diagnosis of celiac disease but only implies increased risk of future development. A better genetic test, ideally one that is able to include or exclude a greater proportion of first-degree relatives than HLA typing currently does, would improve screening efforts and allow for better cost containment. However, celiac disease is a multigenic disorder. Either HLA-DQ2 or DQ8, while necessary, is not sufficient to develop the disease. HLA-DQ2 or DQ8 comprises less than 50% of the genetic risk.[37] There are probably many genes that contribute to the risk of developing celiac disease for there are many candidate genes identified in different studies. More specific genetic tests may well be developed in the future.

The development of celiac disease requires the intake of gluten and other environmental factors. The timing of gluten ingestion in relationship to weaning is important as well as the occurrence of gastrointestinal infections,

 

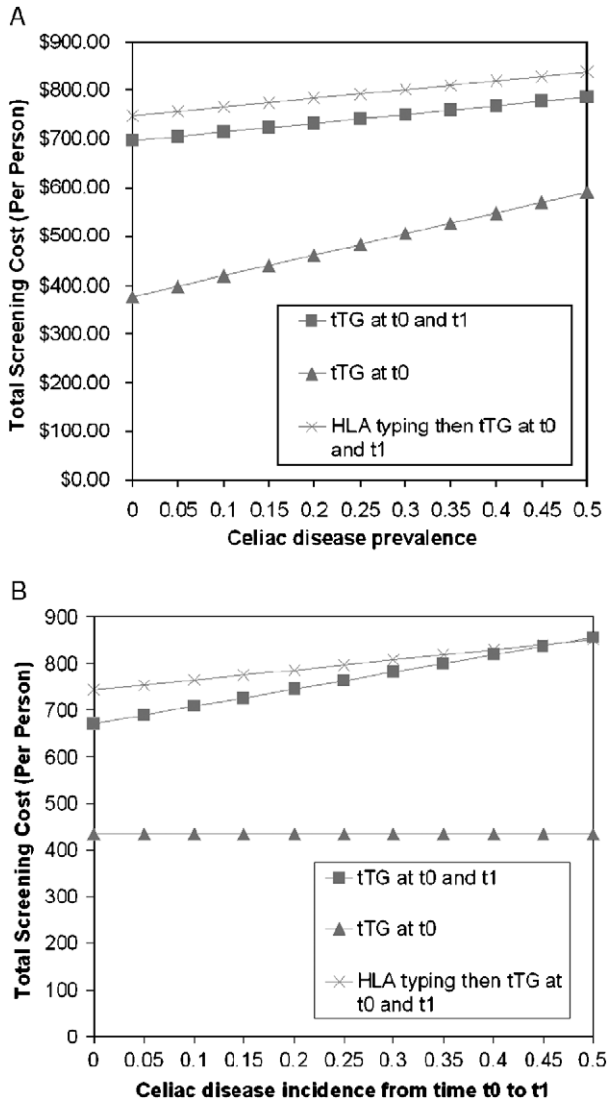


**FIGURE 4.** Sensitivity analysis on celiac disease: (A) prevalence and (B) incidence.

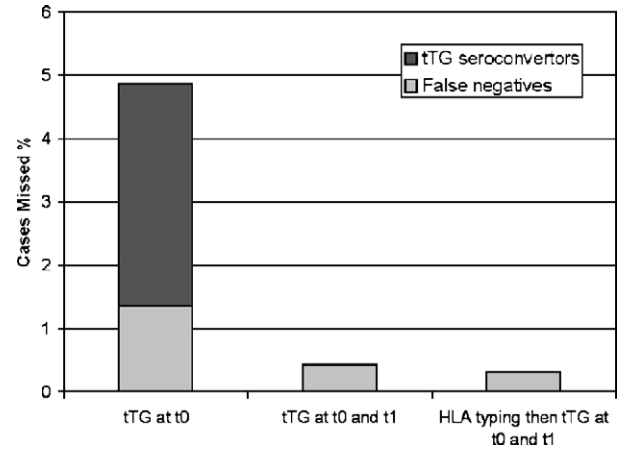


**FIGURE 5.** Percentage of celiac disease cases missed using 3 different screening approaches.

including rotavirus infection.[38] These factors apply to the development of celiac disease in children. Celiac disease can, however, develop at any age, even in the elderly. The mechanism of disease induction in adults, or more specifically in the elderly has not been described. The occurrence of celiac disease in about 1% of both children and adults in populations studied in various countries suggests that most adults have had the disease in childhood.[6,39] This is, however, not clear because the disease may be very mild in many adults. The risk of disease development is therefore not restricted to any age group.

There are also several limitations to our model. Heterogeneous methods for diagnosing celiac disease are often used in actual practice and add to overall costs, but our model demonstrates only 1 method of diagnosis. We opted to use a strategy that would be the least costly to diagnose celiac disease, but the results derived from our model may not entirely reflect current practice.

Because our model did not account for time elements other than a repeat serologic testing period, true cost-effectiveness measured in quality-adjusted life-years was not incorporated into our model. Quality-adjusted life-years is an estimate of mortality benefit in years derived from a treatment (life expectancy) that is adjusted for quality of life (utility) where 0 is death and perfect health is 1, which is calculated as the product of life expectancy and utility. Previous estimations have suggested that appropriate treatment of celiac disease with GFD would produce a utility of 0.99.[40] However, celiac disease has a wide range of clinical manifestations from "silent celiac disease" to the classic enteropathy with a malabsorption syndrome. Thus, different patients may derive highly variable levels of benefit from a GFD, depending on their mode of presentation. It is of interest that a cohort of patients diagnosed with celiac disease, in Finland, through screening reported an improvement in quality of life at a year after diagnosis.[41] In addition, adherence to a GFD is difficult as it is associated with additional cost, compared with a regular diet,[42] which our model did not incorporate and has been estimated to be roughly $1800/y.[43] Dietary adherence is a problem, seen in countries that have governmental financial support of gluten-free food. Rather, we chose to focus strictly on direct costs of the diagnostic workup to determine if HLA typing could decrease expenses enough to allow for more widespread screening of patients at risk for celiac disease. The lifetime rate at which patients develop celiac disease is still unknown, which adds further confusion as to the appropriate time interval in which first-degree relatives of celiac disease patients should be screened. Some have advocated that repeat serologic testing may be justified after 5 to 10 years, once the risk of celiac disease exceeds that of the general population,[36] whereas others are uncertain of the true incidence of celiac disease in relatives and, given the significant cost of repeat screening as demonstrated in our model, question the benefit.[18] It is also reasonable, given the lack of firm data, to follow patients and offer repeat serologic testing only when there is a sufficient clinical suspicion for celiac disease.

Another factor that was not incorporated into the model was the role of very early genetic testing, of infants, before 4 months of age. The testing of infants would allow

 

those at risk to develop celiac disease to be identified and allow parents to introduce gluten, in small amounts, while breast feeding, which may contribute to primary prevention of the disease.[44] Finally, this model did not differentiate among type of relatives (first or second degree), which confers a different degree of risk. Status of parental and sibling HLA genotyping would also alter the risk of developing celiac disease, with the risk ranging anywhere from 0.1% to 29% in 1 study.[37]

Despite the high costs, HLA typing does offer a number of advantages. With each round of serologic testing for celiac disease, false positive results are generated that require further investigation with EGD and biopsy. Although repeat serologic testing does improve the yield of celiac disease cases diagnosed, the number of patients requiring EGD would quickly multiply, adding more cost. HLA typing before serologic screening has the potential to reduce the population of patients being tested initially, which would then reduce the number of false positive results, and thus reduce the total number of EGD required. Patients who are eliminated from further diagnostic work-up by HLA typing would also no longer require surveillance clinic visits.

Ultimately, the use of HLA typing in relatives should be determined on an individual basis, taking into account the patient's other medical conditions and preferences. Although not currently justifiable from a cost perspective alone, HLA typing may spare the individual patient from unnecessary anxiety, diagnostic testing, and its associated risks. Further research is needed to determine the lifetime risk of developing celiac disease, which would guide screening recommendations. With the currently available genetic testing, only high-risk groups would likely benefit from screening, but with future improvements, more investigation would be necessary to evaluate if other populations would also benefit from screening.

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