A PILOT STUDY:

CELIAC DISEASE SCREENING OF HIGH RISK STUDENTS

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To the Dean of the Graduate School:

I am submitting herewith a dissertation written by Claudia Pillow entitled "A Pilot Study: Celiac Disease Screening of High Risk Students." I have examined this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy with a major in Health Studies.

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ABSTRACT

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The purpose of this study was to pilot test a screening tool that identifies children at high-risk for celiac disease which could be administered at the public school level by the school nurse. This instrument validation was designed as a case-control study and had three different sample groups (N=138): one case and two levels of control. The case group was 78 children with diagnosed celiac disease whose parents were recruited from mailing lists made available by their local celiac support groups. The control group was divided into two groups: 45 non-case children without diagnosed celiac disease whose parents were recruited from a published community phonebook; and 15 non-case children known to have tested negative for celiac disease by either blood test or biopsy, whose parents were purposively recruited from three different celiac support groups. The instrument was an original survey containing 16 questions related to the common clinical symptoms and conditions of celiac disease.

Results: the case group mean questionnaire score was 43% higher than the control group ($t=-12.5$, $p=.001$). An ANCOVA of independent variables for celiac disease identified four statistically significant correlations ($r \geq .4$, $p=.001$): anemia with anxiety; anemia with short stature; stomach pain with intestinal pain; and older children and

aches. A factor analysis of the case group identified six subsets of health symptoms and conditions, that when present together, increase a child's risk for celiac disease. The accuracy measurements indicate that the questionnaire has a high degree of predictive validity for celiac disease (82% sensitivity, 94% specificity, 94% PV+, 80% PV-). The reliability test-retest score was relatively high (r=.87).

The pilot test concluded that the questionnaire met the nine recommended policy criteria by the American Academy of Pediatrics for school screening programs, including validity and reliability.

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CHAPTER I

INTRODUCTION

Rationale

Celiac disease (CD) is the most common hereditary autoimmune condition in the United States (North Tarrant Gluten Intolerance Group, 2005). It is a genetic intolerance to gluten, a protein found in wheat, rye, and barley. When a person with celiac disease eats these foods, gluten triggers the immune system to attack the lining of the small intestine. This reaction causes inflammation and interferes with the digestion of vitamins, minerals, and other vital nutrients. Left untreated, the disease can cause malnutrition, diabetes, cancer or autoimmune deficiency disorders.

Once considered rare, a recent study by Fassano and Catassi (2001) suggested that the prevalence of CD is much higher than previous estimates, affecting as many as three million Americans (or approximately one in 100) with peak prevalence rates at the age of six to seven and then again at 45 years of age. Greco (1997) considered celiac disease to be the most under diagnosed, chronic pediatric disease in the U.S. The diagnosis rate is one in 3333 people, leaving 97 percent of the cases undiagnosed and untreated (Green et al., 2001). The average length of time between the onset of symptoms and confirmation of CD diagnosis is nine years (NIH, 2004). Given this major diagnosis gap, there is a strong need for education and screening in order to reduce medical costs, alleviate unnecessary suffering, and improve the quality of life for individuals with celiac disease

(NIH, 2004). Early intervention is necessary to prevent damaging complications of this disease, especially in childhood cases. The longer a child with CD is exposed to gluten, the higher the prevalence of other associated autoimmune disorders, neurological problems, osteoporosis, and cancer (Hoffenberg et al. 2003). Gadewar and Fassano (2005) stated that the best approach to early intervention is "active case finding", which is the process of screening individuals known to have an increased risk for CD.

Statement of the Purpose

The prevalence rate of CD is one in 22 for those with associated risk factors (NIH, 2004). The primary goal of this research was to pilot test a celiac disease screening tool that identified high-risk children and could be administered at the public school level by the school nurse. High risk children were identified as those with a high score from a two page parent questionnaire. They were then referred to their pediatrician for serologic testing. The goal of this study was based on two important points: 1) Early detection in childhood results in decreased lifetime medical costs related to treating CD, and 2) Early detection improves the quality of life of celiac patients by alleviating unnecessary physical and psychological suffering.

The objectives of the pilot test were to: 1) develop a screening tool based on secondary research; 2) test the screening tool for criterion-related validity; 3) test the screening tool for reliability using the test-retest method; and 4) conduct a case factor analysis to identify symptoms with the strongest relationship to celiac disease.

Research Questions

1. Based on published research, what are the most common childhood symptoms in undiagnosed celiac children?
2. Which symptoms in undiagnosed celiac children have the strongest relationship to celiac disease?
3. Is the screening tool valid?
4. Is the screening tool reliable?

Hypotheses

Hypothesis 1: A child with diagnosed celiac disease will have a significantly higher score on the questionnaire than a child without diagnosed celiac disease.

Hypothesis 2: There exist several subsets of health symptoms and conditions, that when present together, increase a child's risk for celiac disease.

Hypothesis 3: The questionnaire will have a high degree of predictive validity for celiac disease.

Hypothesis 4: The correlation between two sets of questionnaire scores for the same child will be relatively high (.80 or above) in order for the instrument to be considered reliable.

Delimitations

The delimitations of this study were as follows:

1. Issues of internal validity include the geographic and demographic homogeneity of the project and its participants.

2. Non-random allocation of participants due to personal relationships with the researcher.
3. Content, context and criterion-referenced factors of the questionnaire.
4. Central to the achievement of credibility in this study is the ability of parents to identify diagnosed medical conditions in their children. The questionnaire served as a vehicle for identification, but was limited by the parent's ability to accurately and truthfully answer the questions, thus possibly introducing information bias.

Limitations

The limitations of this study were as follows:

1. The use of two different non-probabilistic samples of convenience.
2. Other external limitations include confounding factors associated with childhood ailments, conditions and diseases.

Assumptions

The assumptions of this study were as follows:

1. The participants could read and understand English.
2. The participants were honest in their answers to the questionnaire.

Definition of Terms

Gluten - is the water-insoluble fraction of wheat flour, largely composed of two groups of proteins: glutenins (ethanol insoluble) and gliadins (ethanol soluble). Individuals with celiac disease are intolerant to the gliadin fraction of gluten, as well as equivalent prolamins found in rye and barley.

Importance of the Study

Gluten is ubiquitous in western life. Only through innovative screening programs for celiac disease will there be improved understanding of the prevalence of CD, as well as an appreciation of the benefits and limitations of screening. This piloted screening tool is simple, fast, and inexpensive. It has the ability to reach a broad population of high risk children by "active case finding" within the safety of the school environment. Even more significant is the screening program's ability to increase awareness of CD at the public school level, which should increase the rate of early detection. Not only does early detection in childhood result in the highest rates of compliance to a gluten-free diet (Pietzak, 2005), but it also decreases lifetime health care costs and the development of secondary diseases associated with celiac disease.

CHAPTER II

REVIEW OF LITERATURE

The review of literature is divided into the following seven content areas: School Screening Programs; Epidemiology of Celiac Disease; Classifications of Celiac Disease; Symptoms of Celiac Disease; Screening for Celiac Disease; Reasons to Screen for Celiac Disease; and Causes of Celiac Disease.

School Screening Programs

Schools are responsible for ensuring the health of all students while at school. Schools lose federal and state funding for student absences. Many elementary schools currently incorporate early detection and screening for certain diseases and conditions, such as vision, hearing, and speech evaluations. The American Academy of Pediatrics (2000) suggests that schools screen for numerous health-related problems in addition to mandated screens. In recent years, this list has included screenings for mental health problems, substance abuse, hypertension, obesity, type 2 diabetes, high cholesterol, asthma, tuberculosis, and head lice. For school screening programs to be successful, they must be effective and not inadvertently harmful. Evidence to support or oppose screening for many of the aforementioned health problems is still being evaluated. Two examples of recent cost-effective studies include a school-based sexually transmitted disease screening program (Wang, Burstein, & Cohen, 2002) and a school-based tuberculosis screening program (Brassard, Steensma, Cadieux & Lands, 2006). Both programs

targeted low income, urban children and both were found to be cost effective with respect to the use of public funds and helped to reduce the burden of disease among the children.

Another study (Poitra et al., 2003) tested the feasibility of a school-based screening program for fetal alcohol syndrome (FAS) by evaluating the prevalence rate in the screened population and the ability to implement the program using available personnel from the community. The prevalence rate was 4.4%, the sensitivity was 100%, and specificity was 95%. Ninety-five percent of the children were accurately categorized by the 32-item screening tool. The study concluded that the community based utilization of the FAS screen was time efficient (less than 15 minutes per child) and effective (produced a small referral population of 5%).

Population-based case identification and individual case detection offer appropriate approaches for schools to determine which students have common chronic diseases. Population-based case detection uses surveys, tests, examinations, or other procedures to rapidly identify those students who have symptoms but have not been diagnosed. Individual case detection occurs when undiagnosed students present to health care providers with symptoms of the illness or condition (Wheeler, Boss & Williams, 2004).

Redline, Larkin, Kercsmar, Berger and Siminoff (2003) conducted a study to develop and validate a school based asthma and allergy screening instrument for parents and students. Similar to the FAS study, they used a screening questionnaire that was developed through literature review, expert medical and child development input, focus group feedback, and a rigorous trial of the instrument in a public school setting. Validity

was evaluated by blinded comparison of results against a standardized clinical evaluation. The questionnaire was distributed to 2800 children and their families in an urban public school system (K thru 6th). They concluded that administration of a school-based questionnaire was feasible, with a high response rate (74%) and excellent internal consistency. A high sensitivity (80%) and acceptable specificity (75%) were achieved by using one to two questions for asthma, allergic rhinitis, and allergic conjunctivitis. Among the children in grades two or above, comparable level of prediction could be achieved with the student or parent version, with a positive predictive value (PV) of 50% and a negative PV of 92%.

More comprehensive results were found in a 2002 study (Gerald et al.) of 13,247 elementary students conducted by a research group from the University of Alabama. The major hypothesis of the intervention study was that a school-based asthma education and intervention program would result in improved functional status and more appropriate health care utilization in a group of inner-city and largely minority children with asthma. In order to identify at risk children, a multi-stage screening procedure was developed. First, the parents were asked to complete a 12-item screening questionnaire. An 83% response rate was achieved. Those classified as suspected asthma by questionnaire underwent further testing, including spirometry and exercise challenge. Using the questionnaire alone, the measured asthma prevalence was 32%; the addition of further testing reduced the estimate to ten percent. The diagnosis of asthma was confirmed in 96% of children who saw the study physician. The data showed that 19% of asthmatics were undiagnosed prior to this screening procedure, indicating a substantial burden of

undiagnosed asthma. Using the multi-stage screening procedure, the asthma prevalence rate in this population rose by 23% (from 8.05% to 9.89%). The study did not test sensitivity or specificity of the screening procedure. The data showed evidence that screening for asthma with questionnaires of asthma symptoms alone resulted in low specificity and identified large numbers of false positives. False positive screening tests for a serious chronic disease can be stressful for patients and children and could overburden physician offices with referrals. The study concluded that the use of a simple, reproducible, and portable test in conjunction with a screening questionnaire can be used to identify children with suspected undiagnosed asthma in a school-based program.

In an effort to develop screening program policy that will ensure improved functional status and health care utilization of children, the American Academy of Pediatrics (Wheeler, Boss & Williams, 2004) recommended that a school screening program meet the following nine criteria:

1. The disease has a high prevalence or high incidence.
2. Treatment is available and able to prevent or reduce morbidity.
3. The screening test has high sensitivity and specificity.
4. The screener is well trained and experienced.
5. The target population has a high prevalence and will benefit from screening.
6. All positive screens will have definitive referrals and evaluation, and be advised on appropriate treatment.
7. The program is appropriate for a school site.
8. The program can be assessed for efficiency and effectiveness.

9. The program costs less than the benefit of early intervention.

Currently there is no school based screening program for celiac disease.

The Epidemiology of Celiac Disease

Celiac disease, once considered to be a condition that mainly affected people of European descent, is found throughout the world. The prevalence of diagnosed celiac disease varies widely among European and US populations, but the estimates of combined undiagnosed and diagnosed celiac disease are remarkably similar, between 0.7% and 2% (Rewers, 2005). Cases of celiac disease have been reported in children from Eastern Europe, southern and central Asia, and the Middle East. Although the disease is believed to be rare in Africa, the highest prevalence of 5.6% has been reported for children in the North African Sahara region (Catassi et al., 1999). However, few prevalence studies on children have been performed. Studies find the frequency to be one in 67 (Finland) to one in 290 (Estonian) children (Rewers, 2005; Ress et al., 2006). Generally, similar rates have been reported for non-European white populations, such as New Zealand, Australia, Argentina, and Israel.

There are few studies that have specifically screened African Americans, Hispanic or Native American populations in the United States. The prevalence for Hispanic children was reported to be more than three times lower than in non-Hispanic whites (Rewers, 2005). A recent study from Canada described celiac disease among Asian Canadians with origins from northern India, Japan, and China (Rashid et al., 2005).

Rewers, 2005 epidemiology study of celiac disease concluded that the estimates based on sero-epidemiologic studies suggest that, for each diagnosed case of CD, there

may be three to seven undiagnosed cases and that one to three percent of the general population in Europe and the United States is affected at some point in life. Most studies point to a secular increase in the prevalence of celiac disease that is largely due to increasing index of clinical suspicion and availability of highly sensitive and specific serologic screening tests. The recent improvement in serologic screening techniques will enable further testing in different ethnic and racial groups and people of different ages.

Population-based estimates of the incidence of biopsy confirmed celiac disease in adults vary from two to 13 per 100,000 per year (Rewers, 2005). These rates have to be interpreted with caution because many patients diagnosed as adults likely have had 20 to 60 years of untreated CD, and therefore is not a true indicator of new cases.

Fasano (2005) stated that "*the clinical manifestations of celiac disease are protean in nature and vary markedly with the age of the patient, the duration and extent of disease, and the presence of extra intestinal pathologic changes. In addition to the classic gastrointestinal form, a variety of other clinical manifestations of the disease have been described, including atypical and asymptomatic forms. The typical form of celiac disease, characterized by failure to thrive, is still the most frequent presentation in the pediatric age group.*" Because CD often is atypical or even clinically silent, many cases go undiagnosed and are exposed to the risk of long-term complications. The incidence of celiac disease is rising in the United States, but patients are seldom screened in the absence of gastrointestinal symptoms. Atypical presentations increase the delay of diagnosis of CD in children, with a mean duration of 13 months before diagnosis in the USA, compared with three months in Europe (Loma-Sanner et al., 2005).

The morbidity rate of celiac disease can be high. Its complications range from osteopenia and/or osteoporosis to infertility in women, short stature, delayed puberty, anemia, and even malignancies (mostly related to the GI tract, such as intestinal T-cell lymphoma). As a result, mortality is increased by up to six-fold in untreated celiac disease (Busschots, 2006).

In a study by Hill et al. (2000) the prevalence of celiac disease in at-risk groups (presenting with symptoms) of children in the United States was one in 33. The children were screened for IgG and IgA antibodies and antiendomysium (EMA) antibodies. In another large multicenter study of 13,145 subjects by Fasano et al. (2003), prevalence ratios for at-risk groups were 1:22 in first-degree relatives; 1:39 in second-degree relatives; and 1:56 in symptomatic patients. The overall prevalence of celiac disease in not-at-risk groups was 1:133. Serum antigliadian antibodies and antiendomysium antibodies were measured.

A cross-sectional study (Ress et al, 2006) of school children in Estonia found the prevalence rate to be one case per 290 students, a higher rate than in a previous screening. The study tested for the IgA assay only. In comparison, a cross-sectional study (Tommasini et al., 2004) of Italian school children found the prevalence rate to be one in 96 students. The study tested both tissue trans glutaminase (tTG IgA) and EMA assays.

These higher prevalence rates support the growing recognition that celiac disease is much more common than previously recognized and this growth has coincided with the increasingly widespread use of serological testing. A recent 21 year prospective study (Ravikumara et al., 2006) involving a single clinical center, found significant changes in

the presentation of childhood CD, namely a decreased proportion presenting with GI manifestations and a rise in the number of asymptomatic cases picked up by targeted screening. Almost one out of every four children with celiac disease are now diagnosed by targeted screening and two-thirds are asymptomatic (Tommasini et al., 2004). Rampertab et al. (2006) found a similar trend in the presentation of celiac disease in adults. Fewer patients presented with symptomatic celiac disease characterized by diarrhea and more patients presented as asymptomatic adults detected at screening.

The Patwari et al. (2003) prospective study of 65 celiac children found the mean age of diagnosis was 8.7 years (SD=3.3). Diarrhea and failure to thrive were the most common symptoms. At diagnosis, 80% of the cases had anemia. In a different prospective study (Poddar et al., 2006) of 549 Indian children with celiac disease, 91% presented with failure to thrive, 84% with diarrhea and anemia, and 60% had short stature.

The prevalence of celiac disease in 135 children with iron deficiency anemia was 4.4% (Kalayci et al., 2005). In a clinical study (Corazza et al., 1995) of 200 anemic adults, the prevalence rate of CD was 5%. In a more recent European cross-sectional study by Sanders et al. (2003) of undiagnosed adults, the prevalence of celiac disease was 4.7% in participants with iron deficiency anemia, 3.3% in participants with irritable bowel syndrome, and 3.3% in participants with fatigue.

A recent study (Queiroz et al., 2004) concluded that it was important to test all children with short stature for celiac disease since the study found the prevalence of celiac disease in a population of Brazilian children of short stature to be 4.7%. Early

screening is important because, independent of age at diagnosis, children of short stature diagnosed before the age of nine years catch-up in growth to normal growth within two to three years (Damen et al., 1994). Under a gluten free diet, growth velocity, age-related height, predicted height and relative bone age increased (De Luca et al., 1998). In children with late-diagnosed celiac disease, a gluten free diet leads to normalization of body mass and a significant but incomplete recovery in height-for-age Z scores during four years of follow-up (Patwari et al., 2005). Catassi and Fasano (2004) stated that both a rapid diagnosis of celiac disease and a quick initiation of a gluten-free diet are essential to achieving catch-up growth in affected children.

Celiac disease can occur at any stage in life; a diagnosis is not unusual in people older than 60 years. Classic GI pediatric cases usually appear in children aged nine to 18 months (Busschots, 2006).

Celiac disease is a female-predominant disease with a female to male ratio of 3:1 (Green & Jones, 2006). In view of this female predominance, Bai et al. (2005), sought to determine the influence of gender on the clinical manifestations of the disease in a large patient cohort study. They found most gender differences to be physiological with men having a shorter duration of illness before diagnosis and more severe manifestations and malabsorption. They also tended to develop female-predominant diseases at the same rate (30.7%) and severity as women such as anemia, poor bone density, and other autoimmune diseases. There were no gender differences in age of diagnosis, mode of presentation, and prevalence of gastrointestinal symptoms of family history of celiac disease.

Celiac disease is a multigenic disorder associated with the HLA class II genes, HLA-DQ2 and HLA-DQ-8. Almost 100% of affected individuals have either HLA-DQ2 or HLA-DQ8, in comparison with the general population, in which 40% have either DQ2 or DQ8. HLA-DQ2 is expressed in more than 90% of the people with celiac disease. Therefore, the expression of these HLA-DQ2 or HLA-DQ8 molecules is necessary but, not sufficient to develop the disease (Green & Jabri, 2003).

The genetic predisposition to gluten sensitivity is also linked to the list of genetic conditions associated with a higher incidence of celiac disease. Children with Down syndrome (10% CD prevalence), Turner syndrome (5% CD prevalence), and William's syndrome (3% CD prevalence) have a significantly higher incidence of celiac disease than the general population (NASPGHAN, 2004). Children with autoimmune disorders such as type 1 diabetes (8% CD prevalence) (Sumnik et al., 2005), autoimmune thyroiditis (3% CD prevalence), and rheumatoid arthritis (3% CD prevalence) also have a higher incidence of celiac disease with the incidence reported as high as one in 12 children (Pietzak & Thomas, 2003).

Strong evidence suggests that celiac disease occurs more often in family members than in others. Children with at least one first-degree relative with celiac disease have an 8 to 10% prevalence rate (Rashid et al., 2005) and possibly up to 5% for patients with secondary degree relatives with CD (Busschots, 2006). However, lack of a family history for other dietary allergies, including allergy to wheat, should not influence clinical suspicion for celiac disease. Early studies of identical twins failed to prove the disease in all instances. However, studies performed after serologic tests became available and after

subtle changes in duodenal morphology were appreciated as causes, have shown that given the same genetic and environmental factors, concordance is nearly 100% (Green & Jones, 2006).

Classifications of Celiac Disease

The National Institute of Health (2004) identifies four classifications of patients with putative subphenotypes: *Classical celiac disease* is dominated by symptoms and sequelae of gastrointestinal malabsorption. The diagnosis is established by serological testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet. *Celiac disease with atypical symptoms* is characterized by few or no gastrointestinal symptoms, and extra intestinal manifestation predominates. Recognition of atypical features of celiac disease is responsible for much of the increased prevalence, and now may be the most common presentation. The lack of awareness about atypical or mild presentations of celiac disease (such as constipation, anemia, extreme weakness, and mood swings or depression) among health professionals contributes to the CD's delayed diagnosis (Rashid et al., 2005). As with classical celiac disease, the diagnosis is established by serologic testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet. *Silent celiac disease* refers to individuals who are asymptomatic but have a positive serologic test and villous atrophy on biopsy. These individuals usually are detected via screening of high-risk individuals. *Latent celiac disease* precedes diagnosis of CD and is defined by a positive serologic but no villous atrophy on biopsy. These individuals are asymptomatic, but later develop symptoms and/or histologic changes.

The iceberg is often used as a model by researchers to describe the epidemiology of celiac disease. The tip of the iceberg protruding above the surface represents those with classic CD, while the body of the iceberg below the surface represents those with atypical, silent and latent CD.

Symptoms of Celiac Disease

Symptoms of celiac disease are highly variable often resulting in prolonged delays in diagnosis. Fifty percent of newly diagnosed individuals with celiac disease do not have gastrointestinal symptoms at the time of diagnosis (Hill, 2003). Gastrointestinal symptoms of celiac disease vary from severe diarrhea leading to malnutrition and failure to thrive with anemia and abdominal distention, to chronic intermittent, mild gastrointestinal complaints of abdominal pain/bloating diarrhea or constipation, nausea and vomiting. Some children with small bowel biopsies consistent with celiac disease have no signs and symptoms of the condition (silent celiac disease). The classic presentation of celiac disease, the infant who initially does well but after the introduction of cereal become irritable with a potbelly, wasted extremities, bulky loose stools, and weight loss or failure to gain weight, may be less common than the older child with milder disease who has less dramatic or variable symptoms (NASPGHN, 2004). This variability in symptoms leads to delay in diagnosis and treatment, and frustration for families and patients. A recent Canadian survey (Rashid et al., 2005) of children diagnosed with celiac disease found children had symptoms for over a year prior to diagnosis.

The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (2004) recommends that primary care providers consider diagnosing celiac disease early in children with a combination of persistent diarrhea and poor weight gain, weight loss or failure to thrive. Children with food allergies; recurrent gastrointestinal symptoms, including abdominal pain, anorexia, constipation, vomiting; or other global symptoms found in celiac disease should also be evaluated, as part of a differential diagnosis, for the presence of celiac disease. In addition, all children who are first degree relatives of an individual with confirmed celiac disease, have type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency or autoimmune thyroiditis should be screened, even if they are without gastrointestinal symptoms (NASPGHN, 2004). The presence of obesity does not exclude diagnosis (NIH, 2004). In fact, a recent cohort study (Dickey & Kearney, 2006) of 371 celiac patients found that 5% were underweight at diagnosis, 57% were normal, and 39% were overweight or obese, as measured by BMI.

In 2004, The National Institute of Health reported that it is very common for celiac disease to present with extra intestinal manifestations, sometimes with little or no gastrointestinal symptoms. A distinctive example is dermatitis herpetiformis (DH), an intensely pruritic autoimmune blistering skin condition. Almost all patients with dermatitis herpetiformis have CD (Green and Jones, 2006). DH affects 10% to 20% of patients with celiac disease (Reunala, 2001). Other presentations include iron deficiency anemia, delayed puberty, vitamin deficiencies, infertility, recurrent fetal loss, and dental

enamel hypoplasia. In addition, celiac disease may be associated with an autoimmune endocrinologic disorder such as thyroiditis.

Results of a new study (Stenson et al., 2005) report a higher prevalence rate of celiac disease in individuals with osteoporosis than in the general population (3.4% versus 0.2 %). This study validated a 2005 screening study by Murray, in which CD was found in 3.4% of adults with low bone mass, and in 5% of a pediatric population with low bone density. In another study (Gabrielli et al., 2003) of patients with migraines, 4.4% of the patients with migraines tested positive for celiac disease in comparison to 0.4% of patients who did not suffer from migraines. Additionally, when changed to a gluten-free diet for six months following diagnosis, migraine attacks either disappeared completely or reduced in frequency, duration and intensity. These studies may justify screening patients with osteoporosis and migraines for celiac disease.

There is a distinct neurological component to celiac disease that includes taxia, epilepsy, chronic neuropathies and dementia in adults and may be associated with softer neurological signs, such as headaches, learning disorders, ADHD, depression, autism, developmental delay and hypotonia in children. Salur et al. (2000) found the prevalence of CD to be 14.6% among 206 Estonian children with neurological disorders (epilepsy, retardation of psychomotor development, or Down's syndrome) compared with 0.37% for a non-selected group of Estonian children. Phynnonnen et al. (2004) found celiac disease in adolescents to be associated with an increased prevalence of depressive and disruptive behavioral disorders, particularly in the phase before the intervention of a gluten-free diet. Additional non-gastrointestinal symptoms associated with celiac disease

include dental enamel hypoplasia of the permanent teeth, osteoporosis, short stature, delayed puberty, anemia, folate and vitamin K deficiency, arthralgia, alopecia, infertility, and recurrent spontaneous abortions (NASPGHAN, 2004).

In support of the NASPGHN and NIH, a recent study by Rashid et al. (2005) of 168 Canadian children with biopsy-confirmed CD, reported that abdominal pain, gas and bloating were the most common symptoms prior to diagnosis, present in 90% of the respondents. Other presenting symptoms included weight loss (71%), poor growth (70%), diarrhea (65%), weakness (64%), nausea/vomiting (53%), anemia (40%), mood swings/depression (37%), constipation (30%), eczema (24%), short stature (18%), dental enamel defects (15%) and type I diabetes (8%). Eight percent of the children had a first degree relative with biopsy-confirmed CD. Prior to diagnosis, 24% of the families consulted two or more family physicians, 30% consulted at least two pediatricians, and 6% consulted two or more gastroenterologists. Before the recognition of celiac disease, other diagnoses received by the children included anemia (15%), irritable bowel syndrome (11%), gastroesophageal reflux (8%), stress (8%), and peptic ulcer disease (4%). The median time between onset of symptoms and the diagnosis of celiac disease was one year. The median age of presentation was 4.8 years. A serological test of some type was performed to screen for the celiac disease in 70% of the group.

Similarly, in an earlier Canadian celiac health survey for adults by Cranney et al. (2003), the majority of respondents presented with abdominal pain (74%), diarrhea (71%), fatigue (66%), weight loss (64%), anemia (57%), and osteoporosis (27%). Prior to diagnosis, 30% of the respondents consulted four or more family doctors. The median

delay in diagnosis after onset of symptoms was one year after history of weight loss, two years after onset of symptoms of nausea and vomiting, four years after onset of abdominal pain and bloating and ten years after onset of symptoms of constipation. Forty-four percent of the respondents had been told symptoms were due to anemia, 32% due to stress and 24% were told their symptoms were due to irritable bowel syndrome. The mean age at diagnosis was 45 years.

Zelnik et al. (2004) found that there is growing recognition that celiac disease is a multi-system autoimmune disorder with many associated conditions and syndromes. Green and Jones (2006) suggest celiac disease predisposes people to having other autoimmune disorders. The evidence comes from a study demonstrating that children diagnosed before age two developed autoimmune diseases at the same rate as the rest of the general population, 3% to 5%. However, there was a linear increase in the prevalence of autoimmune diseases with the increasing age of diagnosis of celiac disease up to the age of 20, where 30% of the individuals in the study had an autoimmune disease. This study supports the need for early diagnosis of celiac disease.

A study by Kero, Gissler, Hemminki, and Isolauri (2001) found the cumulative incidence of asthma in children with CD was significantly higher than in children without CD. Asthma is generally regarded as a disease with strong T(H)2-type cytokine expression, whereas celiac disease has a T(H)1-type expression. The 1987 Finnish birth cohort study measured the cumulative incidence of asthma in children with celiac disease to be 24.6% compared to 3.4% in children without CD. The data indicates that the T(H)1

and T(H)2 disease can coexist, suggesting a common environmental denominator behind the disease process.

In individuals with significant gastrointestinal symptoms, malnutrition due to poor absorption of nutrients from the small intestine can be significant. Permanent stunting of growth can occur when the disease begins during childhood. The neurological associated manifestations can have profound impacts on school performance and quality of life. Identified long-term complications of untreated celiac disease include increased risk of gastrointestinal malignancies, dental enamel defects, and osteoporosis (Hill, 2005).

Screening for Celiac Disease

Celiac disease can be diagnosed in the presence of characteristic changes in a small intestinal biopsy sample, and by improvements in clinical symptoms or histological tests on a gluten-free diet. Celiac disease affects mucosa of the duodenum in the small intestine. The small intestine is the site of the final stages of digestion and absorption of nutrients. Normal small intestinal mucosa is velvety in appearance and densely covered by minute hair-like projections of epithelial cells, the villi. The absorption of nutrients occurs in enterocytes, specialized cells in the villi. Between the bases of the villi are indentations called crypts, which are tiny pits in the intestinal mucosa and are the site of the creation of new epithelial cells for the intestinal lining. The autoimmune reaction to the toxic gliadin protein fraction of gluten is variable between individuals, with some individuals having more severe mucosal damage to the small intestine than others. Proinflammatory cytokines have also been found to be increased in children with celiac disease and may play a role in mucosal damage (Hoffenberg et al., 2004). The major

histological feature suggestive of celiac disease is an inflammatory response to gliadin molecules in the small intestine, resulting in villous atrophy (flattened) of the intestinal lining, the formation of a dense infiltrate of inflammatory cells forms in the layer of the intestinal wall below the mucosa, and lymphocytic infiltration (NASPGHAN, 2004; Pietzak & Thomas, 2003). Histological changes in the mucosa may be intermittent so multiple biopsies are recommended to fully assess for changes consistent with celiac disease (NIH, 2004). These changes in duodenal mucosa result in malabsorption of nutrients resulting in failure to thrive, and complex anemia from iron, folate, and/or vitamin B12 deficiencies. In children with severe mucosal damage, the absorption of fat-soluble vitamins, zinc, and protein are also affected. The mucosal damage can increase over time so an initial negative small bowel biopsy does not rule out future positive findings.

Although a small bowel biopsy is the gold standard diagnostic test for celiac disease, there are screening tests to help determine those people with high probability of the disease from those with low probability. Current evidence indicates that IgA anti-transglutaminase 2 and IgA antiendomysial antibodies have good sensitivity and specificity and are superior to other markers for celiac disease. The current recommended screening test is either a measurement of IgA antibody to human recombinant tissue trans glutaminase (tTG IgA) or anti-endomysial antibodies (EMA IgA) taken from blood (NASPGHN, 2004). The sensitivity of tTG IgA in both children and adults ranges from 77%-100% and the specificity ranges from 91%-100%. Elevation in tTG IgA level is indicative of celiac disease, but a concurrent IgA deficiency (prevalent in 2% of

symptomatic children) can mask elevations, resulting in a false negative diagnosis. Therefore, measurement of quantitative serum IgA should be taken concurrently. In comparison, the EMA IgA sensitivity is 86%-100% and the specificity is 90%-100% (Liu, 2006).

Hill (2005) performed a literature review of studies that determined the sensitivity and specificity of serological tests for CD. He found both the EMA IgA and tTG IgA highly sensitive and specific with values for both parameters exceeding 95% in most studies. There were no identifiable differences between adults and children with respect to the tests. There was no evidence that a combination of tests was better than a single test using either the EMA IgA or tTG IgA. The variability and generally lower accuracy associated with the AGA IgG test (57%-100% sensitivity; 47%-94% specificity) and AGA IgA test (52%-100% sensitivity; 71%-100% specificity) make them unsuitable for screening purposes. Hill concluded that there was no advantage to using a panel of tests as opposed to a single test.

In support of Hill, several studies (Fabiani & Catassi, 2001; Reeves et al., 2006) have concluded that that AGA antibody test no longer appears to be an essential part of the diagnostic strategy for adult CD. The sensitivity and specificity of the tTG assay were measured at 90% and 96% respectively, demonstrating that the tTG antibodies determination is a reproducible and valuable tool for diagnosis and follow up of celiac disease. Trevisiol et al. (2002) further concluded that the tTG assay is an excellent CD diagnostic tool for mass screening by both specialist and the general clinic.

Bardella et al. (2001) found that both the tTG IgA and EMA IgA are highly efficient for routine laboratory screening; the choice of one or the other will depend on the available facilities. The diagnostic sensitivity and specificity of the tTG IgA and EMA IgA were, respectively, 100% and 98.2%, 100% and 97.3%. In contrast, two 2002 studies by Carroccio et al. concluded that both the EMA IgA sensitivity and specificity were 100% and therefore superior to the IgA or tTG IgA that had lower specificity values, 90% and 87%. The researchers found that tTG antibodies can also be found in patients with inflammatory bowel disease but EMA was only detected in those with celiac disease. EMA IgA also has proven to be a good indicator of latent celiac disease. In a 2002 Italian study (Piccoli et al.), six patients at high risk for CD, tested positive for EMA IgA and HLA genotyping, but had a normal biopsy. A second biopsy performed one to four years later resulted in four of the patients having intestinal damage. The study confirmed that subjects with signs of latent celiac disease should be re-examined.

In contrast to Hill (2005), a 2002 Israeli study (Shamir et al.) concluded that the disparity between the various serological markers suggest that the use of one serological marker is insufficient for establishing the true prevalence of celiac disease. A 2002 Argentina study (Gomez et al.) found that a screening protocol using anti-tissue transglutaminase as first line followed by endomysial antibodies is a cost-effective screening and yielded more realistic figures of prevalence for CD in a community setting than the classic three level sequential evaluation using antigliadin antibodies. Fasano (2005) also agreed with this approach. Citing the NASPGHN, he stated that on the basis

of current evidence and practical considerations, including accuracy, reliability, and cost, measurement of tTG IgA is recommended as the initial test for celiac disease.

The recent development of an enterocytes actin antibody, IgA AAA (Clemente et al., 2004) represents a new addition to diagnostic testing for celiac disease. The assay tested 100% sensitivity to severe intestinal mucosal damage representing another possible stepwise protocol in which symptomatic patients, who test tTG- positive and subsequently anti-actin antibody positive, can avoid intestinal biopsy for diagnostic confirmation (Fasano, 2005). In the prospective study of Clemente et al. (2004) the IgA AAA values of sensitivity, specificity, the positive PV, and the negative PV were, respectively, 84%, 95%, 98% and 69%.

Screening by blood tests may have limitations. Fine (2003) stated that blood tests in the early phase of gluten sensitivity may be negative because the immunologic reaction to gluten begins and occurs inside the intestinal tract rather than the blood. It is only when the immune reaction has been present for long periods of time that antibodies are produced in quantities sufficient to be detected in the blood. These antibodies do not get reabsorbed after entering the intestinal tract but travel through the intestine where they can be recognized in the stool. Therefore, a test that can detect antigliadin antibodies (AGA) in the stool is recommended for early detection (Fine, 2003). However, a recent study by Lass et al. (2006) found that there was no correlation between fecal and serum antigliadin antibodies to celiac disease. They concluded that the appearance of AGA has to be interpreted as a non-specific immune phenomenon, confirming the low specificity of AGA as a serologic market for celiac disease. Additionally, Reeves et al. (2006)

concluded that AGA antibody testing no longer appears to be an essential part of the diagnostic strategy for adult CD.

If the child has normal IgA serum levels and an elevated IgA antibody to human recombinant tissue transglutaminase, an intestinal biopsy should be scheduled to confirm the diagnosis and determine the level of involvement in the small intestine. Intestinal biopsy should also be done in children with negative serological tests but with failure to thrive, chronic diarrhea, or a diagnosis with high incidence of celiac disease as a co-morbid condition (NASPGHN, 2004). A positive serology test and a negative small bowel biopsy may represent a false positive serology test or milder case of the disease without current changes in the small bowel (latent celiac disease). Children must be ingesting gluten for the small intestine to have the characteristic histological changes so clinicians should not prescribe a gluten-free diet prior to completion of testing. As genetic markers for celiac disease become more defined, they will also be used to screen people for this condition.

The diagnosis of celiac disease is made when a child over two years of age, who has symptoms suggestive of celiac disease, is found to have histological changes in the small bowel and resolution of symptoms when put on a gluten-free diet (NASPGHN, 2004). A positive serology test that reverts to negative after compliance with a gluten free diet is considered supportive evidence. In situations where the diagnosis is uncertain in a symptomatic child, HLA typing can be done, repeat small bowel biopsy may be scheduled, or a trial on a gluten-free diet (GFD) can be instituted.

Reasons to Screen for Celiac Disease

Population screening studies have identified that up to two thirds of celiac disease cases are asymptomatic. Research supports the idea that the consequences of testing CD patients who are symptomatic will result in improvements in nutritional status, body mass index, body mass bone mineral density, and reduced risk of mortality and fractures. The prevention of osteoporosis seems to be the strongest indicator of widespread screening today (Collin, 2005). Data on long-term outcomes are less clear for asymptomatic cases that are identified by screening.

Hoffenberg (2005) cites the following reasons to screen the general population versus just high-risk groups: CD is common; gluten is found universally in the Western diet; it is feasible to do large scale screening; high risk groups are defined early to decrease health costs and other autoimmune diseases; and treatment is effective, available and decreases malignancy risk.

Cranney et al. (2005) found that the limitations of screening for CD in the general population include the costs of screening and higher false-positive rates in lower prevalence populations. It is also debatable whether patients found by active screening adhere to a gluten-free diet similarly to symptomatic ones.

There is no data on the cost-benefit of screening for CD in children. The potential harm of screening includes the difficulty in obtaining life or health insurance; the impact on psychological development of the children and their families; and the impact of celiac disease in addition to diabetes or other associated conditions. The optimal age at which to

begin and to repeat testing is undefined. Testing before age three does not seem warranted. Screening school-age children seems likely to detect most, but not all cases. It is suggested that diabetic children be re-screened at two-year intervals (Hoffenberg, 2005).

Currently, the only treatment of celiac disease is a lifelong gluten-free diet, which results in remission for most individuals. A gluten-free diet (GFD) is defined as one that excludes wheat, rye, and barley. In a 2002 prospective study, Mustalahti et al. (2002) found that a gluten-free diet was associated with improved quality of life for patients, both with symptom-detected celiac disease and patients with screen-detected celiac disease. The study concluded that concerns about the burden of a gluten-free diet, at least over the short term, may be unfounded. The 2005 Canadian children's study by Rashad et al. found a 95% strict compliance to a gluten-free diet in children with diagnosis confirmed by intestinal biopsy. These results were consistent with a 2005 Finnish study (Viljamaa et al.) that found long term dietary compliance in screen detected patients was 96%. These studies conclude that active screening in celiac disease risk groups seems to be reasonable rather than harmful.

Compliance is higher in children when the diagnosis is confirmed with intestinal biopsy compared with those who are diagnosed by clinical suspicion of celiac disease, initial response to a GFD and no biopsy. The highest rates of compliance are reported for patients diagnosed with CD at a very young age. In a compliance study by Pietzak (2005), 80% of adults in Sweden were compliant when diagnosed with CD prior to four years of age, but only 36% of those who were older than four years at diagnosis were

compliant. Adolescents diagnosed with celiac disease via serologic mass screening in Italy showed lower compliance in comparison with age-matched patients diagnosed with classic symptoms during childhood. In a five year follow up study by Fabiani et al. (2000), less than one fourth of patients diagnosed via screening followed a strict GFD, and 23% had returned to a completely normal diet five years after the original diagnosis.

More research is needed to assess the cost-effective benefits of mass screening. An example of such a study is the testing for celiac disease in patients with irritable bowel syndrome. Testing would be acceptable when the prevalence of CD is 1% to 3.4% in this population, and the testing would be the dominant strategy when the prevalence exceeds 8% (Spiegel et al., 2004). In the absence of evidence to the contrary, Collin (2005) suggested it is reasonable to assume that celiac screening would be acceptable even when subtle or nonspecific symptoms are present, provided that the estimated prevalence of celiac disease is approximately 4% for that population. Treatment for celiac disease should begin only after a complete diagnostic evaluation, including serology and possibly biopsy.

Causes of Celiac Disease

The two specific genes that have been recognized so far in celiac disease are part of the HLA class II DQ genes, HLA-DQ2 and HLA-DQ8. HLA or human leukocyte antigens are proteins found on the surface of almost every cell in the body. HLA antigens patrol the immune system and identify other cells as a foreign substance. They are found on inflammatory cells throughout the lining of the intestine as part of its constant surveillance of the inflammatory system. HLA antigens are thought to play a role in the

development of certain genetically predisposed diseases such as diabetes and celiac disease because the DQ genes that predispose people to autoimmune diseases may also control HLA. This genetic marker identification gives support to celiac disease being an important candidate for public-health newborn genetic screening based on the HLA-DQ alleles. Mass genetic testing would exclude 60% of the general population. Of those who are DQ2 or DQ8 positive, there would be a 3% risk of developing celiac autoimmunity by age seven, and 33% risk if combined with type 1 diabetes (Liu, 2006).

A multidisciplinary research effort to understand the pathogenesis of celiac disease is currently taking place worldwide. The key mechanisms of celiac disease involve a complex interaction of environmental and genetic factors. Celiac disease is unique from other autoimmune disease because the environmental triggering agent, gluten, has been identified. There is no known environmental trigger for any other autoimmune disease. Scientists view CD as a model to tackle key questions on the pathogenic mechanisms involved in other autoimmune diseases, such as multiple sclerosis, diabetes, and lupus (Fasano, 2001).

In order to have celiac disease, a person must have gliadin from gluten and HLA-DQ2 and DQ8 genes. While gluten ingestion is responsible for the signs and symptoms of celiac disease, it is not known what factors are associated with initial appearance of the disease since 40% of the general population has HLA-DQ2 and HLA-DQ8 lymphocytes but, only 1% has celiac disease. Apart from the gluten, the interaction of the environmental factors in celiac disease is poorly understood. Breastfeeding and the timing of the commencement of gluten ingestion, viral infections that promote the

secretions of interferon ∞, and smoking are some of the factors that might contribute to the occurrence of CD (Green & Jones, 2006).

A 2005 prospective observational study (Norris et al., 2005) of 1560 children at increased genetic risk for celiac disease, examined whether the timing of gluten exposure in the infant diet was associated with the development of CD autoimmunity. Findings indicated that children exposed to gluten-containing foods in the first three months of life had a five-fold increased risk of celiac disease autoimmunity compared with children exposed to gluten-containing foods at four to six months. If a significant dietary influence on CD is found, then there might be a major impetus for newborn screening of HLA.

A 2002 case control study (Vazquez et al., 2001) found that, compared with control subjects, a significantly lower proportion of patients with celiac disease were current smokers (33% of control subjects versus 16% of celiac patients) at the time of diagnosis. In addition, a positive linear correlation was observed between age of diagnosis and daily cigarette consumption in active smokers, suggesting that cigarette smoking delayed diagnosis of celiac disease.

A 2003 research study from Italy (Salvati et al.) and another from England (Monteleone et al., 2000), both presented data indicating that interferon regulatory factor-1 is a hallmark of the gliadin-mediated inflammation in CD and suggested that the interferon signaling pathway can play a key role in maintaining and expanding the local inflammatory response in this disease. A case study from Brazil (Martins & Gaburri, 2004) reported a patient with the onset of CD after interferon use for the treatment of

chronic hepatitis C. It was inferred that the interferon might induce or activate CD in predisposed individuals.

Gadewar and Fasano (2005) reported the major areas in need of further study include: determining the optimal time to initiate and repeat screening; developing methods to detect the transition from autoimmunity (such as having positive serologic tests) to development of disease; determining when to treat; developing predictors of response to treatments to assess the benefit of treatment; and assessing the risks of screening. In addition, the complexity of the interaction between genetic and environmental factors responsible for CD development opens the way to test strategies of primary prevention. It is possible that reducing the strength of the environmental component will prevent disease development in some individuals, for example in those with a lower genetic load of predisposing genes.

In closing, the literature supports six of the nine criteria of the American Academy of Pediatrics (2004) for school screening programs: the disease has one percent prevalence in the general population; treatment of a gluten-free diet is available and effective; school nurses are experienced and trained to perform questionnaire screening programs; the target population of high risk children has a prevalence rate of one in 22; all positive screens will have definite referrals and evaluation, and be advised on appropriate treatment; and this type of screening program is appropriate for a school site. The remaining three criteria will be analyzed in Chapter V.

CHAPTER III

METHODOLOGY

An instrument validation study of school age children with and without diagnosed celiac disease was used to test the four hypotheses. The dependent variable was celiac disease. The independent variables were 15 health related clinical symptoms and conditions of celiac disease: stomach pain, intestinal distress, allergies, poor growth, anemia, mental anxiety, body aches, oral hygiene problems, skin rashes, other autoimmune diseases, diabetes, syndromes such as Down's Syndrome, cognitive learning issues, first degree relative with diagnosed CD, and high absenteeism. The five objectives were to: (1) determine if there is a significant difference between the screening test scores of children with and those without celiac disease; (2) determine if there are two or more clinical symptoms occurring concurrently in children with undiagnosed celiac disease that increase risk for the disease; (3) determine if there are concurring symptoms, which groupings of two or more have the highest positive correlation to CD; (4) test-retest the case group questionnaire; and (5) determine the predictive values of the questionnaire.

Population and Sample

This instrument validation study was designed as a case-control study and had three different sample groups: one case and two controls. The case group was 78 children (N=78) with diagnosed celiac disease whose families are members of the North Texas Gluten Intolerance Group (NTGIG) or the Westchester, New York ROCK (Raising Our

Celiac Kids) Group. The diagnosis of celiac disease was by biopsy or blood test. The NTGIG member families were recruited by mail. The mailing list was supplied by the president of the North Tarrant Gluten Intolerance Group. The Westchester, New York ROCK Group was also recruited by mail. The mailing list was obtained from a resource person within the Westchester ROCK Group. All family names on the list with school age children were mailed a recruitment package. The age of the case group ranged from two to 23, and all the cases were school students (preschool thru college).

The control group (N=60) was divided into two groups: 45 non-case children from Southlake, Texas, a suburb in the Dallas/Fort Worth metroplex, and 15 non-case children known to have tested negative for celiac disease by either a blood test or biopsy. To obtain 45 non-case participants from Southlake, 200 names were selected from the 2006-2007 Southlake Community Phonebook, a publicly published directory. The names were selected by address. The address had to be located within a mile of a local elementary school. The names were mailed a recruitment package. The 15 non-case children, who had tested negative for celiac disease, were purposively recruited from three celiac support groups: the NTGIG, Westchester ROCK, and the New England ROCK. Recruitment packages were made available at the October 2006 meeting of each support group, and an oral request for volunteers was made once by a resource member of the support group. The age range of the control group was two to 20, and all the cases were school students (preschool thru college).

Protection of Human Participants

Texas Woman's University IRB approval was obtained on July 28, 2006. The two main ethical concerns in this study were fully informed consent to participate and the need for participants to emerge from the experience unharmed. Confidentiality was protected to the extent that was allowed by law. A code number, rather than a name, was used on the questionnaire. Only the research team had access to the completed questionnaires. The questionnaires were stored in a locked filing cabinet in the investigator's office and are to be shredded on July 28, 2011. All information was kept highly secure and in the strictest of confidence. No identifying information or names will appear in publications. The participants were the parents. The case and control group populations were the children

To address the issue of informed consent, all participants received a written explanation of the research, its purpose, the time commitment, and how the information was to be used, and full disclosure regarding their rights to make an informed decision to participate. Participants were asked to sign a consent form and return it with the completed questionnaire in the supplied self addressed stamped envelope (SASE). Participation in this study was voluntary. If participants chose not to participate, they were permitted to withdraw from the study at any time, and there was no penalty. Contact information of the research team and TWU was given for any further questions that participants might have had regarding the research.

To insure the participants emerged unharmed, emotional and psychological discomfort was minimized by selecting the private homes of the participants as the setting of the study. The questionnaire was pretested with seven members of the North Texas

Gluten Intolerance Group and five Southlake, Texas parents of public school children, for clarity, readibility and understanding. If participants experienced emotional discomfort while answering the questions they were permitted to stop answering any of the questions at any time. Participants were permitted to discontinue participation in the study at any time without penalty. To prevent coercion of volunteers, there were no negative repercussions or positive monetary incentives for participating. Volunteers were indirectly approached and solicited through the mail or by general announcement at support meetings.

The following disclosure was made to the TWU IRB with respect to the association and affiliation of the principal investigator to the sample populations: the principal investigator knew parents in the NTGIG through her membership in the group and from the gluten-free cooking classes she taught at Market Street in Colleyville, Texas. The principal investigator knew many families in Southlake, Texas, with students aged two to 23 years, because she lived there for ten years and had two children who attended Carroll ISD in Southlake.

Data Collection Procedures

The recruitment package was mailed to 77 NTGIG members during the week of September 5, 2006, one week after the start of the new school year in Texas. The recruitment package was mailed to 30 Westchester ROCK Group members during the week of September 11, 2006, one week after the start of the new school year in New York. The names and addresses were hand written on the envelope. The mailing contained the following: a form letter disclosing the purpose of the screening tool and how the information was to be used (Appendix A); the questionnaire (Appendix B);

consent form (Appendix C); contact information and a SASE. The parent was asked to answer 16 questions about their celiac diagnosed child with respect to the child's health prior to diagnosis. Then the parent was asked to mail back the completed questionnaire and signed consent form in the SASE. In total, 78 questionnaires and consent forms were completed and returned. Thirty days after receiving their completed response, the case respondents received a second mailing to answer and return the questionnaire in the SASE for the test-retest procedure. The test-retest mailing (Appendix D) was sent to the 35 responses received prior to October 30, 2006. Twenty-seven retests were completed and returned. Responses received after October 30, 2006, did not receive a second mailing. The case responses from both the NTGIG and Westchester ROCK groups were combined to form one case group and treated equally with respect to data analysis.

During the week of September 18, 2006, a recruitment package was sent to 200 Southlake, Texas residents. The names and addresses on the envelope were hand written. The package contained: a form letter (Appendix E) explaining the purpose and need of the celiac screening program; the questionnaire (Appendix F) about the health of their child, a confidentiality agreement; parental consent forms (Appendix G); contact names and telephone numbers if more information was needed, and a SASE. Participants were asked to return the consent forms, confidentiality agreement and completed questionnaire in the SASE. No child in this control group had diagnosed celiac disease. The control group did not retest due to the low number of responses received by October 30, 2006 and prior response rates. A sample size of 26 was needed to provide statistical power of r=.8. Forty-five questionnaires and consent forms were completed and returned.

In September 2006, one resource from each of the NTGIG, Westchester ROCK, and New England ROCK, was contacted by phone. They were requested to make available by announcement during the October 2006 support group meeting, recruitment packets to families of children who had tested negative for celiac disease. Ten packets were mailed to each group resource prior to the October meeting. The packets contained a form letter (Appendix H) explaining the purpose and need of the celiac screening program; the questionnaire (Appendix F) about the health of their child, a confidentiality agreement; parental consent forms (Appendix G); contact names and telephone numbers if more information was needed, and a SASE. Participants were asked to return the consent forms, confidentiality agreement and completed questionnaire in the SASE. Each child in this control group had tested negative for celiac disease by biopsy or blood test. This control group did not retest because the responses were received after October 30, 2006. Fifteen questionnaires and consent forms were completed and returned for a combined control group of 60. Total case and control N=138.

Instrumentation

All participants completed an original questionnaire aimed to identify high-risk children for celiac disease. High-risk children were identified by a score greater than 24. The two page questionnaire, targeted to parents of school children, was developed from secondary data in collaboration with the North Tarrant Gluten Intolerance Group (NTGIG). The questionnaire contains 16 questions relating to the clinical and non-clinical symptoms of diagnosed celiac disease in children. The more symptoms a child has, the larger his/her score, and in theory the higher the risk of celiac disease.

The aim of the screening tool is to identify children who are high risk for celiac disease by obtaining accurate and relevant information. Additional objectives are that the screening tool is cheap, quick and easy to administer by a school nurse. To insure validity of the instrument, a list of common symptoms and conditions associated with celiac disease in children was developed from secondary data sources, including but not limited to National Institute of Health Consensus Development Conference Statement: Celiac Disease (NIH, 2004), the NASPGHN 2004 guidelines for the diagnosis and treatment of celiac disease in children, the 2005 study (Rashid, et al.) of 168 Canadian Children with biopsy-confirmed CD, and the 2003 Canadian celiac health survey for adults (Cranney, Zarkadas, Graham, & Switzer). The questionnaire criterion for the health-related symptoms and conditions was a prevalence rate greater than or equal to 8% (Table 1). In addition, informal focus groups were conducted at two gluten-free cooking classes at Market Street in Colleyville, Texas, on August 19, 2006 and September 10, 2006. At both classes a group discussion asked the following two open ended questions to a total of 46 adults on a gluten-free diet: What health-related symptoms and conditions do you remember having as a child? At what age is your first memory of these health-related symptoms and conditions? The open format answers were recorded by hand by the researcher. The questionnaire was then revised. Two leaders of the NTGIG reviewed the questionnaire for content validity. A pretest of the questionnaire was conducted in person on five Southlake parents and five adult members of NTGIG. The questionnaire was then amended according to the pre-test results.

Table 1.

Symptoms of Celiac Disease with Reported Prevalence Rate ≥ 8% in Celiac Populations

Symptom	Prevalence Rate Percent
Abdominal pain	90
Weight loss	71
Poor Growth	70
Diarrhea	65
Weakness	64
Nausea/vomiting	53
Anemia	40
Mood swings/depression	37
Constipation	30
Asthma/allergies	25
Eczema	24
Short stature	18
Learning disorders	15
Dental enamel defects	15
Syndromes	10
Type 1 diabetes	8
Other autoimmune diseases	8

1st degree relative with CD	8
Canker sores	*
Body aches	*

*Focus group feedback
Notes. Data from National Institute of Health (2004), NASPGHN (2004), Canadian Health Survey (Cranney, A., 2003), and Rashid, M., Cranney, A., Zarkadas, M., Graham, I.D., Switzer, C., Case, S., et al. (2005).

The questionnaire consists of four parts. The first part aims to gather basic demographic information of the child: age, grade, sex, and ethnicity. The second part asks nine questions about the physical health of the child. The questions are grouped into categories of nine common celiac symptoms: stomach pain, intestinal distress, allergies, poor growth, anemia, mental anxiety, body aches, oral hygiene problems, and skin rashes. Participants were asked to answer a five choice, Likert-style sliding scale from "Never" having the symptom (score=1), "Seldom" (score 2), "Frequent" (score=3), to having the symptom "A Lot" (score=4). A fifth option of "Don't Know" was scored at 0. The answers appear on one horizontal line below the question. Appendix I displays the scoring method and categories of the instrument.

The third part of the questionnaire aims to explore six common conditions associated with celiac disease: other autoimmune diseases such as IgA deficiency, diabetes, syndromes such as Down's, cognitive learning issues, first degree relative with diagnosed CD, and high absenteeism. Participants were asked to answer "No" (score=1), "Yes" (score=2), or "Don't Know" (score=0) to having the condition. The answers

appear on one horizontal line below the question. The final question aims to evaluate if the child has celiac disease, ("No" =1, or "Yes" =2) and if so, by what test, blood or biopsy.

The case group participants were instructed to answer the 15 health related questions about the health of their child prior to being diagnosed with celiac disease (Appendix B). The control group participants were instructed to answer the 15 health related questions with respect to the current health of their child (Appendix F).

Data Analysis

The data was analyzed by the researcher using SPSS v14 for Windows. For Hypothesis 1, a two-tailed t-test was used to determine significant differences in questionnaire scores between the case and control groups. Clinical symptoms reported by the two groups were analyzed and compared using one-way ANOVA and stepwise regression analysis. The identification of subsets of health symptoms and conditions for Hypothesis 2, that when present together, increase a child's risk for celiac disease, was derived using a factor analysis based on the structural equation modeling (SEM) approach and the method of extraction was roots greater than one. Using SEM, principal component analysis (PCA) models were developed without the assumption of certain correlations among variables. This common form of factor analysis was chosen to develop a linear combination of variables such that the maximum variance was extracted from the variables. It then removed this variance and sought a second linear combination which explained the maximum proportion of remaining variance and so on. A varimax rotation was then used to maximize the variance of the squared loadings of a factor of all

the variables in a factor combination, which has the effect of differentiating the original variables by the extracted factor combination. Each factor combination tended to have either large or small loadings of any particular variable. The varimax solution yielded results which made it possible to identify each variable with a single factor combination of health-related symptoms and conditions of CD (Statistical Solutions, Inc, 2006). Clinical symptoms in the case group were analyzed for covariates using ANCOVA.

For Hypothesis 3, the predictive value of the questionnaire for determining celiac disease was evaluated using the four measures of validity: sensitivity, specificity, Predictive value (+), and Predictive value (-). The accuracy of the instrument was calculated. The reliability test of the questionnaire was performed using Cronbach's coefficient Alpha reliability analysis where r is greater or equal to .80. Logic checks were done using cross tabulation for key variables.

In summary, the case group consisted of 78 participants and the control group consisted of 60 participants (N=138). The samples were collected by mail over a four month period ending December 20, 2006. All participants signed consent forms in accordance with the TWU IRB. The screening tool is a two page instrument containing 16 questions related to common clinical symptoms and conditions of celiac disease. The questionnaire's validity was tested by comparing mean scores between the two groups. A score greater than 24 was chosen to indicate that the child was at high risk for celiac disease. The reliability of the questionnaire was tested by comparing two scores of the same participant taken a month apart. Twenty-seven test-retests from the case group were analyzed. The results of the sampling and data collection follow in Chapter IV.

CHAPTER IV

RESULTS

The screening tool is a two page instrument containing 16 questions related to common clinical symptoms and conditions of celiac disease. The questionnaire data presented in this chapter was collected over a four month period and analyzed using SPSS v14 for Windows. New to the field of celiac research was the use of the factorial analysis of variance to determine if the interaction of two or more independent health related variables increase a child's risk for celiac disease.

The case group was 78 children with diagnosed celiac disease whose parents were recruited from mailing list made available by their local celiac support groups. The response rate of the case group was 73%. The control group was divided into two groups: 45 non-case children without diagnosed celiac disease whose parents were recruited from a published community phonebook; and 15 non-case children known to have tested negative for celiac disease whose parents were purposively recruited from three different celiac support groups. The response rate of the combined control group was 26%.

Table 2 presents the total mean scores of the screening procedures. Using the celiac disease screening questionnaire, the mean score for the case group (N=78) was 29.7, and the mode was 30. The scores ranged from a low of 19 to a high of 45 (SD=5.6). Eighty-two percent of the case group had scores between 24 and 45. The mean score of the control group (N=60) was 20.9 and the mode was 20. The scores ranged from a low

of 16 to a high of 27 (SD=2.6). Eighty-two percent of the control group had scores between 17 and 23. The case group mean score was 8.9 points higher than the control group mean score, resulting in a 43% difference. This difference, displayed in Table 3, appears to be statistically significant, (t = -12.5, p = .0001).

Table 2.

Group Descriptive Statistics of Questionnaire Scores

	N	Min	Max	Mean	SD
Case Group	78	19	45	29.7	5.6
Control Group	60	16	27	20.9	2.6

Notes. Case= case group with diagnosed celiac disease; NC= control group without diagnosed celiac disease.

Table 3.

Paired Sample t-Test of Case-Control Group Questionnaire Scores (N=60)

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	SD	MSE	Lower	Upper	*t*	df	Sig. (2-tailed)
Pair 1	Control - Case	-8.9	5.5	.71	-10.4	-7.5	-12.5	59	.00

The case group descriptive statistics for the independent variables are displayed in Table 4. The sample contained 48 (61%) females and 30 males (39%). The mean age was ten with a mode of 13 years. The ethnicity was 96% white (75 whites, 2 Hispanics, and 1

Asian). The 48 females had a mean age of 10.6 (SD=4.8) and a mean questionnaire score of 30.4 (SD=6.1). The 30 males had a mean age of 9.6 (SD=4.8) and a mean questionnaire score 28.5 (SD=4.5). The gender age difference of one year appears to be statistically significant, ($t = 17.8$, $p = .001$), but not correlated, ($r = .101$, $p = .38$). The gender score difference of 1.9 was 6.7% higher for females than males. The relationship appears to be statistically significant, ($t = -46.6$, $p = .001$), but not correlated, ($r = .164$, $p = .15$).

Table 4.

Case and Control Group Descriptive Statistics for Independent Variables

Variable	Case					Control				
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD
Age	78	2	23	10.2	4.8	60	2	20	11.4	3.5
Gender	78	0	1	0.6	0.5	60	0	1	0.7	0.5
Ethnicity	78	1	4	1.1	0.4	60	1	1	1.0	0
Stomach	78	0	4	3.0	1.1	60	1	3	1.8	0.7
Intestinal	78	1	4	3.0	1.0	60	1	4	1.8	0.6
Allergies	78	0	4	2.4	1.1	60	1	4	1.8	0.9
Growth	78	0	4	2.6	1.4	60	1	4	1.2	0.5
Anemia	78	0	4	2.6	1.3	60	1	4	1.4	0.7
Mental	78	0	4	2.3	1.3	60	1	4	1.6	0.7
Aches	78	0	4	1.9	1.4	60	0	4	1.7	0.7

Mouth	78	0	4	1.8	1.2	60	0	3	1.2	0.7
Skin	78	0	4	2.1	1.2	60	1	4	1.4	0.7
Autoimmune	78	0	2	0.9	0.7	60	0	1	0.9	0.3
Diabetes	78	0	1	1.0	.16	60	1	1	1.0	0.0
Syndromes	78	0	2	1.0	.16	60	1	2	1.0	0.1
Cognitive	78	0	4	1.2	0.6	60	1	2	1.1	0.3
Relative	78	0	2	1.1	0.7	60	0	2	1.1	0.4
Absenteeism	78	0	2	1.2	0.5	60	1	1	1.0	0.0
Celiac	78	1	2	1.7	0.5	60	1	1	1.0	0.0

Notes. Case= case group with diagnosed celiac disease; Control= control group without diagnosed celiac disease.

The control group was divided in two groups: 45 non-case children from Southlake, Texas (NC-1), and 15 non-case children known to have tested negative for celiac disease by either blood or biopsy (NC-2). The response rate for NC-1 was 22.5% and 50% for NC-2. Table 5 displays the comparison of all the group mean questionnaire scores. NC-1 had a mean score of 20.8. The scores ranged from a low of 16 to a high of 27 with a standard deviation of 2.4. NC-2 had a mean score of 21.3. The scores ranged from a low of 17 to a high of 27 with a standard deviation of 3.2. The 0.6 difference between the two control group means in Table 6 appear not to be statistically significant ($t = -.75$, $p = .47$).

Table 5.

Questionnaire Scores of Test-Retest, Case Group and Control Group

Group	N	Min	Max	Mean	SD
Test	27	19	39	29.5	4.8
Retest	27	21	37	28.9	4.3
Control	45	16	27	20.8	2.4
Nonceliac	15	17	27	21.3	3.2

Notes: Test= Case; Retest= Case; Control= NC-1; Nonceliac= NC-2.

The control group descriptive statistics for the independent variables are displayed in Table 4. The sample contained 21 males (35%) and 39 (65%) females. The mean age was 11 with a dual mode of 10 and 13 years of age. The ethnicity was 100% white. Thirty-nine females had a mean age of 11.1 (SD=3.2) and a mean questionnaire score of 20.7 (SD=2.5). The 21 males had a mean age of 12.1 (SD=3.8) and a mean questionnaire score 21.4 (SD=2.7). The gender score difference of 0.7 was 3.4% higher for males than females. The relationship appears not to be statistically significant or correlated ($r = -.133$, $p = .31$).

Table 6.

Paired Sample t-Test of NC-1 and NC-2 Control Group Questionnaire Scores (N=60)

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	SD	MSE	Lower	Upper	*t*	df	Sig. (2-tailed)
Pair 1	Control - Nonceliac	-.60	3.1	.80	-2.3	1.1	-.75	14	.47

The most common symptoms reported by the case group in Table 7 were: (a) intestinal pain categorized by diarrhea, constipation, vomiting or nausea (intestinal); (b) abdominal pain, gas, or bloating (stomach) with 40% of the sample reporting "a lot" of intestinal pain and stomach pain; (c) fatigue, weakness, or anemia (anemia); (d) allergies or asthma (allergy); (e) unexplained mood swings, depression, anxiety or stress (mental); (f) short stature, growth delay, or weight loss (growth); (g) unexplained headaches, joint enamel defects or recurring canker sores (mouth). aches or body aches (aches); (h) skin rashes (skin); and (i) dental.

Table 7.

Case and Control Independent Variable Reporting Percentages

Variable	Cases (%)	Controls (%)	Diff (%)
Females	61	65	-4
Intestinal	91	72	+19
Stomach	89	63	+26
Anemia	73	32	+41
Allergies	70	57	+13
Mental	70	52	+18
Growth	64	12	+52
Aches	60	60	0
Skin	55	30	+25
Mouth	46	22	+24
Relatives	31	13	+18
Cognitive	24	10	+14
Autoimmune	17	0	+17

Only 13 cases had an autoimmune disease and there were no reported cases of type 1 diabetes. One case had Down's syndrome. Cognitive learning problems such as autism, hyperactivity, learning disabilities, and ADD (cognitive), were reported by 24% of the cases. There were 24 cases with known first degree relatives with diagnosed celiac disease (relative). Both genders reported at similar levels for relative (gender mean=1.7, SD=.48). Twenty-seven percent of the cases reported higher than normal absenteeism with both genders reporting similar means (Table 8).

The results of the case group indicated that unexplained headaches, joint aches or body aches (aches) had the greatest gender difference of .8, female = 2.2, male = 1.4. The correlation of gender to aches, ($r = .3$, $p = .02$), appears weak and but statistically significant. Dental enamel defects or recurring canker sores (mouth) was second, with a higher female gender difference of .7, female = 2.1, male = 1.4. The correlation of gender to mouth, ($r = .3$, $p = .01$), also appears weak but statistically significant. Growth had the third greatest gender difference but the data showed there was no correlation or significance between gender and growth.

Upon further gender analysis of the case group, 28 cases (36%) had questionnaire scores greater than 30, 20 females (71%) and eight (29%) males. The mean age of the females was 12.3 years compared to 9.9 years for the males. The mean questionnaire score difference was 36.2 for the females versus 33.9 for the males, 6.7% higher for females than males. Unexplained headaches, joint aches or body aches (aches) had the greatest gender difference of 2.3, female = 3.2, male = 0.9. Dental enamel defects or recurring canker sores (mouth) was second, with a higher female gender difference of

1.7, female = 2.8, male = 1.1. Growth had the third greatest gender difference of 1.1, female = 2.9, male = 4.0. All eight males reported "a lot" of short stature, growth delay, or weight loss. Other symptoms reported "frequently" or "a lot" by all eight males were stomach pain; intestinal pain; fatigue or anemia; and unexplained mood swings, depression, anxiety or stress. All 20 females reported intestinal pain, fatigue or anemia; and unexplained mood swings, depression, anxiety or stress, but at lower levels from "seldom" to "a lot".

Table 8.

Female and Male Case Group Descriptive Statistics

Variable	Female					Male				
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD
Age	48	2	23	10.6	4.8	30	2	18	9.6	4.8
Gender	48	1	1	1.0	0	30	0	0	0	0
Ethnicity	48	1	4	1.1	0.5	30	1	1	1.0	0
Stomach	48	0	4	3.1	1.1	30	0	4	2.8	1.2
Intestinal	48	1	4	3.0	1.0	30	1	4	3.1	1.0
Allergies	48	0	4	2.4	1.1	30	1	4	2.3	1.2
Growth	48	0	4	2.4	1.4	30	1	4	2.9	1.3
Anemia	48	0	4	2.7	1.2	30	0	4	2.5	1.3
Mental	48	0	4	2.5	1.3	30	0	4	2.0	1.2
Aches	48	0	4	2.2	1.4	30	0	4	1.4	1.4

Mouth	48	0	4	2.1	1.3	30	0	4	1.4	0.9
Skin	48	0	4	2.1	1.3	30	1	4	2.0	1.1
Autoimmune	48	0	2	0.9	0.8	30	0	2	0.8	0.5
Diabetes	48	0	2	1.0	0.2	30	1	1	1.0	0
Syndromes	48	0	2	1.0	0.2	30	1	1	1.0	0
Cognitive	48	0	2	1.1	0.5	30	1	4	1.4	0.7
Relative	48	0	2	1.1	0.7	30	0	2	1.2	0.7
Absenteeism	48	0	2	1.3	0.5	30	1	2	1.2	0.4
Celiac	48	1	2	1.7	0.5	30	1	2	1.7	0.5
Score	48	20	45	30.4	6.1	30	1	37	28.5	4.5

The statistically significant independent variables ($r \geq .4$, $p = .001$), affecting the case group questionnaire score were: anemia, $r = .7$; mental, $r = .6$; allergies, $r = .5$; growth, $r = .5$; stomach, $r = .4$; and intestinal, $r = .4$.

The most common symptoms reported by the control group in Table 7 were: (a) intestinal pain categorized by diarrhea, constipation, vomiting or nausea (intestinal) with 72% of the sample reporting it at some time, and of those, 93% reporting "seldom"; (b) abdominal pain, gas, or bloating (stomach) was with 63% of the sample reporting it at some time; (c) unexplained headaches, joint aches or body aches (aches) with 86% of 36 cases reporting at the "seldom" level; (d) allergies or asthma (allergy); (e) unexplained mood swings, depression, anxiety or stress (mental); (f) fatigue, weakness, or anemia (anemia); (g) skin rashes (skin); and (h) dental enamel defects or recurring canker sores

(mouth). The control groups reported symptoms were all at lower levels than the case groups reported symptoms.

There were no reported controls with other autoimmune diseases, type 1 diabetes, high absenteeism, or diagnosed celiac disease. One control had Down's syndrome. ADD was the most common cognitive learning problem. There were eight controls with known first degree relatives with diagnosed celiac disease (relative). Both genders reported at similar levels for relative (gender mean = 1.1, SD =.4). Table 9 displays control group gender differences for the independent and dependent variables. The highest correlation between the questionnaire score and any control group independent variable was stomach, (r =.7, p =.001).The other moderately significant independent variable correlations (p =.001) affecting the questionnaire score were as follows: anemia, r =.6; intestinal, r =.6; allergies, r =.5; and aches, r =.4.

The control group results showed that unexplained headaches, joint aches or body aches had the greatest gender difference of 0.3, female = 1.6, male = 1.9. There appeared to be no statistical correlation of gender to aches (r =-.2, p =.16). Skin rashes was second, with a higher female gender difference of 0.2 (female= 1.5, male = 1.3). There appeared to be no statistical correlation of gender to skin rashes (r =.2, p =.26). Upon further analysis, there was no statistically significant correlation between gender and any of the independent variables for the control group.

The strongest correlation between independent variables for the control group was stomach and anemia (r =.5, p =.001). Stomach was also moderately correlated to

intestinal (r =.4, p =.001). The only other control group correlation with r ≥ .4 was anemia with intestinal and age (See Table 10).

Table 9.

Female and Male Control Group Descriptive Statistics

Variable	Female					Male				
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD
Age	39	2	19	11.1	3.2	21	5	20	12.1	3.9
Gender	39	1	1	1.0	0.0	21	0	0	0	0.0
Ethnicity	39	1	1	1.0	0.0	21	1	1	1.0	0.0
Stomach	39	1	3	1.8	0.6	21	1	3	1.7	0.7
Intestinal	39	1	4	1.7	0.6	21	1	3	1.9	0.5
Allergies	39	1	4	1.7	0.9	21	1	3	2.0	0.8
Growth	39	1	2	1.1	0.3	21	1	4	1.3	0.7
Anemia	39	1	4	1.4	0.8	21	1	3	1.5	0.7
Mental	39	1	4	1.6	0.7	21	1	3	1.5	0.7
Aches	39	0	3	1.6	0.6	21	1	4	1.9	0.8
Mouth	39	0	3	1.1	0.7	21	0	3	1.3	0.6
Skin	39	1	4	1.5	0.8	21	1	3	1.3	0.6
Autoimmune	39	0	1	0.9	0.3	21	0	1	0.9	0.3
Diabetes	39	1	1	1.0	0.0	21	1	1	1.0	0.0
Syndromes	39	1	1	1.0	0.0	21	1	2	1.1	0.2
Cognitive	39	1	2	1.1	0.3	21	1	2	1.1	0.3

Relative	39	0	2	1.1	0.4	21	1	2	1.1	0.4
Absenteeism	39	1	1	1.0	0.0	21	1	1	1.0	0.0
Celiac	39	1	1	1.0	0.0	21	1	1	1.0	0.0
Score	39	16	27	20.7	2.5	21	16	27	21.4	2.7

Table 10.

Correlations of Independent Variables for Case and Control Group where r≥ .4, p=.000 (ANCOVA)

Correlation	Case *(r)*	Control *(r)*
Age/Aches	.4	.3
Stomach/intestinal	.4	.4
Growth/Anemia	.4	.1
Anemia/Mental	.5	.1
Anemia/Age	.1	.4
Anemia/Stomach	.2	.5
Anemia/Intestinal	.1	.5

In comparison, the strongest correlation between independent variables for the case group was anemia with mental, (r =.5, p =.001). The other case group correlations in Table 10 with r ≥ .4 were: (a) anemia with growth; (b) age with aches; and (c) stomach with intestinal. The only two independent variables to have r ≥ .4 (p = .001) for both the case and control group were stomach with intestinal. Also of statistical significance was

age with aches for both groups, with older children in both groups reporting higher rates of unexplained headaches, joint aches or body aches as compared to younger children in both groups.

Table 11 displays the multiple regression analyses performed on the case group data to evaluate the effect of independent variables on predicting celiac disease from questionnaire scores. The sample size (n=78) was based on an excellent statistical power (.90), $R \geq .6$. Of note, at this power, using only anemia as a predictor, $R = .66$, $R^2 = .43$, Adj-$R^2 = .43$, SE =4.21, $F(1, 76) = 58.20$, $p = .0001$. The minimum number of variables to achieve a high Pearson correlation ($R = .9$) was six: anemia, allergies, aches, intestinal, growth and skin ($R = .92$, $R^2 = .84$, Adj-$R^2 = .82$, SE =2.33, $F(6, 71) = 61.27$, $p = .0001$).

Table 12 displays the multiple regression analyses performed on the control group data to evaluate the effect of independent variables on predicting celiac disease from questionnaire scores. The sample size of (n=60) was based on an excellent statistical power (.90), $R \geq .6$. Of note, at this power, using only stomach as a predictor, $R = .71$, $R^2 = .5$, Adj-$R^2 = .5$, SE =1.84, $F(1, 58) = 58.56$, $p = .0001$. The minimum number of variables to achieve a high Pearson correlation ($R = .9$) was five: stomach, allergies, growth, anemia and mental ($R = .91$, $R^2 = .83$, Adj-$R^2 = .82$, SE =1.11, $F(5, 54) = 53.29$, $p = .0001$).

Table 11.

Stepwise multiple correlations of case group questionnaire scores on selected independent variables (ANOVA).

Variable	B	SE B	Beta	t	p
Relative	1.31	.18	.17	7.44	.0001
Absenteeism	1.28	.26	.11	4.85	.0001
Skin	1.09	.11	.24	10.08	.0001
Anemia	1.06	.12	.24	8.51	.0001
Growth	1.03	.11	.25	9.86	.0001
Cognitive	1.02	.22	.11	4.74	.0001
Allergies	0.99	.12	.20	8.66	.0001
Mental	0.97	.12	.22	8.24	.0001
Mouth	0.96	.12	.21	8.26	.0001
Aches	0.93	.10	.24	9.47	.0001
Intestinal	0.86	.14	.15	6.03	.0001
Stomach	0.74	.13	.15	5.87	.0001
Constant	4.82	.71		6.80	.0001

$R=.99$, $R^2=.97$, Adj-$R^2=.97$, $SE=1.03$, $F(14, 63)=156.2$, $p=.0001$

Notes. Regression method: stepwise

Table 12.

Stepwise multiple correlations of control group questionnaire scores on selected independent variables (ANOVA).

Variable	B	SE B	Beta	t	p
Stomach	1.22	.12	.31	10.48	.0001
Mouth	1.15	.10	.29	11.87	.0001
Cognitive	1.03	.18	.11	4.28	.0001
Growth	1.00	.13	.19	7.50	.0001
Intestinal	0.99	.12	.22	8.07	.0001
Allergies	0.96	.07	.32	13.62	.0001
Skin	0.92	.08	.26	10.87	.0001
Aches	0.88	.10	.24	9.12	.0001
Mental	0.84	.09	.22	9.42	.0001
Anemia	0.82	.10	.24	8.12	.0001
Relative	0.75	.18	.11	4.28	.0001
Constant	5.00	.54		9.20	.0001

$R=.99$, $R^2=.98$, Adj-$R^2=.97$, $SE=4.15$, $F(13, 46)=172.61$, $p= .0001$
Notes. Regression method: stepwise.

Table 13.

Factor Analysis for Case Group

Variables	Component Factors**						
	I	II	III	IV	V	VI	h^2
Age	*.70	-.17	.17	-.03	-.27	.11	.64
Gender	*.44	.06	.05	-.25	*.38	*-.52	.67
Stomach	-.05	*.74	.28	-.19	.03	-.16	.70
Intestinal	-.20	*.75	.06	.15	-.12	-.06	.64
Allergies	.19	*.51	.11	.03	.33	*.44	.60
Growth	-.03	.08	.08	*.90	-.02	.07	.83
Anemia	.14	.11	*.60	*.49	.30	-.06	.73
Mental	.09	.09	*.66	.23	.36	-.02	.64
Aches	*.70	.07	.30	-.16	.06	-.03	.62
Mouth	*.71	.03	-.22	.27	.02	-.12	.64
Skin	.05	.07	*.78	-.11	-.18	.08	.66
Cognitive	.00	-.08	.02	-.01	.07	*.85	.73
Relative	.13	.04	-.05.	-.02	*-.81	-.06	.68
Absenteeism	.31	*.56	-.23	.27	.05	.05	.06
Eigenvalue	2.53	1.84	1.42	1.34	1.13	1.04	6.65
% Variance	18.10	13.17	10.12	9.61	8.07	7.45	66.51

Notes. * Variables used in making substantive interpretations of the clusters.
Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization converged in 11 iterations.

** Component Factors: (I) Older girls with body aches and mouth sores; (II) Absent children with gastrointestinal pain and allergies; (III) Fatigued children with anxiety and skin rashes; (IV) Children with poor growth and anemia; (V) Girls with anxiety without 1st degree relative with CD; and (VI) Boys with allergies and learning problems.

Scores for the case group independent variables of the clinical symptoms and conditions of celiac disease were examined using a principal component analysis with varimax rotation ($r \geq .4$). The factor analysis displayed in Table 13, generated six factors that explained 67% of the variance, but were not themselves correlated so that they shared no variance. Factor I correlated older girls with aches and mouth, and explained 18% of the variance. Factor II correlated with items intestinal, stomach, allergies and high absenteeism, and explained an additional 13% of the variance. Factor III correlated with items anemia, mental and skin, and contributed to 10% of the explained variance. Factor IV correlated with growth and anemia, and contributed another 10% to explained variance. Factor V correlated girls with mental and relative, and explained 8% of the variance. Factor VI correlated boys with allergies and cognitive learning, and added 7% to the variance.

To test for validity, a screening score of 24 on the questionnaire was used as the criteria score for predicting celiac disease. This score was determined by the following: the case group mean questionnaire score was 29.7, compared to a control group mean score of 20.9 (Table 2). The difference of 8.9 (8.9/2 = 4.5) was divided in half, and then 4.5 was subtracted from 29.7 and added to 20.9 to find the median of the score difference, 25.3. Tables 14 and 15 display the frequency distributions of questionnaire scores for the two groups. At a predictive score of 25, 14 cases with CD had Type I errors with

Table 14.

SPSS Case Group Frequency Distribution of Questionnaire Scores

Score	Frequency	Percent	Cumulative %
19	1	1.3	1.3
20	1	1.3	2.6
21	1	1.3	3.8
22	2	2.6	6.4
23	6	7.7	14.1
24	3	3.8	17.9
25	4	5.1	23.1
26	4	5.1	28.2
27	7	9.0	37.2
28	4	5.1	42.3
29	8	10.3	52.6
30	9	11.5	64.1
31	6	7.7	71.8
32	2	2.6	74.4
33	2	2.6	76.9
34	4	5.1	82.1
35	2	2.6	84.6
36	2	2.6	87.2
37	3	3.8	91.0
38	2	2.6	93.6

40	1	1.3	94.9
41	1	1.3	96.2
42	1	1.3	97.4
45	2	2.6	100.0
Total	78	100.0	

Table 15.

SPSS Control Group Frequency Distribution of Questionnaire Scores

Score	Frequency	Percent	Cumulative %
16	2	3.3	3.3
17	4	6.7	10.0
18	3	5.0	15.0
19	9	15.0	30.0
20	11	18.3	48.3
21	6	10.0	58.3
22	9	15.0	73.3
23	7	11.7	85.0
24	5	8.3	93.3
25	1	1.7	95.0
27	3	5.0	100.0
Total	60	100	

sensitivity at 77%, and three control cases had Type II errors with specificity at 95% (Tables 16). Sensitivity and specificity scores below 80% were considered undesirable and not valid based on the criteria established in Chapter 2, that school screening programs should have high sensitivity and specificity. Scores greater then 25 further decreased sensitivity in favor of specificity at the expense of the screening tool's accuracy. Scores less then 25 were then evaluated.

A predictive score of 24 resulted in 11 Type I errors with sensitivity at 82%, and four Type II errors with specificity at 93%. Therefore, at a score of 24, there was a 5% point increase in specificity and only a 2% decrease in sensitivity. Overall accuracy between the screening test and the diagnosis of celiac disease was 87%. At a score of 23, accuracy fell slightly to 86%, but at the expense of specificity (Table 16). Scores lower than 23 would further decrease the specificity and accuracy of the screening tool.

Table 16.

Questionnaire Score Comparisons

Score Value	>22	>23	>24	>25
Sensitivity	94	86	82	77
Specificity	73	85	94	95
PV + %	82	88	94	95
PV - %	90	82	80	76
Accuracy %	85	86	87	85

In sum, the analysis suggests a predictive score of 24 will result in the highest degree of agreement between the screening test and the diagnosis of celiac disease by blood or biopsy (Table 17). The summary of the validity measurements are as follows: Sensitivity is the ability of the questionnaire to identify correctly all screened individuals who actually have CD. Sensitivity= A/A+C= 64/78= 82%. Specificity is the ability of the questionnaire to correctly identify all screened individuals who actually do not have CD. Specificity= D/B+D= 56/60= 93%. Predictive value (+) is the proportion of individuals screened positive by the questionnaire who actually have CD. PV+= A/A+B= 64/68= 94%. Predictive value (-) is the proportion of individuals screened negative by the questionnaire who do not have CD. PV-= D/C+D= 56/70= 80%. Accuracy measures the degree of agreement between the screening tool and the diagnosis of celiac disease by blood or biopsy. Accuracy= A+D/A+B+C+D= 120/138= 87%. The prevalence of celiac disease in the total population= A+C/A+B+C+D= 78/138= 57%.

Table 17.

Fourfold table for classification of screening test results for a score > 24.

	Celiac Disease		
	Present	Absent	Total
Positive: Score > 24	True Positives A = 64	False Positives B = 4	All Positives A + B = 68
Negative: Score < 24	False Negatives C = 14	True Negatives D= 56	All Negatives C + D = 70
Total	A + C = 78	B + D = 60	A+B+C+D= 138

Notes. True positives (A) are individuals who both have been screened positive for celiac disease and truly have the condition. False positives (B), or Type II errors, are individuals who have been screened positive for celiac disease but do not have the condition. False negatives (C), or Type I errors, are individuals screened negative for celiac disease who truly have the condition. True negatives (D) are individuals who both have screened negative for celiac disease and do not have the condition.

The test-retest mailing was sent to the 35 case group responses received prior to October 30, 2006. These 35 cases represented 45% of the total case group (N=78). The response rate to the test-retest mailing was 77%, for a total N=27. The 27 case group questionnaires had an initial mean test score of 29.5. The scores ranged from a low of 19 to a high of 39 (SD=4.8). When this group was retested a month later their mean retest score was 28.9, for a score difference of .67 or 2% (Table 5). The scores ranged from a low of 21 to a high of 37 (SD=4.3). The difference between the two means in Table 18 appear not to be statistically significant, ($t = 1.14$, $p = .27$). In Table 19 the reliability

coefficient, Cronbach's Alpha, measured r =.87, suggesting that the questionnaire score measured something in the same way each time the test was used. A cross check in Table 20 of the inter-item correlation of Alpha was .78 (p = .0001), indicating not only statistical significant, but also a rather substantial mean inter-item correlation and good evidence of reliability. The test of reliability results was found to be highly significant, (p =.0001).

Table 18.

Paired Sample t-Test for Test-Retest

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	SD	MSE	Lower	Upper	*t*-score	df	Sig. (2-tailed)
Pair 1	Test-Retest	.7	3.1	.6	.5	1.9	1.1	26	.27

Table 19.

SPSS Reliability Statistics

Cronbach's Alpha	Cronbach's Alpha Based On Standardized Items	N of Items
.87	.88	2

Table 20.

SPSS Reliability Summary Item Statistics for Paired Test-Retest

	Mean	Min	Max	Variance	*p*
Inter-Item Correlations	.78	.78	.78	.78	.0001

In summary, the mean score questionnaire difference between children with diagnosed celiac disease and children without diagnosed celiac disease was 43%, ($t = -12.5$, $p = .001$). The results of the sample t-test indicated that a child diagnosed with celiac disease will have a significantly higher score on the questionnaire than a child without diagnosed celiac disease (Hypothesis I).

The factor analysis of the case group identified six subsets of health symptoms and conditions, that when present together, increase a child's risk for celiac disease: Factor I correlated older girls with aches and mouth; Factor II correlated with items intestinal, stomach, allergies and high absenteeism; Factor III correlated with items anemia, mental and skin; Factor IV correlated with growth and anemia; Factor V correlated girls with mental and relative; and Factor VI correlated with boys with allergies and cognitive learning. In addition, an ANCOVA of independent variables for celiac disease identified the following four statistically significant correlations ($r \geq .4$, $p = .001$): anemia with mental; anemia with growth; stomach and intestinal; and age and aches (Hypothesis II).

The results of the accuracy measurements indicate that the questionnaire has a high degree of predictive validity for celiac disease: 82% sensitivity, 94% specificity, 94% PV+, 80% PV- , 87% accuracy (Hypothesis III). The referral population from the control group (N=60, scores> 24) was 6.7%, of which only one was a known Type II error from NC-2 (non-case children known to have tested negative for celiac disease). Furthermore, the correlation between two sets of questionnaire scores for the same child in the case group was relatively high (r =.87) signifying that the instrument is reliable (Hypothesis IV).

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

The primary purpose of this research was to pilot test a screening tool that identified children at high-risk for celiac disease which could be administered at the public school level by the school nurse. This instrument validation was designed as a case-control study and had three different sample groups: one case and two levels of control. The case group was 78 children with diagnosed celiac disease whose parents were recruited from mailing lists made available by their local celiac support groups. The control group was divided into two groups: 45 non-case children without diagnosed celiac disease whose parents were recruited from a published community phonebook; and 15 non-case children known to have tested negative for celiac disease by either blood test or biopsy, whose parents were purposively recruited from three different celiac support groups. The instrument is an original survey containing 16 questions related to the common clinical symptoms and conditions of celiac disease. The instrument was developed from secondary data sources, focus group input, and target group pre-testing feedback. The data collection method was a recruitment mail package that contained a form letter, the questionnaire, consent forms, contact information and a SASE. The data was collected over a four month period.

Conclusion

Based on published research, the most common childhood symptoms in undiagnosed celiac disease are a combination of persistent diarrhea and failure to thrive. The results of this study are consistent with these findings. Ninety-one percent of the children with diagnosed celiac disease reported intestinal pain, and 64% reported poor weight gain, weight loss, or failure to thrive, prior to being diagnosed with celiac disease.

Other published research and reported results of common symptoms include abdominal pain, gas and bloating; weight loss; poor growth; diarrhea; weakness; nausea and vomiting; anemia; mood swings and depression; constipation; skin rashes such as eczema; short stature and vitamin deficiencies; dental enamel defects and canker sores; asthma and food allergies; headaches, learning disorders, ADHD, and neurological disorders such as autism. In addition, the research supports that all children who have type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, autoimmune thyroiditis, or who are first degree relatives of an individual with confirmed celiac disease, should be screened even if they are without gastrointestinal symptoms.

The data supported five reported types of symptoms of undiagnosed celiac disease that had strong correlations to the disease: (a) short stature, growth delay, or weight loss; (b) fatigue, weakness, anemia or other nutrient deficiencies; (c) abdominal pain, gas or bloating; (d) skin rashes such as eczema, psoriasis or dermatitis herpetiformis; and (e) dental enamel defects or recurring canker sores. In addition, there were four pairs of reported types of symptoms that when present, demonstrated a higher risk for celiac

disease: (a) weakness, anemia, or other nutrient deficiencies with unexplained mood swings, depression, anxiety, or stress; (b) weakness, anemia, or other nutrient deficiencies with short stature, growth delay, or weight loss; (c) abdominal pain, gas, or bloating with diarrhea, constipation, vomiting, or nausea; and (d) older children with unexplained headaches, joint aches, or body aches. This approach of evaluating two different types of symptoms and their connection to celiac disease is new to published research. Previous published studies, such as the 2005 Canadian study (Rashid, et al.), list and analyze only discrete clinical symptoms prior to diagnosis on an individual basis.

The data also supports the existence of several factor subsets of health symptoms and conditions that, when present together, increase a child's risk for celiac disease. The four most significant subsets are: (a) older girls with unexplained headaches, joint aches, or body aches; and dental enamel defects or recurring canker sores; (b) children with gastrointestinal pain; allergies or asthma; and above normal absenteeism; (c) children with fatigue, weakness, anemia, or other nutrient deficiencies; unexplained mood swings, depression, anxiety, or stress; and skin rashes such as eczema, psoriasis, or dermatitis herpetiformis; and (d) boys with allergies or asthma; and cognitive learning problems. Once again, the use of factorial analysis to analyze the relationship of multiple existing symptoms is new to the field of celiac disease. Past studies have only used factorial analysis to evaluate the psychological dimensions of the disease, such as the 2002 study by Ciacci, Iavarone, Siniscalchi, Romano and Rosa.

There were a total of six subsets identified by the factor analysis. Four of the six are listed in the preceding paragraph as significant factor subsets. A fifth factor of

children with poor growth and anemia was acknowledged as a correlation. The sixth factor, girls with anxiety without first degree relatives with CD, was not recommended for use because most people do not know if their first-degree relatives have celiac disease since most people are not screened for the disease in this country. The decision was made to exclude this factor due to the uncertainty of the answer to question #14 (Appendix F) regarding having a first degree relative with diagnosed celiac disease. Ninety-five percent of the North American CD cases are undiagnosed and untreated (Green et al., 2001).

The screening tool appears to be valid at face value because the 15 questions are grouped according to the most common clinical symptoms and conditions of undiagnosed celiac disease. Children with diagnosed celiac disease scored 43% higher on the questionnaire than children without diagnosed celiac disease. The criterion-related validity of the screening tool is supported by an 87% predictive value of the questionnaire to accurately diagnose celiac disease (82% sensitivity; 94% specificity; 94% PV+; 80% PV-). The screening tool appears reliable because the correlation between two sets of questionnaire scores for the same child in the test-retest was relatively high ($r = .87$), and 9% above the target of $r = .8$.

Hypothesis 1: A child with diagnosed celiac disease will have a significantly higher score on the questionnaire than a child without diagnosed celiac disease ($p \leq .01$).

Outcome: Not Rejected ($t = -12.5$, $p = .001$).

Hypothesis 2: There exist several subsets of health symptoms and conditions, that when present together, increase a child's risk for celiac disease (rho≥.4; p≤ .01; h^2≥.4; Eigenvalue≥1; %Variance≥16)

Outcome: Not Rejected (rho≥.4; p≤ .01; h^2≥.54; Eigenvalue=6.7; % Variance=67)

Hypothesis 3: The questionnaire will have a high degree of predictive validity for celiac disease (sensitivity≥ 80%; specificity≥ 80%; PV+≥ 80%; PV-≥ 80%).

Outcome: Not Rejected (82% sensitivity; 94% specificity; 94% PV+; 80% PV-).

Hypothesis 4: The correlation between two sets of questionnaire scores for the same child will be relatively high in order for the instrument to be considered reliable (r≥.80).

Outcome: Not Rejected (r≥.87).

Discussion and Implications

In the past several years, there has been a growing consensus that celiac disease (CD) is much more common than previously thought, affecting one percent of the population, including children. At-risk individuals have higher prevalence rates of one in 22. For each diagnosed person with CD there are 89 undiagnosed. The diagnosis of celiac disease is frequently missed for several reasons. First, there is a lingering perception among health care professionals that the disease is rare, when in fact, it is one of the most

common inherited diseases and is considered to be the most under-diagnosed common disease today (Fasano, 2001). This continuing false perception causes many in the health care field to look elsewhere for a cause when the symptoms of celiac disease present themselves in patients. CD is often misdiagnosed as irritable bowel syndrome or lactose intolerance and up to one third of celiac disease patients have been previously diagnosed with IBS. Secondly, approximately 50% of new patients present with atypical symptoms. This failure by physicians to appreciate that many individuals with the disease initially present without gastrointestinal symptoms is another reason why CD testing may not be performed. Lastly, physicians may use more widely known but less accurate serologic testing, such as the AGA IgA test that can result in missed diagnosis (Fasano, 2001). Greater awareness of the disease by health care professionals and patients will lead to increased rates of diagnosis. Targeted education and screening programs are necessary to increase recognition and awareness of CD.

The literature indicates an increased quality of life for people diagnosed through screening. This indication suggests that even though people who do not think they are ill and seek health care, are better off being diagnosed with celiac disease if they do have it (Green & Jones, 2006). Patients diagnosed at a young age report the highest rates of compliance to a gluten-free diet which is currently the only effective method of treatment. In addition, the consequences of screening for at-risk and symptomatic patients appear to be beneficial, since these patients are more compliant with a gluten-free diet (Rostom et al., 2004).

Currently the only accepted screening methods for celiac disease are by serologic tests and intestinal biopsy. Neither is appropriate for school health services or for a school setting due to cost and equipment requirements. Up to 21% of internal biopsies are rejected by insurance companies, claiming the cost of the testing isn't justified by the symptoms (Fasano, 2001). A recent 2006 study by Shamir, Hernell, and Leshno, to examine the cost-effectiveness of screening for CD in the adult population estimated an incremental cost-effectiveness ratio of $44,941 per life year gained by screening compared to no screening using EMA serological tests. The authors concluded that screening for CD is cost effective in populations with a relatively high prevalence of CD. The cost of evaluating a patient suspected of having CD included two office visits (each visit cost $40), routine blood tests ($15), a serological test ($70), and endoscopy ($1105). Costs attributable to ongoing care for those diagnosed with CD were estimated to be $130 annually. As multiple serological tests approach 100% sensitivity, such as the combined use of tTG-IgA and IgA AAA blood test, the need for endoscopy will decrease, further decreasing the cost of diagnosing CD. As the cost barrier of diagnosis decreases, more people in high prevalence populations should be routinely screened and diagnosed. Once again, increased CD screening will result in increased rates of diagnosis which will result in increased prevalence rates. The literature supports that screening is an acceptable strategy when the prevalence of CD is greater than one percent and would be the dominant strategy when the prevalence exceeds 8%. It is therefore imperative to develop an efficient multi-stage screening procedure for celiac disease to take advantage of any future diagnostic strategy changes for the disease. The results of this instrument

validation study support the use of the developed questionnaire as the first step in screening for CD in children. In addition, the questionnaire is appropriate for a school setting. The questionnaire can be used as part of a flexible, continuous screening process because it is inexpensive, time efficient, reliable, and valid.

Increased recognition and awareness of celiac disease will have a significant positive impact on the quality of life of children with CD and their families, and will reduce the costs associated with the disease. This celiac disease screening questionnaire can serve as the first "standard" in a school CD screening program to raise awareness and educate health care professionals about celiac disease, and its symptoms, diagnosis and treatment, because it is designed to be used in the school setting by the school nurse.

The school setting, ranging from preschool to university, is an important avenue to reach the entire population and specifically to educate children and youth. Schools have more influence on the lives of young people than any other social institution except the family, and provide a setting in which friendship networks develop, socialization occurs, and norms that govern behavior are developed and reinforced. Each school day about 48 million youth in the United States attend almost 110,000 elementary and secondary schools for about six hours of classroom time. More than 95 percent of all youth aged five to 17 years are enrolled in school. Schools are second only to homes among the primary places that children spend their time. Because healthy children learn better than children with health problems, schools also have an interest in addressing the health needs of students. In addition, schools receive federal and state dollars per day per student in attendance and therefore have a financial incentive to minimize daily

absenteeism. Although schools alone cannot be expected to address the health and related social problems of youth, they can provide, through their climate and curriculum, a focal point for efforts to reduce health-risk behaviors and improve the health status of youth (Kann, Collins, & Pateman, 1995).

School health services are services provided for students to appraise, protect, and promote health. They are part of the coordinated school health program model that consists of eight interactive components: health services; physical education; health education; nutrition services; counseling, psychological and social services; healthy school environment; health promotion for staff; and family and community involvement (CDC, 2005). These services are designed to ensure access or referral to primary health care services and provide educational and counseling opportunities for promoting and maintaining individual, family, and community health. Screening programs are the responsibility of school health services.

School nurses are the largest providers of health services in schools. The National Association of School Nurses (NASN) reports 40,000 school nurses work within the United States and would like to collaborate more with pediatricians to effect change for children's health. School nurses serve as case managers, especially for children having complex and chronic health conditions that need management at school. Caring is at the heart of school nursing practice. School nurses have greater potential through their weekly and daily access to children and families to apply caring interventions, such as active listening and care planning. This caring intervention is important because chronic health conditions are often associated with chronic absenteeism (American Academy of

Pediatrics, 1998). School screening programs are often the best way to detect problems that interfere with a student's education, such as poor vision or hearing, and high absenteeism. Children with undiagnosed celiac disease report a 20% higher absenteeism rate than children within the general population.

This pilot tested celiac disease screening instrument would equip the school nurse with the knowledge and skills necessary to make appropriate student referrals to physicians for further medical evaluation. School screening does not replace a comprehensive exam by a physician. Good screening instruments should have the following attributes: a clear purpose; succinct directions; use clear and understandable words for the target audience; be relatively easy to use for both the administrator and target audience; be of minimal expense; have a determined cut score; be valid and reliable; and be pilot tested with the same population as the target audience. Currently there is not a standard questionnaire for the mass screening of children for celiac disease.

The purpose of this study was to develop and then pilot test a screening tool that identified high-risk children and could be administered at the public school level by the school nurse. The questionnaire has a clear purpose: identify children at high-risk for celiac disease. The questionnaire provides succinct, clear and understandable directions as displayed in Appendix B. There was only one returned questionnaire that was not used because the parent did not complete the consent form. There were no phone calls from participants during the pilot test. The questionnaire is easy to administer and takes less than five minutes for the parent to complete. Scoring by the school nurse is straight forward and takes less than two minutes. The screening tool will be available on line at

no cost and will be of minimal expense with respect to the school nurse's time. The screening tool has a determined cut score of 25. The screening tool is statistically reliable (r =.87), valid (87% accuracy), and has been pilot tested with 138 students, pre-k through college. In addition, school nurses currently conduct various student screening programs, such as vision, hearing and asthma. School nurses are knowledgeable about screening programs, educated about the importance of following proper screening protocols, and understand the value efficient screening programs have on student health.

The questionnaire can be the important first step for use in screening children for celiac disease. When children present themselves to health services with delayed growth, fatigue, abdominal pain, skin rashes, dental enamel defects or canker sores, the nurse should further evaluate the child's health. Children with celiac disease reported 52% higher rates for short stature, growth delay, or weight loss; 41% higher rates for fatigue, weakness, or anemia; 26% higher rates for abdominal pain, gas or bloating; 25% higher rates for skin rashes; and 24% higher rates for dental enamel defects or recurring canker sores. High scoring boys on the questionnaire all reported "a lot" of delayed growth. High scoring girls reported "a lot" of aches and canker sores. Therefore, these health symptoms of delayed growth in boys, and "a lot" of body aches and canker sores in girls, should be trigger points for active case finding and CD screening by questionnaire. Young children with recurring gastrointestinal pain and stomach aches, especially after lunch, should also be screened for CD, especially when anemia or fatigue are present.

Nurses for elementary schools should routinely screen both boys and girls, especially those in kindergarten thru second grade, who have above-normal absenteeism,

gastrointestinal pain and allergies. In addition, anxious, fatigued children with skin rashes should be candidates for CD screening. Boys with delayed growth and anemia are also at higher risk for celiac disease and should be screened. School nurses for grades six thru twelve should screen for all the above profiles in addition to female students who present with body aches and canker sores. The factor analysis identified older girls with a lot of body aches and mouth sores as the most common subset at risk for CD and, therefore, strong candidates for case identification.

Girls with diagnosed celiac disease had questionnaire scores 6.7% higher than boys with diagnosed celiac disease, but girls from the general population reported 3.4% fewer health conditions and symptoms than boy peers. Girls with diagnosed celiac disease had questionnaire scores 47% higher than girl peers. Boys with diagnosed celiac disease had questionnaire scores 33% higher than boy peers. Therefore, it can be reasoned that girls with undiagnosed celiac disease may present with more health symptoms and conditions than boys with undiagnosed celiac disease, and they may have significantly more health problems than their peers. School nurses need to be attuned to this situation when identifying candidates for individual CD case detection. Children with questionnaire scores of 25 and greater should be referred to their family physician for further examination.

This questionnaire overcomes certain limitations of one shot screening programs, such as vision and hearing where a test is given at one point in time and cannot be assumed to reflect the child's status at a later time, often leading to high numbers of false positives or negatives. Children's health is dynamic. The questionnaire queries parents

about the child's health over a period of time that is determined by the parent. In addition, the factor analysis provides identifiable health symptoms associated with celiac disease that serves as a guide to active case finding for screening. The health symptoms and high risk student profiles can be part of a check list employed by the school nurse in the written guidelines for a school celiac disease screening program. Most importantly, the questionnaire is a pilot tested, reliable and valid instrument that can serve as the new "standard" first step to celiac disease screening by all school health service departments with internet access.

As this assessment shows, this pilot tested celiac disease screening instrument meets all nine of the recommended policy criteria by the American Academy of Pediatrics (2004) for school screening programs that will contribute to improved student health, as presented in Chapter II.

1. The disease has a prevalence rate of one percent in the general population and children at risk for the disease have rates as high as one in 22.

2. The only current treatment for celiac disease is a gluten-free diet. Complete removal of gluten from the diet in a child with celiac disease should result in symptomatic, serologic, and histologic remission.

3. The screening questionnaire has high sensitivity and specificity (82% sensitivity; 94% specificity; 94% PV+; 80% PV-).

4. The nurse is well trained and experienced to screen children through active case finding, and by questionnaire as part of the normal school health services' function that

appraises, protects, and promotes health. School nurses routinely screen for hearing, vision, asthma, mental health, and diabetes.

5. The target populations of children at high risk for celiac disease have prevalence rates greater than four percent. In addition, the research supports the idea that early screening results in higher rates of compliance to a gluten- free diet, thereby reducing health costs and other autoimmune diseases that are a result of undiagnosed or untreated CD.

6. All positive screens of questionnaire scores greater than 24 will have definitive referrals for further evaluation, diagnosis and treatment by a family physician or other healthcare professional. The school nurse will also be able to offer information about the gluten-free lifestyle and local celiac disease support groups.

7. The screening program is appropriate for a school site because it is inexpensive, time efficient, simple, reliable, and valid. No special diagnostic tools or training are necessary.

8. The CD screening program can be assessed for efficiency and effectiveness by following up referrals with a phone call to the parents. The nurse can record the results of the referral, such as parental reaction to the referral; the outcome of any pediatric visits and serologic tests; and adoption and compliance rates to a gluten-free diet. The school nurse can assist families in finding good-quality medical care including dieticians. The program can then be periodically evaluated for efficiency and effectiveness from the recorded referral outcome data.

9. The screening program costs less than the benefit of early intervention. The questionnaire and program instructions will be available on the internet at no financial cost to the school other than printing. The other costs associated with the program are five minutes of the parent's time to complete the questionnaire and two minutes of the nurse's time to score the questionnaire. These minimal costs are less than the benefit of early intervention, because once a child presents with symptoms and conditions of celiac disease, families, schools and the medical community have already collectively experienced higher rates of absenteeism, costs incurred in diagnosis of the disease, costs incurred in treating symptoms and conditions of the disease, and diminished quality of life. The high specificity of the questionnaire will help to minimize false positives that may create stress and unnecessary medical costs for families.

Limitations

A major limitation of this research is the inability to evaluate the accuracy of all the test-negatives. Forty-five of the 60 participants in the control group were not tested for celiac disease and the prevalence rate of this group was unknown. The 45 were all of white ethnicity. The literature supports a prevalence rate of one percent in European-American populations. Therefore, assuming statistically that one person of the 45 has CD, the accuracy would be 86% (82% sensitivity; 92% specificity; 93% PV+; 80% PV-) compared to the results of 87% (82% sensitivity; 94% specificity; 94% PV+; 80% PV-). The adjusted accuracy measurements still indicate that the questionnaire has a high degree of predictive validity for celiac disease, with all values greater or equal to 80%.

A second limitation is that the test-retest for reliability was not performed on the control group due to lower response rates and sample sizes. To overcome issues of statistical power, it is recommended that the study be expanded to a larger number of control group participants.

Another limitation is bias on the part of the parents of children with celiac disease who were very supportive of the research (as evident by the 73% postal response rate) and who have a vested interest in the development of a celiac screening tool. These parents may have been more diligent and detailed about the health of their child when completing the questionnaire than parents recruited from the Southlake community phonebook (with a 23% postal response rate), resulting in the highly significant mean questionnaire score difference between the two groups.

Selection bias may be another limitation of the study since the case and control groups were non-probabilistic samples of convenience because of time and financial resource constraints. Most of the control group resided in the affluent community of Southlake, Texas, where the annual household income is greater than $150,000, 97% of the residents have a high school degree, and 95% of the residents are white (Southlake, Texas, 2004). Neither the questionnaire's readability nor content appeared to be issues for this group. In an effort to bring some geographic diversity, the case group, and 15 non-case children known to have tested negative for celiac disease, included participants from the states of Maine, Vermont, New York and New Jersey. Further research in diverse geographic and economic communities is recommended to reduce the potential for selection bias.

Pilot tests, like this one, are intended to assess the adequacy of the research design and of the instrumentations to be used for data collection. The research did not attempt to represent the correct proportions of different types of individuals in the population because it was an instrument validation study (Sapsford & Jupp, 1998).

Recommendations

Fasano (AMA, 2003) states that CD occurs frequently not only in patients with gastrointestinal symptoms, but also in relatives and patients with numerous common disorders even in the absence of gastrointestinal symptoms. Given the high morbidity and mortality related to untreated celiac disease and the prolonged delay in diagnosis in the United States, active case finding of at-risk patients is important to alleviate unnecessary suffering, prevent complications, and to improve the quality of life of a multitude of individuals with CD.

Based on the reported results of the pilot test and published data, the following five changes were made to the questionnaire:

1. Parents self identify student ethnicity to eliminate multiple checked boxes.

2. The final question about celiac disease on page 2 was relocated to page 1 below the demographic questions. The rationale for this change was that if a child has diagnosed celiac disease there would be no need for further screening.

3. Scoring areas were added to the first and second page to facilitate and reduce scoring time.

4. Comment space for both the school health provider and parent/guardian were added to provide an open-ended response area in case all the health symptoms and

conditions could not be categorized by the 15 questions. Many participants wrote detailed notes.

5. Parent/guardian signature and date lines were added for implied consent.

Appendix J displays the amended parent questionnaire for celiac disease screening.

The pilot test did not have significant numbers of participants with diabetes, or Down's syndrome, but these questions were not removed due to the high prevalence rate of CD in these populations. Further screening in these populations is recommended. Both the case and control groups reported 60% levels for unexplained headaches, joint aches, or body aches. However, this question was not removed because aches, when present in girls with canker sores, showed an increased risk for celiac disease. All the other questions related to the health conditions and syndromes associated with celiac disease had significantly higher reporting percentages for children with, than for children without, CD.

An efficient and effective celiac disease screening program should employ the fewest procedures needed to identify students at high-risk for CD. The following strategies are recommended:

1. Focus on student "case identification" of existing health information and evaluate risk using the five descriptive component factors for children identified at high risk for celiac disease: (a) older girls with unexplained headaches, joint aches or body aches; and dental enamel defects or recurring canker sores; (b) children with gastrointestinal pain; allergies or asthma; and above normal absenteeism; (c) children

with fatigue, weakness, anemia or other nutrient deficiencies; unexplained mood swings, depression, anxiety or stress; and skin rashes such as eczema, psoriasis or dermatitis herpetiformis; (d) children with weakness, anemia or other nutrient deficiencies; and short stature, growth delay, or weight loss; and (e) boys with allergies or asthma, and cognitive learning problems. Then contact the student's parents or guardian to discuss the issue and complete the questionnaire.

2. Provide individual case detection when students not diagnosed with celiac disease present to the nurse's office with symptoms of CD.

3. Refer positive screens to primary care providers for further testing.

4. Avoid population-based case detection that increases false positive celiac disease screening tests, resulting in unnecessary stress for the families and unnecessary referrals to physicians offices.

5. Follow-up with referral. Assist families in receiving or in finding good-quality medical care and provide local support group information. Collaborate with community partners to ensure care and adherence to a gluten-free diet.

6. The value of the celiac disease screening program should be regularly assessed. It should be determined the extent to which families follow through with school referrals. Community based assessments that occur as a result of school referrals of students with positive screens should be ascertained. If families do not act, the screening program should be evaluated for improvements.

Based on the preceding strategies, the proposed five step program guidelines are:

Step One: "Active Case Finding". School health providers employ active case detection and individual case finding based on the descriptive components in the nurse instruction sheet of children at high risk for celiac disease.

Step Two: "Case Screening". The parent/guardian of suspected cases complete a five minute questionnaire and parent consent form about the general health of their child as it relates to the common symptoms and conditions of celiac disease. Appendix K displays a sample of a parent consent form. Participation is voluntary. The parents/guardians have a choice not to participate. Questionnaire results are kept confidential and the screening results will not be kept in the child's academic records.

Step Three: "Case Referrals" The school health provider scores the questionnaire. If the score is greater than 24, the parent/guardian is notified by phone call or in person, and referred to their family physician for further evaluation and testing. If the family does not have a physician, the school health provider provides the family with a referral to a local and knowledgeable health care professional.

Step Four: "Case Follow-Up". The school health providers follow-up the referral with a phone call or meeting with the parent/guardian and record the results of the referral, including outcomes of any diagnostic tests and compliance rates to a gluten-free diet. The school health providers note if evaluation and treatment for positively diagnosed children are consistent and current with the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition recommendations.

Step Five: "Program Evaluation". The school health providers evaluate the screening program at the end of every semester.

A sample screening program parent consent form is displayed in Appendix K and the sample draft of the celiac disease screening program's professional cover sheet is displayed in Appendix L.

Several action steps should be taken to facilitate the development of the screening program at the public school level. The screening tool should be presented at the annual summer conventions of the National Association of School Nurses and the American School Health Association. The pilot test research results should be printed in the *Journal of School Nursing, Journal of School Health* and *Health in Action.* The questionnaire with directions for use, a professional handout including internet resources offering information about celiac disease (including symptoms, diagnosis and treatment), celiac disease support group contacts and an explanation of a gluten-free diet, should be made available free on the internet. School nurses, representing geographically and economically diverse school systems, should be enlisted to participate, use the screening program, and provide feedback via the internet.

Future research and action steps include the following:

1. Expand the pilot test. Obtain grant money and partner with several geographically and economically diverse school districts within the United States, to conduct a broad based population screening program of elementary students using the amended questionnaire.

2. Develop a multi-stage school screening procedure to increase the sensitivity and specificity of the screening program. The Gerald 2002 study of elementary students concluded that using a reproducible and portable test in conjunction with a screening questionnaire increased specificity and reduced false positive screens. ANI Biotech of Finland makes the Biocard® Celiac Test, a simple, low-cost repeatable diagnostic screening procedure that is based on the rapid detection of celiac antibodies. The Biocard® Celiac Test is portable, takes less than five minutes to complete, and is appropriate for a school setting, depending on the unit cost. The company currently markets and sells the product in Europe and Canada, and is currently awaiting FDA approval. A 2005 screening study (Korponay-Szabo, Ludmany, & Imre) using the Biocard® Celiac Test on 2676 European elementary students found the school nurse detected celiac disease prevalence of CD to be 1.1% with 100% PV+ (81% Sensitivity; 100% Specificity). Sensitivity increased to 96% after school nurses were trained to read the Biocard®. The study concluded that nurses were able to detect the majority of celiac children during their routine primary care work, and that screen-detected celiac children had worse health status than normal peers. Also of interest in the study was that antibody-positive girls weighed nine percent less than antibody-negative girls; antibody-positive boys weighed 24% less than antibody-negative boys and were four percent shorter. These results are consistent with the results of this study that the symptoms of short stature, growth delay, and weight loss are strongly correlated to celiac disease.

Once ANI Biotech obtains FDA approval, collaboration with the company is recommended to develop a school based multi-step program using the questionnaire and Biocard®, where both sensitivity and specificity are equal or greater than 95%.

3. Develop a targeted media campaign to build awareness of the celiac disease screening program that encourages families to ask their school nurse and family physicians about celiac screening services for their children. The campaign would be a partnership between the NASN, AAP, and national supermarket chains that specialize in gluten-free products, such as Whole Foods, Kroger and Wal-Mart. Members of both the NASN and AAP would send personalized form Op-eds to their local newspapers discussing the 2006 Food Allergen Labeling and Consumer Protection Act, its relevance to celiac disease, and why parents should ask their school nurse or pediatrician if their children should be tested for the disease. The NASN nurses will distribute one page celiac screening information pamphlets in their schools through student health services. AAP pediatricians would also provide the same pamphlets in their offices. The supermarkets would distribute the same pamphlet in their weekly circular or make the pamphlet available at their stores. The rationale behind these actions is to "pull" demand by families for more information. The rationale behind partnering with national supermarket chains is that as more children are diagnosed with celiac disease, gluten-free product demand would increase sales and store traffic for the supermarkets. Currently gluten-free products are growing 25% annually (Browne, 2005), compared to a total industry average supermarket growth rate of less than two percent (Food Industry Center, 2000). The pamphlet would be available free to download from the internet, and the

printing and distribution costs of the media campaign would be funded by the partnering entities. A celiac disease support group, such as the Celiac Disease Alliance or the Gluten Intolerance Group, should be approached to initiate the program.

It took 50 years to identify a treatment for celiac and then another 30 years to develop diagnostic tests. The last five years has focused on increasing physician awareness to get the diagnosis rate to the level it needs to be. There is a current effort to develop a vaccine to make gluten more tolerable for celiacs but conclusive results are at least ten years away. In the meantime, "active case finding", as demonstrated in this celiac disease screening program for schools, will not only decrease the size of the celiac "iceberg" and with it health care costs associated with undiagnosed CD, but increase the quality of life for students with undiagnosed celiac disease. As awareness grows and more people are diagnosed with CD, compliance to a gluten-free diet will become easier because food manufacturers, grocery stores, restaurants, businesses and schools will respond to the increase in demand and offer more and better tasting gluten-free food choices.

In closing, the pilot tested celiac disease screening questionnaire is a valid and reliable instrument that identifies children at high-risk for celiac disease and is appropriate for use at the school level. It is recommended that the celiac disease screening program be further packaged to include all the necessary marketing and instructional materials, and be made available to geographic and economically diverse school systems throughout the United States for further testing and use.

LIST OF REFERENCES

American Academy of Pediatrics [AAP], 1998. *Only the best will do for our children!* School Health Newsletter, Winter/Spring. Retrieved February 8, 2007 from http://www.schoolhealth.org/article.cfm?contentID=43.

American Academy of Pediatrics [AAP] Committee on School Health, 2000. School health assessments. *Pediatrics, 105(4), 875-877.*

American Medical Association (AMA), 2003. *Celiac disease more common than previously thought.* Medical Library. Retrieved August 1, 2004 from http://www.medem.com/medlb/article_detaillb.cfm?article_ID=ZZZ1W61C2CD &sub_cat=2

Bai., D., Brar, P., Holleran, S., Ramakrishnan, R., & Green, P. (2005). Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men. *Scandinavian Journal of Gastroenterology, 40,* 183-187.

Bardella, M., Trovato, C., Cesana, B., Pagliari, C., Gebbia, C., & Peracchi, M. (2001). Serological markers for celiac disease: Is it time to change? *Digestive Liver Disease, 33*(5), 426-431.

Brassard, P., Steensma, C., Cadieux, L., & Lands, L. (2006). Evaluation of a school-based tuberculosis-screening program and associate investigation targeting recently immigrated children in a low-burden country. *Pediatrics 117*(2), 148-156.

Browne, D. (2005). *Sales figure on gluten-free products*. Public Meeting Food and Drug Administration, College Park, Maryland, August 19, 2005. Retrieved on February 9, 2007 from http://www.fda.gov/ohrms/dockets/dockets/05n0279/05N-0279-EC87-Attach-1.pdf.

Busschots, G. (2006). *Sprue.* Retrieved October 12, 2006, from http://www.emedicine.com/ped/topic2146.htm.

CDC, 2005. *Healthy youth! Coordinated school health program*. National Center for Chronic Disease Prevention and Health Promotion. Retrieved February 8, 2007 from http://www.cdc.gov/healthyyouth/CSHP/.

Carroccio, A., Di Prima, L., Falci, C., Le Moli, C., Soresi, M., Montalto, G., et al. (2002). Predictive value of serological tests in the diagnosis of celiac disease. *Annual Annali Italians di Medicina Interna, 17*(20), 102-107.

Carroccio, A., Vitale, G., Di Prima, L., Chifari, N., Napoli, S., La Russa, C., et al. (2002). Comparison of anti-transglutaminase ELISAs and an anti-endomysial antibody assay in the diagnosis of celiac disease: a prospective study. *Clinical Chemistry, 48*(9), 1546-1550.

Catassi, C., Ratsch, I.M., Gandolfi, L., Pratesi, R., Fabiani, E., El Asmar, R., et al. (1999). Why is coeliac disease endemic in the people of the Sahara? *The Lancet, 354*(9179), 647-8.

Catassi, C., & Fasano, A. (2004). Celiac disease as a cause of growth retardation in childhood. *Current Opinion in Pediatrics, 16*, 445-449.

Ciacci, C., Iavarone, A., Siniscalchi, M., Romano, R., & De Rosa, A. (2002). Psychological dimensions of celiac disease: toward an integrated approach. *Digestive Diseases and Sciences, 47*(9), 2082-2087.

Clemente, M., Musu, M., Troncone, R., Volta, U., Congia, M., Ciacci, C., et al. (2004). Enetercyte actin antibodies: a new tool in celiac disease diagnosis. *American Journal Gastroenterology, 99*, 1551-1556.

Corazza, G., Valentini, R., Andreani, M., D'Anhino, M.., Leva, M., Ginadli, L., et al. (1995). Subclinical coeliac disease is a frequent cause of iron-deficiency anaemia. *Scandinavian Journal of Gastroenterology, 30*(2), 153-156.

Collin, P. (2005). Should adults be screened for celiac disease? What are the benefits and harms of screening? *Gastroenterology, 128*(4), S104-S108.

Cranney, A., Rostom, A., Sy, R., Dube, C., Saloogee, N., Garritty, C., et al. (2005). Consequences of testing for celiac disease. *Gastroenterology, 128*, S109-S120.

Cranney, A., Zarkadas, M., Graham, I., & Switzer, C. (2003). The Canadian celiac health survey: The Ottawa chapter pilot. *BMC Gastroenterology, 11*, 3-8.

Damen, G.M., Boersma, B., Wit, J.M., & Heymans, H.S. (1994). Catch-up growth in 60 children with celiac disease. *Journal Pediatric Gastroenterology Nutrition, 19*, 394-400.

De Luca, F., Astori, M., Pandullo, E., Sferlazzas, C., Arrigo, T., Sindoni, A., et al. (1988). Effects of a gluten-free diet on catch-up growth and height prognosis in celiac children with growth retardation recognized after the age of 5 years. *European Journal Pediatrics, 145*, 188-191.

Dickey, W., & Kearney, N. (1999). Overweight in celiac disease: Prevalence, clinical characteristics, and effect of a gluten-free diet. *The American Journal of Gastroenterology, 94*(8), 2182.

Fabiani, E., & Catassi, C. [International Working Group] (2001). The serum IgA class anti-tissue transglutaminase antibodies in the diagnosis and follow up of celiac disease. *Europe Journal Gastroenterology Hepatology, 13*(6), 659-65.

Fabiani, E., Taccari, L., Ratsch, I., Giuseppe, S., Coppa, G., & Catassi, C. (2000). Compliance with gluten-free diet in adolescents with screening detected celiac disease: A 5-year follow-up study. *Journal of Pediatrics, 136*, 841-843.

Fasano, A. (2005, May 14-19). Sprue: Serology endoscopic biopsy for diagnosis and monitoring: Serologic testing for GI disease: Are non-invasive tests helpful? *Digestive Disease Week.* Chicago Illinois [Sp197].

Fasano, A. (2005). Clinical presentation of celiac disease in the pediatric population. *Gastroenterology, 128*, 68-73.

Fasano, A. (2001). Celiac disease: The past, the present, the future. *Pediatrics, 107(4)*, 768-770.

Fasano, A, & Catassi C. (2001). Current approaches to diagnosis and treatment of celiac disease: An evolving spectrum. *Gastroenterology, 120*, 636–51.

Fasano, A., Berti, I., Gerarduzzi, T., Not, T., Colletti, R.B., Drago, S., et al. (2003). Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: A large multi-center study. *Gastroenterology, 126*, 359-61.

Fine, K. (2003, June). *Early diagnosis of gluten sensitivity: before the villi are gone.* Paper presented at the Greater Louisville Celiac Sprue Support Group. Louisville, Kentucky.

Food Industry Center (2000). *The 2000 supermarket panel executive summary report.* Retrieved on February 9, 2007 from http://foodindustrycenter.umn.edu/sites/5c885e8d-c78d-4f49-9336-ad1a9ccfce4a/uploads/ExecSumm_6-14-2002.pdf

Gabrielli, M., Cremonini, F., Fiore, G., Addolorato, G., Padalino, C., & Candelli, M. (2003). Association between migraine and celiac disease: Results from a preliminary case-control and therapeutic study. *American Journal Gastroenterology, 98*(7), 1674.

Gadewar, S., & Fasano, A. (2005) Celiac disease: Is the atypical really typical? *Current Gastroenterology Reports, 7*, 455-461.

Gerald, L., Redden, D., Turner-Henson, A., Feinstein, R., Hemstreet, M., Hains, C., et al. (2002). A multi-stage asthma screening procedure for elementary school children. *Journal of Asthma, 39*(1), 29-36.

Gomez, J., Selvaggio, G., Pizarro, B., Viola, M., La Motta, G., Smecuol, E., et al. (2002). Value of a screening algorithm for celiac disease using tissue transglutaminase antibodies as first level in a population–based study. *American Journal of Gastroenterology, 97*(11), 2785-2790.

Greco, L. (1997). Epidemiology of coeliac disease. In M. Mäki, P. Collin, & J. Visakorpi J (Eds.), *Coeliac disease*. Proceedings of the seventh international symposium on coeliac disease (pp. 9-14). Tampere, Finland: Coeliac Disease Study Group.

Green, P., & Jabri, B. (2003). Coeliac disease. *The Lancet, 362*(9381), 383-391.

Green, P., & Jones, R. (2006). *Celiac Disease*. New York, NY: HarperCollins Publishers.

Green, P.H., Stavropoulos, S.N., Panagi, S.G., Goldstein, S.L., Mcmahon, D.J., Absan, H., et al. (2001). Characteristics of adult celiac disease in the USA: Results of a national survey. *American Journal of Gastroenterology, 96*(1), 126-131.

Hill, I. (2003). Celiac disease: a never ending story. *Journal of Pediatrics, 143*(3), 289-291.

Hill, I. (2005). What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology, 128*, 25-32.

Hill, I., Fasano, A., Schwartz, R., Counts, D., Glock, M., & Horvath, K. (2000). The prevalence of celiac disease in at-risk groups of children in the United States. *Journal of Pediatrics, 136*, 86-90.

Hoffenberg, E. (2005). Should all children be screened for celiac disease? *Gastroenterology, 128*, S98-S103.

Hoffenberg, E., Emery, L., Barriga, K., Baos, F., Taylor, J., & Eisenbarth, G. (2004). Clinical features of children with screening-identified evidence of celiac disease. *Pediatrics, 113*(5), 1254-1259.

Hoffenberg, E.J., MacKenzie, T., Barriga, K.J., Eisenbarth, G.S., Bao, F., Haas, J.E., et al. (2003). A prospective study of the incidence of childhood celiac disease. *Journal of Pediatrics, 143*(3), 308-314.

Kalayci, A., Kanber, Y., Birinci, A., Yildiz, L., & Albayrak, D. (2005). The prevalence of celiac disease as detected by screening in children with iron deficiency anaemia. *Acta Paediatrics, 949*(6), 678-81.

Kann, L., Collins, J., Pateman, B., (1995). The School Health Policies and Programs Study (SHPPS): Rationale for a nationwide status report on school health programs. *Journal of School Health,* 65(8), 291-294.

Kero, J., Gissler, M., Hemminki, E., & Isolauri, E. (2001). Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac diseases, type 1 diabetes, or rheumatoid arthritis: A register study. *The Journal of Allergy and Clinical Immunology, 108*(5), 781-783.

Korponay-Szabo, I., Ludmany, K., & Imre, A. (2005). *Population decentralized rap: celiac disease study group.* University of Debrecen, Debrecen Hungary, County Institute of Public Health, Budapest, Hungary, Paediatric Research.

Lass, M., Koch, T., Losel, A., Conrad, K., Henker, J. (2006). Longitudinal follow-up examination of antigliadin antibody positive children and adults. *European Journal of Gastroenterology and Hepatology*, 18(5), 503-6.

Liu, E. (2006, January). Genetic testing for celiac disease. *Medical Laboratory Observer.* Retrieved February 1, 2006 from http://www.mlo-online.com.

Loma-Sanner, I., Kang, E., Sepehrdad, S., Goldstein, S., Herman, M., Accardo, P., et al (2005). A floppy child with failure to thrive. *Lancet, 366*, 176.

Martins, E., & Gaburri, A. (2004). Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arquivos de Gastroenterologia, 41(2).*

Monteleone, G., Pender, S., Alstead, A., Hauer, P., Lionetti, T, & McDonald, T. (2001). Role of interferon ∞ in promoting T helper cell type 1 response in the small intestine in celiac disease. *Gut, 48*, 425-429.

Murray, J. (2005). Celiac disease in patients with an affected member, type 1 diabetes, iron-deficiency, or osteoporosis. *Gastroenterology, 128*, S52-S56.

Mustalahti, K., Lohiniemi, S., Collin, P., Vuolteenaho, N., Laippala, P., & Maki, M. (2002). Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Effective Clinical Practitioner, 5*(3), 105-113.

National Institutes of Health [NIH]. (2004, September 11). *National Institutes of Health Consensus Development Conference Statement: Celiac Disease*. Retrieved June 13, 2005 from http://consensus.hih.gov/cons/118/118cdc_intro.htm.

Norris, J., Barriaga, K., Klingensmith, G., Hoffman, M., Eisenbarth, G., Erlich, H., et al. (2003). Timing of cereal exposure in infancy and risk of silent autoimmunity: The Diabetes Autoimmunity Study in the Young (DAISY). *JAMA, 290*, 1713-1720.

Norris, J., Barriga, K., Hoffenberg, E., Taki, I., Miao, D., Haas, J., et al. (2005). Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA, 293*(19), 2343-51.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition [NASPGHN] (2004). *Guidelines for the diagnosis and treatment of Celiac Disease in children*. Retrieved June 14, 2005, from http://www.naspghan.org/sub/celiac_disease.asp.

North Texas Gluten Intolerance Group [NTGIG]. (2005). *North Texas gluten intolerance support group*. Retrieved June 13, 2005, from http://www.northtexasgig.com.

Not, T., Tommasini, A., Tonini, G., Buratti, E., Pocecco, M., Torul, C., et al. (2001). Undiagnosed celiac disease and risk of autoimmune disorders in subjects with Type 1 diabetes mellitus. *Diabetologia, 44*, 151-155.

Patwari, A.K., Anand, V.K., Kapur, G., & Narayan, S. (2003). Clinical and nutritional profile of children with celiac disease. *Indian Pediatrics, 40*, 337-342.

Patwari, A.K., Kapur, G., Satyanarayana, L., Anand, V.K., Jain, A., Gangil, A., et al. (2005). Catch-up growth in children with late-diagnosed celiac disease. *British Journal of Nutrition, 94*, 437-442.

Piccoli, A., Capelli, P., Castagnini, A., Cipolli, M., Contreas G., Ulmi, D., et al. (2002). Latent celiac disease in subjects with serum anti-endomysial antibodies and normal intestinal biopsy. *La Pediatria Medica e Chirurgica, 24*(5), 358-362.

Pietzak, M.M. (2005). Follow-up of patients with celiac disease: Achieving compliance with treatment. *Gastroenterology, 128*, S135-S141.

Pietzak, M.M., & Thomas, D.W. (2003). Childhood malabsorption. *Pediatrics in Review, 24*(6), 195-204.

Poddar, U., Thapa, B.R., & Singh, K. (2006). Clinical features of celiac disease in Indian children: Are they different from the West? *Journal of Pediatric Gastroenterology Nutrition, 43*, 313-317.

Poitra, B., Marion, S., Dionne, M., Wilkie, E., Dauphinais, P., Wilkie-Pepion, M., et al. (2003). A school-based screening program for fetal alcohol syndrome. *Neurotoxicology and Teratology, 25*, 725-729.

Pynnönen, P.A., Isometsä, E.T., Aronen, E.T., Verkasalo, M.A., Savilahti, E., & Aalberg, V.A. (2004). Mental disorders in adolescents with celiac disease. *Psychosomatics, 45*(4), 325-335.

Queiroz, M.S., Nerry, M., Cancado, E.L., Gianella-Neto, D., & Liberman, B. (2004). *Brazilian Journal of Medical Biology Research, 37*, 55-60.

Rampertab, S., Pooran, N., Brar, P., Singh, P., & Green, P. (2006). Trends in the presentation of celiac disease. *American Journal of Medicine, 119*(4), 9-14.

Rashid, M., Cranney, A., Zarkadas, M., Graham, I.D., Switzer, C., Case, S., et al. (2005). Celiac disease: Evaluation of the diagnosis and dietary compliance in Canadian children. *Pediatrics, 116*(6), 754-759.

Ravikumara, M., Tuthill, D.P., & Jenkins, H.R. (2006). The changing clinical presentation of celiac disease. *Archives of Disease in Childhood, [Epub ahead of print].*

Redline, S., Larkin, E., Kercsmar, C., Berger, M., & Siminoff, L. (2003). Development and validation of school-based asthma and allergy screening instruments for parents and students. *Annual Allergy Asthma Immunology, 90*(5), 461-463.

Reeves, G.E., Squance, M.L., Duggan, A.E., Murugasu, R.R., Wilson, R.J., Wong, R.C., et al. (2006). Diagnostic accuracy of celiac serological tests: A prospective study. *European Journal Gastroenterology Hepatology, 18*(5), 493-501.

Ress, K., Harro, M., Maaroos, H.I., Harro, J., Uibo, R., & Uibo, O. (2006). High prevalence of celiac disease: Need for increasing awareness among physicians. *Digestive Liver Disease, [Epub ahead of print].*

Rewers, M. (2005). Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease? *Gastroenterology, 128*, S47-S51.

Reunala, T. (2001). Dermatitis herpetiformis. *Clinical Dermatology, 19*, 728-36.

Rostom, A., Dube, C., Cranney, A., Saloojee, N., Sy, R., Garritty, C., et al. (2004).Celiac disease: summary, evidence report/technology assessment. *Agency for Healthcare Research and Quality Publication,* 290, 02-0021.

Salur, L., Uibo, O., Talvik, I., Justus, I., Metskula, T., Talvik, T., et al. (2000). The high frequency of celiac disease among children with neurological disorders. *European Journal of Neurology, 7*, 707-711.

Salvati, V., MacDonald, T., Vecchio Blanco, G., Mazzarella, G., Monteleone, I., Vavassori, P., et al. (2003). Enhanced expression of interferon regulatory factor-1 in the mucosa of children with celiac disease. *Pediatric Research, 54*, 312-318.

Sanders, D., Patel, D., Stephenson, T., Ward, A., McCloskey, E., Hadjivassiliou, M., et al. (2003). A primary care cross-sectional study of undiagnosed adult celiac disease. *European Journal of Gastroenterol Hepatology, 15*(4), 407-413.

Sapsford, R., Jupp, V. (1998). *Data Collection and Analysis*. Thousand Oaks, California: Sage Publications.

Shamir, R., Hernell, O., Leshno, M. (2006). Cost-effectiveness analysis of screening for celiac disease in the adult population. Medical Decision Making, 26, 282-293.

Shamir, R., Lerner, A, Shinar, E., Lahat, N., Sobel, E., Bar-or, R., et al. (2002). The use of a single serological market underestimates the prevalence of celiac disease in Israel: a study of blood donors. *American Journal Gastroenterology, 97*(10), 2589-2594.

Southlake, Texas (2004). *Southlake, Texas- fast facts 2004*. Department of Economic Development, City of Southlake, Texas.

Spiegel, B., Derosa, V., Grainek, M., Wang, V., & Dulai, G. (2004). Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: A cost-effectiveness analysis. *Gastronenterolgy, 126*, 1721-1732.

Statistics Solutions, Inc. (2006). *Factor Analysis*. Clearwater, Florida: Statistics Solutions, Inc. Retrieved November 14, 2006, from http://www.statisticssolutions.com/factor-analysis.htm.

Stenson, W.F., Newberry, R., Lorenz, R., Baldus, C., & Civitelli, R. (2005). Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. *Archives of Internal Medicine*, *165*, 393-399.

Sumnik, Z., Kolouskova, S., Malcova, H., Vavrinec, J., Venhacova, J., Lebl, J., et al. (2005). High prevalence of celiac disease in siblings of children with type 1 diabetes. *European Journal of Pediatrics, 164*, 9-12.

Tommasini, A., Not, T., Kiren, V., Baldas, V., Santon, D., Trevisiol, C., et al. (2004). Mass screening for celiac disease using antihuman transglutaminase antibody assay. *Archives of Disease in Childhood, 89*, 512-515.

Trevisiol, C., Ventura, A., Baldas, V., Tommasini, A., Santon, D., Martelossi, S., et al. (2002). A reliable screening procedure for celiac disease in clinical practice. *Scandinavian Journal of Gastroenterology, 37*(6), 679-684.

Vazquez, H., Smecuol, E., Flores, D., Mazure, R., Pedreira, S., Niveloni, S., et al (2001). Relationship between cigarette smoking and celiac disease: Evidence from a case-control study. *American Journal of Gastroenterology, 96*(3), 798-80.

Viljamaa, M., Collin, P., Huhtala, H., Sievanen, H., Maki, M., & Kaukinen, K. (2005). Is celiac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance. *Ailment Pharmacol Therapy, 22*(4), 317-324.

Wang L., Burstein, G., & Cohen, D. (2002). An economic evaluation of a school-based sexually transmitted disease screening program. *Sexually Transmitted Diseases, 29*(12), 737-45.

Wheeler, L., Boss, L., & Williams, P. (2004). School-based approaches to identifying students with asthma. *Journal of School Health, 74*(9).

Zelnik, N., Pacht, A., Obeid, R., & Lerner, A. (2004). Range of neurological disorders in patients with celiac disease. *Pediatrics, 113*(6), 1672-1676.

APPENDIX A

North Tarrant Gluten Intolerant Group Parental Informational Cover Letter

NTGIG PARENT INFORMATIONAL COVER LETTER

Dear NTGIG Parent,

Many of you know me as a NTGIG member and the gluten-free cooking instructor for Market Street but, I am also a PhD candidate in the Department of Health Studies at Texas Woman's University in Denton, Texas. My dissertation research is to pilot test a celiac disease screening tool that identifies children at high risk for celiac disease, which can be administered at the public school level by the school nurse. The goal of the study is to increase awareness of celiac disease at the public school level which in turn will increase the rate of early detection of the disease.

I am requesting your participation which will involve completing a two page questionnaire about the health of your child *prior to being diagnosed with celiac disease*. If you have been diagnosed with celiac disease and can remember symptoms, conditions, and the age you experienced them as a child, please complete an additional questionnaire. You will be asked to complete only the questionnaire for your child twice, once now and again in 30 days. Your total time commitment is estimated to be 30 minutes, 15 minutes each time. Your participation in this study is voluntary. If you choose not to participate or to withdraw from the study at any time, there will be no penalty. The results of the research study may be published, but your name will not be used.

If you choose to participate, I will need you to do the following:

1. Read and sign the attached consent form. Write your initials at the bottom of page 1; and sign your name and the date on the signature line, page 2.
2. Read and answer all the questions on the questionnaire. If you are answering a questionnaire about yourself, use *your age as a child when you experienced any symptoms and conditions*.
3. Return the completed questionnaire and consent form in the self-addressed stamped envelope.

If you have any questions concerning the research study, please call me at 817-416-8460 or email me at foodphilosopher@verizon.net.

Sincerely,

Claudia Pillow

APPENDIX B

Parent/Guardian Questionnaire for Child with Diagnosed Celiac Disease

PARENT/GUARDIAN QUESTIONNAIRE FOR CHILD WITH DIAGNOSED CELIAC DISEASE

Child's Age____ Grade_____ Sex _____
Student's Race: ____ African American ____Asian American ____Hispanic ____White ____ Other

Please tell us how often your child had any of the following prior to being diagnosed with celiac disease by circling the best answer.
Did your child have ....

1. Abdominal pain, gas or bloating?
   Never Seldom Frequent A Lot Don't Know

2. Diarrhea, constipation, vomiting or nausea?
   Never Seldom Frequent A Lot Don't Know

3. Allergies or asthma?
   Never Seldom Frequent A Lot Don't Know

4. Short stature, growth delay, or weight loss?
   Never Seldom Frequent A Lot Don't Know

5. Fatigue, weakness, anemia or other nutrient deficiencies?
   Never Seldom Frequent A Lot Don't Know

6. Unexplained mood swings, depression, anxiety or stress?
   Never Seldom Frequent A Lot Don't Know

7. Unexplained headaches, joint aches or body aches?
   Never Seldom Frequent A Lot Don't Know

8. Dental enamel defects (vertical or horizontal grooves in permanent teeth that are chalky white) or recurring canker sores in mouth?
   Never Seldom Frequent A Lot Don't Know

9. Skin rashes such as eczema, psoriasis, or dermatitis herpetiformis (itchy, blistering skin)
   Never Seldom Frequent A Lot Don't Know

10. Any autoimmune syndrome such as IgA deficiency or autoimmune thyroiditis
No Yes Don't Know

---

11. Type I diabetes
No Yes Don't Know

---

12. Down's syndrome, Turner's syndrome, or William's syndrome
No Yes Don't Know

---

13. Autism, hyperactivity, learning disabilities or attention deficit disorder
No Yes Don't Know

---

14. A first degree relative with diagnosed celiac disease
No Yes Don't Know

---

15. Higher than normal absenteeism due to sickness (more than 15 days)
No Yes Don't Know

Has your child been biopsy diagnosed with Celiac Disease? ___ Yes ___ No

---

Thank you for your time.

Code #_____ (please leave blank)

APPENDIX C

Texas Woman's University Case Consent to Participate in Research Form

TEXAS WOMAN'S UNIVERSITY Case
CONSENT TO PARTICIPATE IN RESEARCH

Title: A Pilot Study: Celiac Disease Screening of High Risk Students in Southlake, Texas.

Investigator: Claudia Pillow.....817/XXX-XXX.....foodphilosopher.com
Advisor: Jody Terrell, Ph.D.....940/898-2844.....jterrell@mail.twu.edu

Explanation and Purpose of the Research

You are being asked to participate in a research study for Claudia Pillow's dissertation at Texas Woman's University. The purpose of this research is to test the reliability and validity of a screening tool that identifies high risk children for celiac disease, which can be administered at the public school level. In the United States, celiac disease is a chronic pediatric condition affecting one in every 100 children and one in 22 for those associated with risk factors. Ninety-seven percent of the cases remain undiagnosed and untreated. This study will attempt to increase the awareness of celiac disease at the public school level which in turn will increase the rate of early detection of the disease. Early detection in childhood results not only in a decrease in lifetime health costs and other diseases associated with celiac disease but, an increase in the quality of life for the child.

Research Procedures

For this study, the investigator will survey parents of children with diagnosed celiac disease. The two page questionnaire attached in this package will ask 15 questions about the health of your child prior to being diagnosed with celiac disease. Your total time commitment in the study is estimated to be 30 minutes (15 minutes to answer the questionnaire the first time, and another 15 minutes to answer the questionnaire a second time in 30 days). The purpose of answering the questionnaire twice is to test the questionnaire's reliability.

Potential Risks

A potential risk related to your participation in this study is emotional discomfort regarding the survey questions. If you experience emotional discomfort while answering the questions you may stop answering any of the questions at any time.

_____
Parent/Guardian Initials

Another possible risk to you as a result of your participation in the study is release of confidential information. Confidentiality will be protected to the extent that is allowed by law. A code number, rather than your name, will be used on the questionnaire. Only the research team will have access to the completed questionnaires. The questionnaires will be stored in a locked filing cabinet in the investigator's office. The questionnaires will be shredded within 5 years. It is anticipated that the results of this study will be published in the investigator's dissertation as well as in other research publications. However, no names or other identifying information will be included in any publication.

To prevent coercion of volunteers, there are no negative repercussions or positive monetary incentives for participating.

The research team will try to prevent any problem that could happen because of this research. You should let the research team know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research.

Participation and Benefits

Your involvement in this research is completely voluntary, and you may discontinue your participation in the study at any time without penalty. The only direct benefit of this study to you is that at the completion of the study a summary of the results will be mailed to you upon request.*

Questions Regarding the Study

If you have any questions about the research study you may ask the research team; their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3378 or via e-mail at IRB@twu.edu. Please keep a copy of this signed and dated consent form to keep.

_____ _____

Signature of Parent/Guardian Date

***If you would like to receive a summary of the results of this study, please provide an address to which the summary should be sent:**

_____

_____

APPENDIX D

Test-Retest Informational Cover Letter

TEST-RETEST INFORMATIONAL COVER LETTER

Title: A Pilot Study: Celiac Disease Screening of High Risk Students in Southlake, Texas

Investigator: Claudia Pillow.....817/XXX-XXX.....foodphilosopher.com
Advisor: Jody Terrell, Ph.D.....940/898-2844.....jterrell@mail.twu.edu

Dear NTGIG Parent,

Thank you for completing the first questionnaire that was sent a month ago. I have enclosed some of the preliminary findings from the first round. As part of the **retest** of the pilot study for the screening tool that identifies children at high risk for celiac disease, the identical questionnaire is enclosed along with a self-addressed stamped envelope.

I am requesting your participation which will involve completing the two page questionnaire (about the health of your child *prior to being diagnosed with celiac disease),* for a second time. Your total time commitment is estimated to be 15 minutes. If you choose not to participate or to withdraw from the study at any time, there will be no penalty. The results of the research study may be published, but your name will not be used.

If you choose to participate, I will need you to do the following:
4. Read and answer all the questions on the questionnaire.
5. Return the completed questionnaire in the self-addressed stamped envelope.

If you have any questions about the research study you may ask the research team; their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3378 or via e-mail at IRB@twu.edu.

Sincerely,

Claudia Pillow

APPENDIX E

Southlake Parent Informational Cover Letter

SOUTHLAKE PARENT INFORMATIONAL COVER LETTER

Dear Parent,

I am a CISD parent and Ph.D. candidate in the Department of Health Studies at Texas Woman's University in Denton, Texas. ***I am conducting a research study to test a screening tool that identifies children at high risk for celiac disease, which can be administered at the public school level by the school nurse***. I am requesting you and your child's participation in this study.

Celiac disease is the most under diagnosed, chronic pediatric disease in the U. S. affecting one in 100 children and one in 22 for those associated with risk factors. The disease is a genetic intolerance to gluten, a protein found in wheat, rye, and barley. When a person with celiac disease eats these foods, gluten triggers the immune system to attack the lining of the small intestine. The reaction causes inflammation and interferes with the digestion of vitamins, minerals and other vital nutrients. Left untreated, the disease can cause malnutrition, diabetes, cancer or autoimmune deficiency disorders. Research has shown that timely diagnosis of celiac disease is essential to treating or preventing its complications. The goal of the study is to increase awareness of celiac disease at the public school level which in turn will increase the rate of early detection of the disease.

Your participation will involve answering the attached two page questionnaire about the health of your child. You will be asked to sign this consent form and return it with the completed questionnaire in the SASE. Your total time commitment is 10 minutes. Your participation in this study is voluntary. If you choose not to participate, you may withdraw from the study at any time, and there will be no penalty. The results of the research study may be published, but your name will not be used.

If you do choose to participate, I will need you to do the following:

1. Read and sign the attached consent form. Write your initials at the bottom of page 1 and sign your name and date on the signature line on page 2.
2. Read and answer all the questions on the questionnaire.
3. Return the completed questionnaire and consent form in the self-addressed stamped envelope.

If you have any questions concerning the research study, please call me at 817-416-8460 or email me at foodphilosopher@verizon.net.

Sincerely,

Claudia Pillow

APPENDIX F

Parent/Guardian Questionnaire for Celiac Disease Screening

PARENT/GUARDIAN QUESTIONNAIRE FOR CELIAC DISEASE SCREENING

Code #_____(leave blank) Age____ Grade_____ Sex _____
Student's Race: African American ____ Asian American ____ Hispanic ____White ____Other ____

Please tell us how often your child has any of the following by circling the best answer. Does your child have ....

1. Abdominal pain, gas or bloating?
   Never Seldom Frequent A Lot Don't Know

2. Diarrhea, constipation, vomiting or nausea?
   Never Seldom Frequent A Lot Don't Know

3. Allergies or asthma?
   Never Seldom Frequent A Lot Don't Know

4. Short stature, growth delay, or weight loss?
   Never Seldom Frequent A Lot Don't Know

5. Fatigue, weakness, anemia or other nutrient deficiencies?
   Never Seldom Frequent A Lot Don't Know

6. Unexplained mood swings, depression, anxiety or stress?
   Never Seldom Frequent A Lot Don't Know

7. Unexplained headaches, joint aches or body aches?
   Never Seldom Frequent A Lot Don't Know

8. Dental enamel defects (vertical or horizontal grooves in permanent teeth that are chalky white) or recurring canker sores in mouth?
   Never Seldom Frequent A Lot Don't Know

9. Skin rashes such as eczema, psoriasis, or dermatitis herpetiformis (itchy, blistering skin)
   Never Seldom Frequent A Lot Don't Know

10. Any autoimmune syndrome such as IgA deficiency or autoimmune thyroiditis
    No Yes Don't Know

11. Type I diabetes

No Yes Don't Know

---

12. Down's syndrome, Turner's syndrome, or William's syndrome

No Yes Don't Know

---

13. Autism, hyperactivity, learning disabilities or attention deficit disorder

No Yes Don't Know

---

14. A first degree relative with diagnosed celiac disease

No Yes Don't Know

---

15. Higher than normal absenteeism due to sickness (more than 15 days)

No Yes Don't Know

Has your child been diagnosed with Celiac Disease? ___ Yes ___ No

If so by which test: _____blood _____ biopsy _____ both blood & biopsy

---

Thank you for your time.

APPENDIX G

Texas Woman's University Control Consent to Participate in Research Form

TEXAS WOMAN'S UNIVERSITY Control
CONSENT TO PARTICIPATE IN RESEARCH

Title: A Pilot Study: Celiac Disease Screening of High Risk Students in Southlake, Texas.

Investigator: Claudia Pillow.....817/XXX-XXX.....foodphilosopher.com
Advisor: Jody Terrell, Ph.D.....940/898-2844.....jterrell@mail.twu.edu

Explanation and Purpose of the Research

You are being asked to participate in a research study for Claudia Pillow's dissertation at Texas Woman's University. The purpose of this research is to test the reliability and validity of a screening tool that identifies high risk children for celiac disease, which can be administered at the public school level. In the United States, celiac disease is a chronic pediatric condition affecting one in every 100 children and one in 22 for those associated with risk factors. Ninety-seven percent of the cases remain undiagnosed and untreated. This study will attempt to increase the awareness of celiac disease at the public school level which in turn will increase the rate of early detection of the disease. Early detection in childhood results not only in a decrease in lifetime health costs and other diseases associated with celiac disease but, an increase in the quality of life for the child.

Research Procedures

For this study, the investigator will survey parents of children being tested for celiac disease. The two page questionnaire attached in this package will ask 15 questions about the health of your child. You will be asked to complete the questionnaire, sign the consent form, and mail both in the self addressed stamped envelope. Your total time commitment in the study is estimated to be 10 minutes.

Potential Risks

A potential risk related to your participation in this study is emotional discomfort regarding the survey questions. If you experience emotional discomfort while answering the questions you may stop answering any of the questions at any time.

_____
Parent/Guardian Initials

Another possible risk to you as a result of your participation in the study is release of confidential information. Confidentiality will be protected to the extent that is allowed by law. A code number, rather than your name, will be used on the questionnaire. Only the research team will have access to the completed questionnaires. The questionnaires and test results will be stored in a locked filing cabinet in the investigator's office. The questionnaires and test results will be shredded within 5 years. It is anticipated that the results of this study will be published in the investigator's dissertation as well as in other research publications. However, no names or other identifying information will be included in any publication.

To prevent coercion of volunteers, there are no negative repercussions or positive monetary incentives for participating.

The research team will try to prevent any problem that could happen because of this research. You should let the research team know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research.

Participation and Benefits

Your involvement in this research is completely voluntary, and you may discontinue your participation in the study at any time without penalty. The only direct benefit of this study to you is that at the completion of the study a summary of the results will be mailed to you upon request.*

Questions Regarding the Study

If you have any questions about the research study you may ask the research team; their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3378 or via e-mail at IRB@twu.edu. Please keep a copy of this signed and dated consent form to keep.

_____ _____

Signature of Parent/Guardian Date

Mailing Address: _____

***If you would like to receive a summary of the results of this study, please provide an address to which the summary should be sent, if different from above:**

_____

_____

APPENDIX H

NC-2 Parent Informational Cover Letter

NC-2 PARENT INFORMATIONAL COVER LETTER

Dear Friends,

As many of you know, I am a Ph.D. candidate in the Department of Health Studies at Texas Woman's University in Denton, Texas. ***I am conducting a research study to test a screening tool that identifies children at high risk for celiac disease, which can be administered at the public school level by the school nurse***. I am requesting your participation in this study.

Celiac disease is the most under diagnosed, chronic pediatric disease in the U. S. affecting one in 100 children and one in 22 for those associated with risk factors. The disease is a genetic intolerance to gluten, a protein found in wheat, rye, and barley. When a person with celiac disease eats these foods, gluten triggers the immune system to attack the lining of the small intestine. The reaction causes inflammation and interferes with the digestion of vitamins, minerals and other vital nutrients. Left untreated, the disease can cause malnutrition, diabetes, cancer or autoimmune deficiency disorders. Research has shown that timely diagnosis of celiac disease is essential to treating or preventing its complications. The goal of the study is to increase awareness of celiac disease at the public school level which in turn will increase the rate of early detection of the disease.

Your participation will only involve the following: reading and signing the enclosed consent form, answering the attached two page questionnaire about the health of your child, and then returning both in the self addressed envelope. If you have more than one child, please complete a questionnaire for each. Your total time commitment is estimated to be 10 minutes. Your participation in this study is voluntary. If you choose not to participate, you may withdraw from the study at any time, and there will be no penalty. The results of the research study may be published, but your name will not be used.

If you do choose to participate, I will need you to do the following:

1. Read and sign the attached consent form. Write your initials at the bottom of page 1 and sign your name and date on the signature line on page 2.
2. Read and answer all the questions on the questionnaire.
3. Return the completed questionnaire and consent form in the self-addressed stamped envelope.

If you have any questions concerning the research study, please call me at 817-416-8460 or email me at foodphilosopher@verizon.net. Thank you for your time and interest.

Sincerely,

Claudia Pillow

APPENDIX I

Questionnaire Scoring Methods and Categories

QUESTIONNAIRE SCORING METHOD & CATEGORIES

Child's Age____ Grade_____ Sex _____
Student's Race: African American ____ Asian American ____ Hispanic ____ White ____ other ____

Scoring: Never=1; Seldom= 2; Frequent=3; A Lot=4; Don't Know=0;
No=1; Yes=2

1. Abdominal pain, gas or bloating? STOMACH
   Never Seldom Frequent A Lot Don't Know

2. Diarrhea, constipation, vomiting or nausea? INTESTINAL
   Never Seldom Frequent A Lot Don't Know

3. Allergies or asthma? ALLERGIES
   Never Seldom Frequent A Lot Don't Know

4. Short stature, growth delay, or weight loss? GROWTH
   Never Seldom Frequent A Lot Don't Know

5. Fatigue, weakness, anemia or other nutrient deficiencies? ANEMIA
   Never Seldom Frequent A Lot Don't Know

6. Unexplained mood swings, depression, anxiety or stress? MENTAL
   Never Seldom Frequent A Lot Don't Know

7. Unexplained headaches, joint aches or body aches? ACHES
   Never Seldom Frequent A Lot Don't Know

8. Dental enamel defects (vertical or horizontal grooves in permanent teeth that are chalky white) or recurring canker sores in mouth? MOUTH
   Never Seldom Frequent A Lot Don't Know

9. Skin rashes such as eczema, psoriasis, or dermatitis herpetiformis (itchy, blistering skin) SKIN
   Never Seldom Frequent A Lot Don't Know

10. Any autoimmune syndrome such as IgA deficiency or autoimmune thyroiditis AUTOIMMUNE

No Yes Don't Know

---

11. Type I diabetes DIABETES

No Yes Don't Know

---

12. Down's syndrome, Turner's syndrome, or William's syndrome SYNDROME

No Yes Don't Know

---

13. Autism, hyperactivity, learning disabilities or attention deficit disorder COGNITIVE

No Yes Don't Know

---

14. A first degree relative with diagnosed celiac disease RELATIVE

No Yes Don't Know

---

15. Higher than normal absenteeism due to sickness (more than 15 days) ABSENTEEISM

No Yes Don't Know

Has your child been biopsy diagnosed with Celiac Disease? ___ Yes ___ No
CELIAC

Thank you for your time.

Code #_____ (please leave blank)

APPENDIX J

Amended Parent/Guardian Questionnaire for Celiac Disease Screening

AMENDED PARENT/GUARDIAN QUESTIONNAIRE FOR CELIAC DISEASE SCREENING

Child's Name: _____

Age: _____ Grade: _____ Sex: _____ Student Ethnicity: _____

Does your child have diagnosed celiac disease: No_____ Yes _____

Please tell us how often your child has any of the following by circling the best answer. Does your child have ...?

Score:

16. Abdominal pain, gas or bloating?
Never Seldom Frequent A Lot Don't Know

17. Diarrhea, constipation, vomiting or nausea?
Never Seldom Frequent A Lot Don't Know

18. Allergies or asthma?
Never Seldom Frequent A Lot Don't Know

19. Short stature, growth delay, or weight loss?
Never Seldom Frequent A Lot Don't Know

20. Fatigue, weakness, anemia or other nutrient deficiencies?
Never Seldom Frequent A Lot Don't Know

21. Unexplained mood swings, depression, anxiety or stress?
Never Seldom Frequent A Lot Don't Know

22. Unexplained headaches, joint aches or body aches?
Never Seldom Frequent A Lot Don't Know

23. Dental enamel defects (vertical or horizontal grooves in permanent teeth that are chalky white) or recurring canker sores in mouth?
Never Seldom Frequent A Lot Don't Know

24. Skin rashes such as eczema, psoriasis, or dermatitis herpetiformis (itchy, blistering skin)
Never Seldom Frequent A Lot Don't Know

Page 1 Score and comments (school use only):

25. Any autoimmune syndrome such as IgA deficiency or autoimmune thyroiditis
No Yes Don't Know

---

26. Type I diabetes
No Yes Don't Know

---

27. Down's syndrome, Turner's syndrome, or William's syndrome
No Yes Don't Know

---

28. Autism, hyperactivity, learning disabilities or attention deficit disorder
No Yes Don't Know

---

29. A first degree relative with diagnosed celiac disease
No Yes Don't Know

---

30. Higher than normal absenteeism due to sickness (more than 15 days)
No Yes Don't Know

Page 2 Score and comments (school use only):

Any other comments, concerns, or information you would like to share?

Thank you for your time.

_____ _____

Parent/Guardian signature date

Page 1 Score (school use only):
Page 2 Score (school use only):

Total Score (Page 1 + 2):

APPENDIX K

Sample of Celiac Disease Screening Program Parent Consent Form

SAMPLE OF CELIAC DISEASE SCREENING PROGRAM
PARENT CONSENT FORM

Why screen for Celiac Disease?

The purpose of this screening program is to identify children at high risk for celiac disease, which is a genetic intolerance to gluten, a protein found in wheat, rye, and barley. When a person with celiac disease eats these foods, gluten triggers the immune system to attack the lining of the small intestine. The reaction causes inflammation and interferes with the digestion of vitamins, minerals and other vital nutrients. Left untreated, the disease can cause malnutrition, diabetes, cancer or autoimmune deficiency disorders. Research has shown that timely diagnosis of celiac disease is essential to treating or preventing its complications. In the United States, celiac disease is a chronic pediatric condition affecting one in every 100 children and one in 22 for those associated with risk factors. Ninety-seven percent of the cases remain undiagnosed and untreated. This screening program will increase the awareness of celiac disease at the school level which in turn will increase the rate of early detection of the disease. Early detection in childhood results not only in a decrease in lifetime health costs and other diseases associated with celiac disease but, an increase in the quality of life for the child.

How does the program work?
You will be asked to complete a five minute questionnaire about the general health of your child. Your involvement is completely voluntary. If the questionnaire results reveal your child to be at high risk for celiac disease, you will be notified by (Program Contact) by phone or in person.

Does the program recommend treatment?
No, the celiac disease screening program only refers children identified at high risk for the disease to their family physician, or the program staff can recommend a local and knowledgeable health care professional for further medical evaluation and testing.

How accurate is the screening questionnaire?
Research has concluded that the questionnaire is 87% effective in identifying children at high risk for celiac disease. However, the questionnaire results are not a medical diagnosis and the screening program does not replace a comprehensive exam by a trained physician.

Are the screening results confidential?
The questionnaire results will be kept confidential and the screening results will not be kept with your child's academic records. Teachers will not be involved in the screening procedure.

_____ _____
Parent/Legal Guardian Initials Date

(SCHOOL) provides this screening at no cost, but does not provide further evaluation or treatment services. It is up to you to decide if you want to obtain additional services for your child. If you do decide to participate and complete the questionnaire, we request your support in the evaluation follow-up phone call of your child's results.

If you have any questions about the program, please contact (Program Staff) at (Contact Information).

I have read and understand the description of the Celiac Disease Screening Program offered at (SCHOOL) on (DATE).

_____ I want to participate in the Celiac Disease Screening Program

_____ I do not want to participate in the Celiac Disease Screening Program

Parent/Legal Guardian's Name (Print):_____

Student's Name (Print): _____Grade:____

Parent/Legal Guardian's Address (Print):_____

_____

Home Telephone #:_____ Cell Phone #:_____

E-mail Address: _____

_____ _____

Signature of Parent/Guardian Date

APPENDIX L

Sample Draft of Celiac Disease Screening Program Professional Cover Letter

SAMPLE DRAFT OF CELIAC DISEASE SCREENING PROGRAM
PROFESSIONAL COVER LETTER

Dear School Health Service Provider:

Celiac disease is the most under diagnosed, chronic pediatric disease in the U. S. affecting one in 100 children and one in 22 for those associated with risk factors. The disease is a genetic intolerance to gluten, a protein found in wheat, rye, and barley. When a person with celiac disease eats these foods, gluten triggers the immune system to attack the lining of the small intestine. The reaction causes inflammation and interferes with the digestion of vitamins, minerals and other vital nutrients. Left untreated, the disease can cause malnutrition, diabetes, cancer or autoimmune deficiency disorders. Research has shown that timely diagnosis of celiac disease is essential to treating or preventing its complications. The goal of this celiac disease screening program is to increase awareness of celiac disease at the public school level by screening students at high-risk for the disease, which in turn will increase the rate of early detection of the disease.

The screening tool is a two page health related questionnaire that is to be completed by a child's parent or guardian. The parent's total time is expected to be less than five minutes and is completely voluntary. Your scoring time is expected to be less than two minutes.

Research has shown that the most common childhood symptoms in undiagnosed celiac disease are a combination of **persistent diarrhea and failure to thrive**. *Of special concern are boys with short stature and girls with recurring canker sores.* Other common symptoms and conditions to be noted include **anemia and skin rashes**. Research has shown that when a child presents with the following two combinations of symptoms, they are at an increased risk for celiac disease:

1. anemia or fatigue with unexplained mood swings, depression, anxiety or stress;
2. anemia or fatigue with short stature;
3. abdominal gas or bloating with diarrhea or constipation; and
4. older children with unexplained headaches, joint aches, or body aches.

In addition, there appears to be subsets of health symptoms that when present together, increase a child's risk for celiac disease:

1. older girls with unexplained body aches, and canker sores;
2. young children with gastrointestinal pain, allergies or asthma, and above normal absenteeism;
3. children with anemia or fatigue, unexplained mood swings, depression, anxiety or stress, and skin rashes;
4. boys with allergies or asthma, and cognitive learning problems.

The celiac disease screening program has five steps:

1. **"Active Case Finding".** School health providers employ active case detection and individual case finding based on the above combinations of health symptoms and conditions. It is recommended that when a child presents to health services with any of the above combinations of health symptoms and conditions they be considered for screening.

2. **"Case Screening".** The parent/guardian of the suspected case is asked to complete a parental consent form and the five minute questionnaire about the general health of their child as it relates to the common symptoms and conditions of celiac disease. Participation is completely voluntary. The parents/guardians have a choice not to participate. Questionnaire results are kept confidential and the screening results will not be kept in the child's academic records.

3. **"Case Referral".** The school health provider scores the questionnaire. If the child *scores 25 or above*, the parent/guardian is notified by phone call or in person, and referred to their family physician for further evaluation and testing. If the family does not have a physician, the school health provider provides the family with a referral to a local and knowledgeable health care professional.

Scoring: Never=1; Seldom= 2; Frequent=3; A Lot=4; Don't Know=0; No=1; Yes=2

4. **"Case Follow-Up"**. The school health providers follow-up the referral with a phone call or meeting with the parent/guardian and record the results of the referral, including outcomes of any diagnostic tests and compliance rates to a gluten-free diet. The school health providers note if evaluation and treatment for positively diagnosed children are consistent and current with North American Society of Pediatric Gastroenterology, Hepatology and Nutrition recommendations.

5. **"Program Evaluation"**. The school health providers evaluate the screening program at the end of every semester.

North American Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines for the diagnosis and treatment of celiac disease in children can be retrieved from http://www.naspghan.org/sub/celiac_disease.asp.

Information about local chapters of the Gluten Intolerance Group, a national celiac disease support group, can be retrieved at http://www.gluten.net.

General information can be retrieved from Columbia University Celiac Disease Center's website at http://www.celiacdiseasecenter.org.

For more celiac disease information, including current research, diagnosis, treatment, gluten-free diet guidelines, local and knowledgeable health care professionals and support group contacts, please go to http://www.foodphilosopher.com.