CELIAC DISEASE RISK ESTIMATION AND DECISION-MAKING

EXPERT SYSTEM

by
Robert Pastore

A Dissertation Submitted
In partial fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Biomedical Informatics

Department of Health Informatics
Rutgers, the State University of New Jersey
School of Health Professions

March 2018
Final Dissertation Defense Approval Form

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ABSTRACT

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Background: Celiac disease is a genetic autoimmune disease affecting people of all ages that results in small intestine enteropathy and is caused by the permanent intolerance to gliadin and glutenin, two proteins found in gluten containing grains. Celiac disease is considered to be a clinical chameleon. The disease can also be asymptomatic. Average prevalence of celiac disease in the population is one out of 100 people with data indicating the risk may be as high as 22% for those with first-degree relatives that have the disease. Research suggests 83% of people with celiac disease may be undiagnosed and the average duration for diagnosis is 10 years. Data indicates there is a lack of consensus regarding methodology used to diagnose celiac disease and poor knowledge of associated diseases and symptomatology. A review of the literature determined a celiac disease risk estimation and decision-making expert system including signs, symptomatology, manifestations and associations, with serology and histology based on the Mayo Clinic algorithm, using Exsys Corvid Software, did not currently exist.

Method: A new clinical decision support system (CDSS) was developed using Exsys Corvid for expert analysis. The CDSS was divided into symptoms and manifestations with 80 points of navigation, and a serology section, and was validated by 13 experts in the field of celiac disease using a 10 statement, 5-point Likert scale.
**Results:** This scale was analyzed using Cronbach’s alpha reliability coefficient, which was calculated using SPSS. Cronbach’s alpha revealed good internal consistency and reliability with a result of 0.813. One-hundred percent of the experts agreed with the system and that the CDSS is capable of guiding a healthcare professional through the diagnostic process, contains an accurate list of symptoms based on the clinical literature, can foster improved awareness and education about celiac disease, and that there is a need for this system. Over 90% agreed the system is a good tool for training medical students or residents.

**Conclusion:** A celiac disease risk estimation and decision-making expert system was successfully developed and evaluated by medical professionals, with 100% agreeing that this CDSS is medically accurate and can guide healthcare professionals through the diagnostic process.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my dissertation supervisor Dr. Shankar Srinivasan for lending his brilliance and creative insight to my research. Special thanks to my dissertation committee members, Dr. Antonina Mitrofanova for providing an incredible education and sparking my interest in CDSS and artificial intelligence; Dr. Fredrick Coffman for believing in me since my first semester and also providing a phenomenal educational experience; Dr. Joseph Murray, an exceptional researcher and my academic hero who had me interested in celiac disease research early on in my career. I am forever in your debt.
DEDICATION

For Shauna and Elle – all because of you, I am. With undying love, Robert.
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Celiac disease is a genetic autoimmune disease affecting people of all ages that results in small intestine enteropathy.\textsuperscript{1-3} It is caused by the permanent intolerance to gliadin and glutenin, two proteins found in gluten (figure 1), and found in gluten containing grains.\textsuperscript{1-3} The most common gluten containing grains are barley, rye, wheat, spelt, triticale, einkorn, faro and kamut.\textsuperscript{4} Gliadin is considered the most toxic component of gluten for those with celiac disease.\textsuperscript{4} Thompson and colleagues identified broad-spectrum contamination of oats, which is normally gluten free, with gluten from processing wheat.\textsuperscript{5}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The structure of gluten.\textsuperscript{6} Copyright 2011, The American Physiological Society.}
\end{figure}

Glutenin forms a fibrous mesh that traps gliadin peptides forming the gluten structure. On the right of figure 1 is an electron micrographic view of the structural relationship of gliadin and glutenin.\textsuperscript{6}
Celiac disease is considered to be clinically challenging as it can mimic many other diseases and conditions, eluding doctors and patients. The disease can be asymptomatic, presenting with abnormal serology and nutritional deficiencies of unknown etiology.

1.1 History of Celiac Disease

Aretaeus Cappadocia, a first century Greek physician wrote of the “Coeliac Affection”, naming the condition koiliakos which is derived from koelia, the Greek word for abdomen. Aretaeus wrote "If the stomach be irretentive of the food and if it pass through undigested and crude, and nothing ascends into the body, we call such persons koeliacs." An early 19th century a physician named Mathew Baillie wrote of his observations of a chronic diarrheal disorder that caused malnutrition in a patient, but was mitigated by prescribing an almost exclusive rice diet. In 1888, English physician Samuel Gee lectured to medical students on the “celiac affection” describing cases of treatment based completely on diet modification. In 1924, a physician named Sidney Haas spoke of his success treating eight pediatric cases of celiac disease with what he called a banana diet, which eliminated all grains and potatoes. Six children went into remission and two not following the diet died. Willem Dicke, a Dutch pediatrician, strongly believed wheat was the culprit behind celiac disease, and completed his doctoral dissertation on how eliminating wheat, rye and oat from the diet led to improvement in celiac patients. The catalyst for Dicke’s hypothesis was observing children become symptom free with the lack of bread in the Netherlands during World War II, and the subsequent severe recurrence of symptoms coinciding after Allied planes dropped bread into the area.
In the 1950s the first biopsies were performed using an apparatus that reached the distal duodenum. In 1955, Samman was the first to associate a relationship between celiac disease and dermatitis herpetiformis. In the 1960s there was a common understanding that grain starch and eventually gluten was the cause of celiac disease and an identifiable mucosal lesion would develop which could be measured by taking a biopsy of the small intestines. In 1964, Berger discovered the appearance of antigliadin antibodies in the blood of celiac patients. In 1965, Shuster and Marks established the connection between dermatitis herpetiformis and celiac disease, confirming Samman’s suggestion 10 years earlier. In 1971, Seah and colleagues discovered autoantibodies in the serum of celiac disease patients in the form of anti-reticulins.

In the early to mid 1980s research started to appear linking this gluten induced disease with other diseases including Down syndrome and type 1 diabetes. In the late 1980s diagnostic criteria was adopted by the medical community that positive serology and biopsy could identify 95% of celiac disease cases. After the 1990s celiac disease received medical community acceptance as an autoimmune disease with a genetic manifestation and involvement of the HLA-DQ2 or DQ8 alleles. Tissue transglutaminase antibodies became the standard of serology assessment, while intestinal biopsy became the definitive procedure for diagnosis.

1.2 A Clinical Chameleon

Celiac disease encompasses many different diseases, leaving signs to alert practitioners to start the diagnostic process. The Canadian Dental Association released a clinical diagnosis guide for dentists based on the oral manifestations of celiac disease, which include chronic dental carries, weak enamel and aphthous stomatitis, in an effort to
screen patients for further testing. The American Journal of Clinical Dermatology published a guide for dermatologists to enhance the recognition of cutaneous manifestations of celiac disease, with dermatitis herpetiformis being the primary sign. Turco and colleagues noted an increase in anxiety and depression in children with celiac disease and functional intestinal disorders.

Due to the fact that celiac disease can present as a clinical chameleon, alter the microbiome, is implicated in other autoimmune diseases, and can present with signs and symptoms that will most likely be seen by many different specialists in health care, a focus on obtaining an accurate diagnosis is key. If all these specialists are linked together in a health care information system, the sharing of data via an electronic health record may create an environment for a more accurate and prompt diagnosis, and improved continuity of care. There is a clear need for a celiac disease risk estimation and decision-making expert system that should be widely available to health care professionals, to foster education on the disease and allow users to be more equipped to identify and navigate at risk patients through the diagnostic process. Since a diagnosis may be a health care team effort, research into a celiac disease risk estimation and decision-making expert system based on natural language experienced in a health care environment, and a navigation portal for serology and histology, and how that may enhance obtaining an accurate diagnosis, is an area of study currently not addressed in the clinical literature. This void must be filled. The final outcome of the celiac disease risk estimation and decision-making expert system is to advise the end user according to the entered data to:

1. Identify patients at risk for celiac disease via symptomatology and serology.
2. Navigate the medical student/health care professional through the process of ordering the correct serology to move toward an accurate diagnosis.

3. Foster improved awareness and education about celiac disease based on identification of symptomatology and correct serology based on clinical data.

4. Fortify the correct decision to order a biopsy when warranted.

1.3 Objectives and Goals of the Study

1. To design and develop a new clinical decision support system (CDSS) built upon evidence-based knowledge that acts as a training tool as well as a robust system for the clinical environment. A main goal for this CDSS is that it takes into account the need for an educational model, combining accurate language of signs, symptomatology and other associated diseases, that would be part of an EHR and the advances in celiac disease testing with the serology and histology component based on the accepted and thorough Mayo Clinic celiac disease testing algorithm.

2. To make sure the CDSS is user friendly and easily accessible: As the literature review will thoroughly explain, a large percent of patients with celiac disease will never receive a diagnosis, therefore, in order to remove any impediment to access this CDSS, a key goal is for it to not require special software to run and to operate in a standard web browser.

1.4 Hypotheses

1. Is it possible to design and develop a new CDSS built upon evidence-based knowledge that can act as a teaching tool to help increase clinician knowledge to identify at risk patients for celiac disease?
2. Can this CDSS also be used by the clinical professional to obtain an accurate diagnosis?
CHAPTER 2

REVIEW OF RELATED LITERATURE

2.1 Celiac Disease is Underdiagnosed

Of critical importance are the patients that are missing an accurate diagnosis, how to quickly identify them and make the proper diagnosis. Using National Health and Nutrition Examination Survey (NHANES) 2009–2010, which included 7,798 people, Rubio-Tapia and colleagues elucidate that 83% of people with celiac disease may be undiagnosed.\(^{17}\) This is in accord with Maki and colleagues in their examination of prevalence among children in Finland.\(^{18}\)

Celiac disease seems to be a perfect example of medicine based upon data as many different biomarkers can lead to a single diagnosis, based on the individual’s antibody response, and or genetic carrier status. It is also important to apply the principles of health informatics and identify if there is an additional societal prevalence that has been missing and leading to missing diagnosis. Regarding socioeconomic status, Roy and colleagues carried out a retrospective cohort study using biopsy confirmed celiac disease patients from The Celiac Center at Beth Israel Deaconess Medical Center in Boston, Massachusetts. They examined 872 cases and divided the subjects into two categories: the presentation of diarrhea and any gastrointestinal symptoms at the time of diagnosis, and the absence of such symptoms, which included anemia and osteoporosis. Socioeconomic estimations were provided by GeoLystics, Inc. of East Brunswick, New Jersey.\(^{19}\) The data revealed that lower socioeconomic status subjects presenting with non-classical celiac disease symptoms are typically undiagnosed.\(^{19}\) It is possible that lack of
access to health care or reduced interest in seeking medical care in this demographic could be responsible for this outcome.\textsuperscript{19}

Though the American College of Gastroenterology (ACG) released the most recent clinical guidelines for the diagnosis and management of celiac disease in 2013, there is concern over practitioner understanding and adherence.\textsuperscript{20} There is a potential explanation why there are still so many undiagnosed celiac disease patients. McCormick, Sultan and Charabaty discovered that there is a lack of consensus regarding methodology used to diagnose celiac disease and which associated diseases should be followed up on, including known nutritional deficiencies.\textsuperscript{21} McCormick and colleagues sent a survey based on the ACG guidelines to 450 health care providers in the United States.\textsuperscript{21} Eighty responded and their specialties were divided into 37\% primary care physicians, 23\% gastroenterologists, and 36\% doctors of osteopathy, nurse practitioners and obstetricians with 49\% practicing for more than five years.\textsuperscript{21} Sixty-five percent of responders stated they learned about celiac disease in medical school, 72\% stated their knowledge was from residency or postgraduate training, and 29\% from continuing medical education.\textsuperscript{21} The survey results indicated only 63\% order serology when they strongly suspect celiac disease.\textsuperscript{21} Only 19\% order both serology and endoscopy, which is a major cause for concern as intestinal biopsy is the gold standard for a clinical diagnosis.\textsuperscript{20} Mills and Murray after an exhaustive review of the improvements in accuracy of serological testing in 2016 are confident that duodenal biopsy will remain the gold standard.\textsuperscript{22} Fifteen percent of the survey participants will refer to a gastroenterologist for a full examination and nine percent refer directly to a nutritionist to start a gluten free diet.\textsuperscript{21} Post diagnosis, only 58\% of responders test B12, 52\% check thyroid stimulating hormone (TSH), 37\%
measure bone mineral density via a dual energy X-ray absorptiometry (DEXA) scan, and <25% test vitamin K status.\textsuperscript{21} With regard to the questioning on how a health care provider should follow up upon diagnosis of celiac disease, nine percent of responders did not believe it was necessary to start a gluten free diet.\textsuperscript{21} Clearly there is a lack of consensus on how to diagnose and treat celiac disease and a need to create consensus.

Similar to the discovery of McCormick and colleagues, Zipser and colleagues used a survey to measure physician understanding of celiac disease in Southern California, cross-referenced with 2,440 celiac disease patients obtained from the database of The Celiac Disease Foundation, a patient support group.\textsuperscript{23} The researchers received 132 primary care physician responses to the survey and the results indicated only 32% were aware that the disease can present with symptoms in adulthood.\textsuperscript{23} Moreover, only 44% of responders understood that endomysial antibody analysis could assist in obtaining a diagnosis.\textsuperscript{23} Responders were also not fully aware of the fact that abdominal pain, myalgias, fatigue, seizure disorder, unexplained infertility, lymphoma and symptoms akin to irritable bowel syndrome (IBS) are associated with celiac disease.\textsuperscript{23} Due to the selection of health care providers in Southern California, these data should not be extrapolated to the rest of the population, but is nonetheless important as it adds to potential reasons for undiagnosed celiac disease.

In Riyadh, Saudi Arabia, Assiri and colleagues examined physician knowledge of celiac disease using a cross-sectional survey.\textsuperscript{24} Of the 123 surveys given to physicians in primary care, secondary care, and tertiary care, as well as private hospitals, 109 were completed, with 86% from public hospitals and 13.7% from private health care institutions.\textsuperscript{24} Sixty-four of respondents were male (58.7%) and 45 female (41.2%).\textsuperscript{24}
The survey consisted of 25 true or false questions specific to the clinical presentation of celiac disease. Results were classified as poor if less than 40% correct, fair if 40 to 60% correct and good if greater than 60% correct. Based on this grading system of the 109 physician respondents, 19.2% scored as having poor knowledge. Of this demographic, 33% percent were senior physicians. As Assiri, McCormick and Zipser and colleagues agree, health care personnel commonly delay the diagnosis of celiac disease due to a poor understanding of the symptom complex and poor understanding of the path to accurate diagnosis. Rubio-Tapia and colleagues who authored the most recent clinical guidelines for diagnosis and management of celiac disease state even with current educational efforts, celiac disease is highly underdiagnosed.

According to the first global estimates of celiac disease and associated mortality, 2.2 million children under the age of five had undiagnosed celiac disease in 2010. Predicted death rate from undiagnosed celiac disease in the pediatric population is estimated to be 42,000 annually, with Africa and Asia having the highest population in that figure. In 2016, Rubio-Tapia and colleagues analyzed males aged 50 or older that have been diagnosed with elevated tissue transglutaminase IgA using NHANES III data and identified an increased mortality compared to controls (average 72 years vs. 74 years). Unfortunately, many individuals with celiac are undiagnosed or misdiagnosed with other conditions.

Examining how economics is impacted by obtaining an accurate diagnosis, Long and colleagues revealed a total savings of $1,764 the year after celiac disease diagnosis, in a study that examined direct medical costs of 133 pre and post celiac disease patients.
over a 1-year period, against 153 controls in Olmsted County, Minnesota.\textsuperscript{28} Economics will likely differ by location and requires further study.

Research has shown that celiac disease is not just a disease that only causes small intestine enteropathy, rather it is a systemic autoimmune disease that may damage any organ.\textsuperscript{2,7,8} Therefore, it is essential to obtain a timely and accurate diagnosis.

Underdiagnosis of celiac disease increases mortality and is negatively impacted by socioeconomic status.\textsuperscript{19,20} To fully comprehend the apparent disconnect of health care practitioners, resulting in widespread underdiagnosis, it is important to understand the complexities of celiac disease including the prevalence, genetics, pathophysiology, various biomarkers used in serology, diagnostic procedures, symptomatology, and associated diagnoses and autoimmunity. Once understood it becomes clear a celiac disease risk estimation and decision-making expert system can help put these complex pieces together, optimize diagnosis and reduce the rate of misdiagnosed or undiagnosed celiac disease.

\textbf{2.2 Prevalence}

Average prevalence of celiac disease in the population is one out of 100 people.\textsuperscript{7} Having a first degree relative with the disease increases the odds to 1:10, or 10\.\textsuperscript{20} Moreover, some data indicates the risk may be higher for those with first-degree relatives, as high as 22\.\textsuperscript{27,29,30} To put this into perspective, the prevalence of type 1 diabetes is 1:500 and the prevalence of inflammatory bowel disease is 1:1000.\textsuperscript{7} Epidemiological data suggests the average age of diagnosis is 50 years old, with a female predominance.\textsuperscript{29-34} Shah and Leffler discovered that 60\% to 70\% of those diagnosed with celiac disease are women.\textsuperscript{34} Cabre and colleagues note that prevalence could be higher
with more accurate diagnosis as many individuals with celiac disease are never formally
diagnosed as they are asymptomatic.\textsuperscript{35}

\subsection*{2.3 Genetics}

The manifestation of celiac disease relies on the interplay between genes and
environment (gluten).\textsuperscript{6} The human leukocyte antigen system alleles (HLA) are highly
specific toward self and non-self immune system recognition and the HLA-DQ cell
surface receptor is highly specific for antigen production in celiac disease.\textsuperscript{36} Green and
Cellier state that 95\% of celiac disease patients are positive for HLA-DQ2 (DQA1*05
and DQB1*02) or HLA-DQ8 (DQA1*03 and DQB1*0302) allele.\textsuperscript{7} Testing for these
alleles is important in screening relatives of those with celiac disease for further
biomarker analysis, and to assist in making a diagnosis of those already on a gluten free
diet where no official diagnosis has been made.\textsuperscript{7} Celiac disease seems to be more
common in individuals that are HLA-DQ2 positive than HLA-DQ8 positive counterparts,
though this population makes up the remaining cases.\textsuperscript{37}

HLA testing can be a valuable tool in practice as testing is not influenced by a
gluten free diet, which is not the case with the blood biomarker tissue transglutaminase
IgA.\textsuperscript{38} Figure 2 depicts a simplified path to inclusion or exclusion of further analysis for a
potential celiac disease patient, enhancing clinical decisions in practice.
In 2016, Sharma and colleagues published data of a 15-year follow up study of 8,676 children in Sweden. Genotype analyses were completed on 6,010 children using Illumina ImmunoChip. Fifty-four single-nucleotide polymorphisms (SNPs) were associated with five genes (TAGAP, IL18R1, RGS21, PLEK, and CCR9) with 13 non-HLA regions in celiac disease.

While Sharma and colleagues have made significant advancements in non-HLA associations to celiac disease with their identification of 54 SNPs on five new genetic areas, they agree these should be considered candidate SNPs as further confirmation studies must be completed to rule out any false positives. An additional interesting thought of the Sharma study that relates to the striving for precision medicine, is the fact that the genes identified in the pediatric population can be distinctive from those in celiac disease diagnosis in adulthood. Furthermore, there are two factors that require critical examination. First, the children used in the Sharma study were at an elevated risk for celiac HLA markers. Therefore, this data may not transfer to the general population.
discovered SNPs dataset\textsuperscript{39} which reinforces the need to verify these data and eliminate any false positives.

2.4 Pathophysiology

A graphic depiction of the steps to villous atrophy can be seen in figure 3.\textsuperscript{7} When a patient with celiac disease consumes gluten, it enters the submucosa in the duodenum resulting in a production of autoantibodies to tissue transglutaminase prior to the disassociation of tissue transglutaminase from the gluten molecule.\textsuperscript{7} This changes the charge and form of the gluten molecule, promoting an autoimmune attack and fostering the binding of gluten to HLA-DQ2 and DQ8 receptors.\textsuperscript{7} Proinflammatory cytokines including interferon-gamma are secreted into the location, along with a lymphocyte presence and gliadin specific CD 4+T cells, resulting in atrophy of the duodenal villi and microvilli.\textsuperscript{7}
A spectrum of pathological abnormalities may be present in the celiac disease patient such as intraepithelial lymphosis without or with associated glandular hyperplasia and possibly completely normal villous architecture. This state can present asymptomatically or with peculiar symptoms, confusing the patient and physician.

### 2.5 Celiac Disease Diagnosis

The celiac disease patient generally develops antibodies to gliadin and tissue transglutaminase. Since a selective IgA deficiency has a rate of occurrence 10 to 15
times more frequent in celiac disease patients than their non-celiac counterparts, it is wise for physicians to measure total serum IgA first, because that should dictate the correct testing course of action.\textsuperscript{41} Since celiac disease can present with a total IgA insufficiency, the patient will not produce the antibody response that alerts the practitioner to take action and request an intestinal biopsy.\textsuperscript{2,7,20}

For example, if a selective IgA deficiency is present, a different path of testing should be followed, including tissue transglutaminase IgG, and gliadin deaminated antibody IgG.\textsuperscript{2,20,41} In the absence of a selective IgA deficiency but in the case where the individual is below age reference values, tissue transglutaminase IgA and gliadin deaminated antibodies IgG and IgA should be measured.\textsuperscript{41} If total IgA is normal, testing should start with tissue transglutaminase IgA.\textsuperscript{41} A tissue transglutaminase IgA antibody result of 4 to 10 U/mL should result in further testing including deaminated gliadin peptide (DGP) or gliadin deaminated antibody (DAGL) and endomysial antibodies IgA.\textsuperscript{2,20,41} In addition, HLA-DQ2/DQ8 may be required biomarkers toward an accurate diagnosis.\textsuperscript{20,38} Abnormal results should lead to a biopsy.\textsuperscript{20,41}

### 2.6 Biomarkers Sensitivity and Specificity

Table 1 depicts the sensitivity and specificity along with the confidence intervals of common serologic tests used to help diagnose celiac disease.\textsuperscript{41-43}

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA EMA-ME, Adult</td>
<td>0.974</td>
<td>0.957-0.985</td>
<td>0.996</td>
<td>0.988-0.999</td>
</tr>
<tr>
<td>IgA EMA-ME, Child</td>
<td>0.961</td>
<td>0.945-0.973</td>
<td>0.974</td>
<td>0.963-0.982</td>
</tr>
<tr>
<td>IgA EMA-HU, Adult</td>
<td>0.902</td>
<td>0.863–0.925</td>
<td>0.996</td>
<td>0.984–0.999</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Heterogeneity</td>
<td>Test Name</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>IgA EMA HU, Child</td>
<td>0.969</td>
<td>0.935–0.986</td>
<td>0.99</td>
<td>H</td>
</tr>
<tr>
<td>IgA tTGA-GP, Adult</td>
<td>0.90</td>
<td>H</td>
<td>0.953</td>
<td>0.925–0.981</td>
</tr>
<tr>
<td>IgA tTGA-GP, Child</td>
<td>0.931</td>
<td>0.888–0.959</td>
<td>0.963</td>
<td>0.931–0.980</td>
</tr>
<tr>
<td>IgA tTGA-HR, Adult*</td>
<td>0.951</td>
<td>0.918–0.981</td>
<td>0.983</td>
<td>0.971–0.996</td>
</tr>
<tr>
<td>IgA tTGA-HR, Child*</td>
<td>0.957</td>
<td>0.903–0.981</td>
<td>0.990</td>
<td>0.946–0.998</td>
</tr>
<tr>
<td>a-DGP IgA, Child</td>
<td>0.874</td>
<td>0.79-0.92</td>
<td>0.972</td>
<td>0.92-0.99</td>
</tr>
<tr>
<td>a-DGP IgA, Adult</td>
<td>0.983</td>
<td>0.91-0.997</td>
<td>0.938</td>
<td>0.862-0.979</td>
</tr>
<tr>
<td>a-DGP IgG, Adult</td>
<td>0.967</td>
<td>0.884-0.995</td>
<td>100.0</td>
<td>0.955-100.0</td>
</tr>
</tbody>
</table>

Table 1: Sensitivity and specificity of common biomarkers in celiac disease.\(^{41-43}\)

Table 1\(^{41-43}\) H\(^{a}\) - Heterogeneity in analysis; ME – monkey esophagus; HU – human umbilical cord; GP – guinea pig liver; HR – human recombinant or red blood cell derived tTG; EMA - Endomysial Antibodies; tTGA – tissue transglutaminase; DGP – deamminated gliadin peptide. *Denotes most commercial tests for IgA tTGA.

The gold standard for diagnosing celiac disease is four to six biopsy samples of the duodenum to search for villous morphology.\(^{2,4,39,20,22}\) Biopsy samples are graded by Marsh categories.\(^{2}\) In Marsh stage 0 we see normal mucosa.\(^{2}\) At stage 1 there is an increased number of intra-epithelial lymphocytes and mucosal inflammation.\(^{2}\) Stage 2 presents with proliferation of the crypts of Lieberkuhn.\(^{2}\) Marsh stage 3 a-c presents with partial to complete villous atrophy.\(^{2}\)
Figure 4 to the left is an endoscopy image of the duodenum of a celiac disease patient, clearly depicting scalloped folds and a cracked appearance to the mucosa, while the figure on the bottom left depicts a normal duodenum of a non-celiac patient.  

Figure 4: Duodenum of celiac and non-celiac patient.


Ludvigsson and colleagues state patients with positive serology but normal mucosa remain at an increased risk for developing celiac disease later in life, and should be monitored. Halblaub and colleagues discovered that in patients with normal serology but with elevated fecal and salivary antigliadin IgA antibodies, can have celiac disease confirmed with a biopsy. However, such tests are not recommended as a method to diagnose celiac disease as they lack consistent evidentiary validation.

2.7 Nutritional Deficiencies

Since celiac disease primarily affects the duodenum, it can be considered a disease that attacks the nutrient absorption areas of the small intestine. Nutrients
typically deficient in celiac disease include vitamins A, D, E, K, folic acid, B6, B12, calcium, copper, magnesium, zinc, selenium and iron.\cite{7,47}

### 2.8 Symptomatology and Clinical Manifestations

Considered a clinical chameleon, table 2 below reveals the diverse set of classic and non-classic symptoms and manifestations for celiac disease derived from the work of Rampertab and colleagues, Green and colleagues, Henri-Bhargava and colleagues, Rubio-Tapia and colleagues, Ciacci and colleagues, Al-Bawardy and colleagues, Bai and colleagues, as well as the National Institutes of Health for the adult population and Ludvigsson and colleagues and Walker-Smith for the pediatric population\cite{3,7,47-53}

Table 2: Classic and Non-Classic Symptomatology\cite{3,7,47-53-53}

<table>
<thead>
<tr>
<th><strong>Classic Symptoms and Manifestations</strong></th>
<th><strong>Non-Classic Symptoms and Manifestations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain (particularly post prandial)</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Bloating/Gas</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Aphthous Ulcers/Stomatitis</td>
</tr>
<tr>
<td>Dermatitis Herpetiformis</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Down’s and Turner’s Syndrome</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Edema (hypoproteinemia)</td>
<td>Cognitive Impairment</td>
</tr>
<tr>
<td>Fatigue/Lethargy</td>
<td></td>
</tr>
<tr>
<td>Iron Deficiency Anemia</td>
<td>Constipation</td>
</tr>
<tr>
<td>Severe Itchy Rash</td>
<td>Delayed Onset of Puberty / Delayed Menarche</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>Dental Defects/Enamel Defects</td>
</tr>
<tr>
<td>Weight Loss, unexplained</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Fertility Problems (male and female)</td>
</tr>
<tr>
<td></td>
<td>Headaches</td>
</tr>
<tr>
<td><strong>Pediatric Presentation (&gt;2 and &lt;15)</strong></td>
<td>Heartburn/GERD</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>Hyposplenia</td>
</tr>
<tr>
<td>Personality Disorders</td>
<td>Irritability</td>
</tr>
<tr>
<td>Short Stature</td>
<td>Lactose Intolerance</td>
</tr>
<tr>
<td>Thin Extremities</td>
<td>LFT Elevations</td>
</tr>
<tr>
<td><strong>Pediatric Population &lt;2</strong></td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Nutritional Deficiencies (B12, Folate, Zinc, Vitamins A, D, E, K, etc.)</td>
<td></td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Osteopenia/Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Hemosiderosis</td>
</tr>
<tr>
<td></td>
<td>Seizure Disorders</td>
</tr>
<tr>
<td></td>
<td>Thyroid Disorders</td>
</tr>
<tr>
<td></td>
<td>Refractory Vitamin D Deficiency</td>
</tr>
<tr>
<td></td>
<td>Urinary Stone Disease</td>
</tr>
</tbody>
</table>

Employing all these sources provides a comprehensive list for symptomatology. Creating an amalgam of all of these lists of terms, categorized for the adult and pediatric population, and turned into an algorithm as the starting point of a CDSS is the ideal precursor to serology and histology toward diagnosis.

### 2.9 Environmental factors

The timing of the introduction of gluten in the infant diet has been associated with the onset of celiac disease in children at an increased risk for the disease.\(^5\) For these increased risk children, gluten consumption before the fourth month presents a large increased risk and consumption prior to the seventh month a marginal increased risk.\(^4\) In 2016, Szajewska and colleagues concluded the risk of celiac disease occurring due to gluten consumption requires carrying the minimum of one risk alleles.\(^5\) According to epidemiological studies, breastfeeding may have a protective effect because it can delay the introduction to gluten, may offer a type of oral tolerance because a small amount of gluten appears in breast milk, and may reduce the risk of gastrointestinal infection, which
can increase intestinal permeability. Gastrointestinal infections such as rotavirus and candida albicans can initiate the development of celiac disease.

2.10 Treatment

The current treatment for celiac disease is the adoption of a life long gluten free diet. All dietary gluten containing substances must be avoided, this not only includes barley, rye, wheat, einkorn, farro, spelt, triticale, kamut, semolina, durum flour and contaminated oats, but also all hidden sources of dietary gluten. Seemingly innocuous terms such as hydrolyzed plant protein, and textured vegetable protein, are actually another method of listing wheat on a food label. Prescription medication may use gluten as a binder or filler. It is critical that the prescribing clinician is aware of such risk and communicates with the pharmacist or compounds any medication that may normally contain gluten in order to avoid consumption by the celiac patient. Further, nutritional supplements may contain gluten, so it is imperative to always check with the manufacturer.

In 2010, Thompson and colleagues had twenty-two gluten free grains and seeds sent to a lab for gluten analysis. Seven of the products were contaminated with gluten. These products were considered gluten free by default because they are naturally gluten free and therefore were not labeled gluten free. Products studied included millet flour, millet grain, buckwheat, soy, brown rice, amaranth and flaxseed. These are gluten free foods by nature, but obviously gluten contamination occurred via processing. Strict gluten free labeling and testing is required to assure a product is gluten free.

Pharmaceutical research spawned the development of Larazotide Acetate, a potential zonulin inhibitor that has been studied in over 500 celiac disease subjects geared
to offer reduced inflammation cell signaling, improving symptoms.\textsuperscript{62-64} Trials have not been very successful at this time as a sole treatment for celiac disease other than a strict gluten free diet.\textsuperscript{20,61,62}

\textbf{2.11 Zonulin and Intestinal Barrier Function}

The balance of immunity to non-self antigens is dependent upon the tight junctions of the intestinal epithelial barrier, which, like a conductor, directs the orchestra of the gut-associated lymphoid tissue and the neuroendocrine network of the intestines.\textsuperscript{6} The only physiological modulator that regulates the tolerance and immune response balance by controlling the flux of macromolecules across the intestinal barrier is the protein zonulin.\textsuperscript{6}

Fasano discovered that small intestine exposure to gliadin is a powerful trigger of zonulin release.\textsuperscript{6} While Drago and colleagues noted zonulin release by enteric bacterial infection of the small intestine, gliadin remains the most powerful zonulin stimulant.\textsuperscript{65} Lammers and colleagues have shown that the chemokine receptor CXCR3, which has an increased expression in celiac disease patients, co-localizes with gliadin, recruiting the adaptor protein MyD88, resulting in zonulin release and consequent separation of the tight junctions of intestinal cells.\textsuperscript{66} This is critical information as impaired tight junctions of small intestinal cells with a subsequent increase in permeability is associated with numerous disease states.\textsuperscript{41,67-69} In various autoimmune diseases such as multiple sclerosis, type 1 diabetes and rheumatoid arthritis, what is shared with celiac disease is a breach of the tight junctions of the small intestine cells that allows antigens to pass through the intestinal lumen, provoking an immunological reaction that can then impact any organ, tissue or gland.\textsuperscript{69,70} Zonulin is over expressed in tissues of individuals with autoimmune
diseases.\textsuperscript{5}

Fasano and colleagues have shown that within minutes of gliadin exposure, human intestinal cells secrete large amounts of zonulin.\textsuperscript{6}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{zonulin.png}
\caption{Zonulin After Gluten Exposure.\textsuperscript{6} Copyright 2011, The American Physiological Society.}
\end{figure}

Figure 5 to the left depicts zonulin appearance within minutes after gliadin exposure to a human intestinal epithelial cell.\textsuperscript{6} The nucleus is in blue, cytoskeleton in red and zonulin in green.\textsuperscript{6}

\section*{2.12 The Celiac and Obesity Connection and Subsequent Relation to Autoimmunity}

According to the CDC, 70.7\% of the US adult population age 20 years and over are overweight or obese.\textsuperscript{71} In a study of 369 adult celiac disease patients where 32\% were overweight or obese, Cheng and colleagues observed 54\% of overweight and 47\% of obese lost weight on a gluten free diet.\textsuperscript{72} According to Venkatasubramani and colleagues, children with celiac disease may be overweight, and the stigma associated with celiac disease patients as being thin, may influence the path of diagnosis.\textsuperscript{73} Research discovered that celiac disease must be considered in obese children and once identified, a gluten free diet may improve body mass index (BMI).\textsuperscript{72,73} Children that were underweight gained weight and those that were obese or overweight lost weight.\textsuperscript{72,73}
This is not new information. Back in 1999 Murray published that the presence of obesity did not discount the possibility of celiac disease. Back in 1999 Murray published that the presence of obesity did not discount the possibility of celiac disease. In a screening at the department of gastroenterology at Altnagelvin Hospital, Londonderry, Northern Ireland, Dickey and Kearney examined the prevalence of overweight in patients with celiac disease, going back 10 years. They discovered that only a small number of patients were underweight when they were diagnosed, with the majority being overweight.

The individual with untreated celiac disease preferentially utilizes carbohydrates as a fuel source, most likely because of lipid malabsorption and a high carbohydrate diet. Untreated celiac patients have an increase in circulating ghrelin, which stimulates appetite, inducing overeating and these concentrations reduce after implementation of a gluten free diet.

One set of symptoms of hypothyroidism is weight gain and refractory obesity, and there seems to be a higher incidence of thyroid abnormalities in celiac disease. While these thyroid abnormalities may be autoimmune based due to celiac disease, another issue that decreases metabolism in hypothyroid patients is an error in beta-oxidation, which has been linked to insulin resistance and obesity. There is clinical evidence that celiac disease can result in such an organic acid abnormality, leading to sluggish fat metabolism and thus obesity. Celiac disease patients poorly absorb the nutrient carnitine, which plays an essential role in proper beta-oxidation. Serum carnitine levels typically increase when a celiac patient is put on a gluten free diet.

Lukens and colleagues have identified a cellular pathway connecting obesity to autoimmunity. In obesity, a highly regulated protein complex called the inflammasome triggers caspase-1 activation, which initiates the release of inflammatory interleukins IL-
This pro-inflammatory response is linked to the induction and pathogenesis of multiple autoimmune disorders including multiple sclerosis and type 1 diabetes, which are linked to zonulin activity via gluten exposure in the celiac patient. Additionally, Pontillo and colleagues identified the specific polymorphisms that stimulate inflammasome activity in the obese celiac patient which are NLRP1 haplotype in combination with rs35829419 major C allele.

2.13 Microbiota

There are over 1000 species of microbes of four main phyla (Bacteroidetes, Actinobacteria and Proteobacteria) in the human gastrointestinal (GI) tract, contributing over 3 million genes. Research has shown that the microbiota of celiac disease patients has increased bacteroides and enterobacteria (gram-negative bacteria) and reduced quantities of gram-positive species such as bifidobacteria. During the period of prediagnosis, the microbiota can be more dominant in Enterobacteriaceae, Staphylococcaceae, Klebsiella oxytoca, S. epidermidis, and S. pasteuri. The quantity of these species attenuate after adherence to a gluten free diet. Thus, celiac disease presents with an increased growth of unfavorable bacteria in the intestines and treatment with a gluten free diet has been shown to improve gastrointestinal microbiota. This is significant because the microbiota is important for systemic and local immunity, including the movement of T-cells, such as CD4+ T cells, and B-cells in mesenteric lymph nodes and Peyer’s patches. Cicerone and colleagues have shown an increased Th17 response to the change in microbiota and presence of gliadin in celiac disease patients which can increase pro-inflammatory interleukins (IL-17A and IL-22) and cytokines, playing a role in the cycle of the disease and symptomatology.
colleagues identified strains of Bifidobacterium (*B. longum* ES1 and *B. bifidum* ES2) that may suppress this proinflammatory response in celiac disease patients.\(^6\)

### 2.14 Autoimmune Comorbidities

Rodrigo and colleagues noted an increased prevalence of celiac disease in multiple sclerosis patients suggesting a rate of gluten intolerance 11 times higher than the general population.\(^6\) Mormile agrees with Rodrigo and recommends celiac disease patients be evaluated for multiple sclerosis and vice versa.\(^8\) Mormile states that celiac disease and multiple sclerosis may share osteopontin gene splice variants, acting as inducers toward a multiple sclerosis diagnosis in celiac disease patients.\(^8\)

Fasano has linked various neurological diseases such as multiple sclerosis to zonulin release in celiac disease patients.\(^6\) Chromosome 16 is the location of the zonulin gene.\(^6\) Fasano’s chart of comorbidities connects the diseases induced by gliadin stimulating zonulin and chromosome 16.\(^6\) Figure 6 below depicts a side-by-side comparison.\(^6\)

![Figure 6: Major diseases associated with zonulin](https://example.com/figure6.png) Copyright 2011, The American Physiological Society.
Asleh and colleagues have associated gliadin and the stimulation of zonulin to type 1 diabetes autoimmunity in human studies. Yachyshyn and colleagues discovered an increase in serum zonulin in multiple sclerosis patients. Celiac disease and the autoimmune thyroid diseases Grave’s disease, Hashimoto’s thyroiditis and idiopathic myxedema, share the DQ2 allele, which explains why there is a higher incidence of such endocrinopathies in celiac disease. Celiac disease has also been implicated in hypo and hyper primary and secondary parathyroidism. Heneghan and colleagues have found a 100-fold increase in Addison’s disease among celiac disease patients and suggest that Addison’s disease patients should be screened for celiac disease. The suspected connection is via the HLA-DQ8 allele. Zhernakova and colleagues have established a shared genetic basis between rheumatoid arthritis and celiac disease, with an overrepresentation of T-cell signaling. Fourteen loci were identified that are shared between celiac disease and rheumatoid arthritis, indicating an overlapping genetic basis for both diseases and implicating altered T-cell activation and differentiation as a similar stimulating matter of autoimmunity.

Using an autoimmune comorbidity model, we can see how consumption of gluten in the celiac patient can lead to a compromise of the intestinal tight junctions via zonulin release, with continued hyperpermeability from the presence of zonulin occludens toxin, resulting in circulating immune complexes, creating a secondary autoimmune presentation. If the celiac patient falls into the obese category, inflammasome activation continues this autoimmune cascade. Using pathology as an example, a celiac disease patient may present with a diagnosis of rheumatoid arthritis, multiple sclerosis, type 1 diabetes, anklyosing spondylitis, or another disease due to the circulating
autoimmune complexes that may infiltrate through the intestinal lumen. This creates a different viewpoint of the diagnosis of celiac disease. This is why a sequelae of celiac disease should be used as part of a diagnostic algorithm (Table 3). Those with celiac disease should be tested for other diseases and vice versa.

<table>
<thead>
<tr>
<th>Anemia with resistance to oral iron and iron deficiency anemia</th>
<th>Enamel defects</th>
<th>Relative with celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anklyosing spondylitis</td>
<td>Hypothyroidism and Hyperthyroidism</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Cancers – gliomas, breast, lung, lymphomas, ovarian, pancreatic</td>
<td>Infertility, recurrent miscarriage, Intrauterine growth restriction</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Multiple nutrient deficiencies</td>
<td>Thyroid disease – Hashimoto’s and Grave’s Disease</td>
</tr>
<tr>
<td>Early onset osteopenia or osteoporosis</td>
<td>Neurological issues: ataxia, CIDP, peripheral neuropathy, epilepsy, Multiple Sclerosis</td>
<td>Unexplained gastrointestinal symptoms</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>Refractory vitamin D deficiency</td>
<td>Weight loss or weight gain</td>
</tr>
</tbody>
</table>

Table 3: Sequelae of celiac disease: diagnostic algorithm.

In celiac disease, if a strict gluten free diet is followed, the villous architecture begins to normalize, as does the integrity of the tight junctions of the intestinal lumen. The cessation of gluten induces a decrease of zonulin levels with resultant normalization of intestinal barrier function and attenuation in autoantibody production.

**2.15 Clinical Decision Support Systems**

Clinical decision support systems (CDSS) are developed to assist in obtaining an accurate diagnosis and make more informed health care decisions for a patient.
population. Castaneda and colleagues believe CDSS enhance the accuracy of diagnoses, and state “properly equipped CDSS will significantly benefit patient care at all levels.”

Prior to 2011, a review of the literature reveals no significant study has been undertaken examining CDSS in celiac disease. In 2011, Tenório and colleagues developed a CDSS for celiac disease designed in three phases. In the first phase they developed a web-based system for acquiring and retrieving clinical data and was evaluated by attending physicians in the outpatient clinic of the department of pediatrics in Hospital São Paulo. In the second phase, with the data coded, a database of automated classifiers was set and tested using accurate parameters and was put into the web-based system. Thirty-five attributes of classic and non-classic symptoms were included, as well as notations for high-risk groups such as diagnosed first-degree relatives. In the final phase, the CDSS was evaluated. At the completion of study, using the Bayesian classifier: averaged one-dependence estimator, accuracy reached 80%, sensitivity 0.78 and specificity 0.80 with an AUC of 0.84. This study explicated that a CDSS could be beneficial in identifying positive from negative celiac disease diagnosis.

In 2013, Shirts and colleagues focused on illustrating a positive tissue transglutaminase IgA antibody and positive duodenal biopsy using a simple nearest neighbor algorithm. The concept of nearest neighbor algorithms in the Shirts and colleagues trial was to plot to predict all the subject’s tissue transglutaminase IgA results to predict biopsy results, using previous plotted negative and positive celiac disease patient data. These diagnostic measures define a separate dimension and are distributed in a multidimensional test space. Each value defines a point within this
multidimensional space.\(^9\) This data is evaluated and organized into the proximity of an unknown subject’s diagnostic point, which contains confirmed diagnostic subjects and controls.\(^9\) The data was derived from 3,207 patients from 17 hospitals or 70 participating clinics within Intermountain Healthcare in Utah from January 2008 to October 2011.\(^9\) Specifically, Shirts and colleagues “used counts of cases and controls in the near-neighbor space to calculate the binomial probability and confidence intervals that the unknown patient is a case.”\(^9\) Figure 7 is a graphical depiction of the near-neighbor method used in the trial.\(^9\)

![Figure 7: Near-neighbor method for biopsy predictions.](image)

Shirts and colleagues were able to make clinically relevant predictions that could assist clinical decision-making. Table 4 summarizes several predictions.
Table 4: Near-neighbor space predictive reports for positive and negative celiac diagnoses.

| Near-neighbor space surrounding a 14 year old patient with tTG IgA of 4 units encompasses 33 similar patients, 1 with positive biopsy. | Example report: tTG IgA – negative. 3% chance for positive biopsy (CI[0% to 16%]). |
| Near-neighbor space surrounding a 63-year old patient with a tTG IgA of 11 units encompasses 16 similar patients, 5 with positive biopsy. | Example report: tTG IgA negative. 31% chance for positive biopsy (CI[11% to 59%]). |
| Near-neighbor space surrounding a 23-year old with a tTG IgA of 130 units encompasses 13 similar patients, 12 with positive biopsy. | Example report: tTG IgA moderate to strong positive. 92% chance for positive biopsy (CI[62% to 100%]). |

Using a different focus than Shirts and colleagues, Ludvigsson and colleagues created a computerized algorithm to attempt to ascertain individuals that should be tested for celiac disease using a natural linguistic programming (NLP) algorithm at the Mayo clinic (Rochester, Minnesota USA). The team searched text and related terms in electronic medical records using 216 celiac patients and 280 controls. Text terms included “anorexia, hyperthyreosis/hypothyreosis, hyperthyroidism, Hashimoto, Down syndrome, malabsorption, abnormal weight loss, short stature, growth failure, failure to thrive, poor growth, frequent stools, watery stools, diabetes type 1/type 1 diabetic, small-bowel, irritable bowel syndrome (IBS), abdominal, autoimmune thyroid, diarrhea, low ferritin, microcytic, iron supplement, depression, and Fosamax.” While Ludvigsson and colleagues state they achieved sensitivity of 72.9% and a specificity of 89.9%, it is important to note they relied upon a closed tertiary center, the Mayo Clinic, and not in a common gastroenterology, or internal medicine environment. Further, Ludvigsson and colleagues state their algorithm “is not intended for individual physicians.” This can perpetuate a lack of understanding by the physician when they leave the Mayo clinic environment and enter another gastrointestinal practice environment. Further, physicians
seemingly cannot use the algorithm in an outside facility. What is the physician really learning if they do not understand the nuances of the disease? Said physicians can end up leaving the Mayo clinic, working in other gastrointestinal environments and miss numerous cases of celiac disease because they were not exposed to a proper training tool. In this study the chosen celiac disease subjects had an average age of 42 and the controls had an average age of 70 years. This completely ignores the pediatric segment at risk for celiac disease that present with different symptomatology that would not be picked up by the NLP algorithm used in this study. For example, in 2004 Ludvigsson and colleagues published findings on the signs and symptoms of celiac disease in a pediatric population that were part of an previous prospective cohort study that aimed to identify risk in the pediatric population of Sweden for immune system diseases, including celiac disease. The researchers agree with Walker-Smith and Murch that celiac disease presents with different symptoms in pediatric cases. Combining Walker-Smith, Murch and the findings of Ludvigsson and colleagues, dominant celiac disease symptoms in children >2 but <15 years of age include having short stature, thin extremities, fatigue, abdominal distension, delayed onset of puberty, personality disorders and anemia. Adding strength to these findings is the fact that the Ludvigsson study was a multicenter study from rural and city areas (academic and nonacademic). Moreover, the algorithm work by Ludvigsson and colleagues is not a complete CDSS and certainly cannot be used as an educational tool for healthcare professionals. Ideally, an amalgam of accepted common natural language terms, with clinical decision support for the proper path of a full serological and histological work up in the adult and pediatric population, would foster the complete celiac disease CDSS for educational and diagnostic purposes.
Regarding the near-neighbor study of Shirts and colleagues, and is a similar concern with the work of Ludvigsson and colleagues, is the difficulty for other health care institutions replicating the study, primarily for lack of size (as is the case for Shirts et al.) or outside the tertiary environment of the Mayo Clinic (as is the case for Ludvigsson et al.). Shirts and colleagues ignore symptomatology. Another issue is Shirts and colleagues suggestion that local data may be superior to a meta-analysis of peer-reviewed published data. Safran states sufficient quantity of local data on each subject including all celiac disease biomarkers can be deficient when compared with that of a well researched meta-analysis.

In the Tenório and colleagues research, attributes were based on a set of 35 signs and symptoms of celiac disease, which is greater than the Ludvigsson model, and akin to Ludvigsson, not based on serology and histology, which is an important component in celiac disease diagnosis, particularly in individuals that are sIgA deficient. Could patients have received a non-celiac disease diagnosis determined upon just the serology? In the presence of an sIgA deficiency, tissue transglutaminase IgA will be negative, but other paths of serology should be undertaken. Through retrospective data collection, Sweis and colleagues revealed that a small number of celiac disease patients could be misdiagnosed as being negative by solely relying on serology. Sweis and colleagues examined data on 3,056 patients at Medway Hospital, Kent, UK. Ten patients diagnosed on biopsy had negative tissue transglutaminase antibodies, 13 had negative IgA anti-gliadin antibodies and 12 had negative IgG anti-gliadin antibodies. When combining all negative serology to enhance sensitivity, five patients had completely negative serology and six with equivocal serology. If these results were extrapolated to
a larger population size, a larger undiagnosed patient population may be identified. Limitations include only focusing on very specific serology and missing key biomarkers from the Mayo Clinic celiac disease testing algorithm. In this algorithm tests are ordered only as needed, and positive or negative results can guide the physician through the test ordering process, leading to a diagnosis. This can reduce costs, focusing the test ordering process to only what is needed based on the specific results of the patient, and can expedite obtaining an accurate diagnosis.

A review of the literature determined a celiac disease risk estimation and decision-making expert system including symptomatology, similar diseases and resultant autoimmunity, with serology and histology based on the Mayo Clinic algorithm, using Exsys Corvid Software does not currently exist as the closest produced was an Exsys Corvid expert system designed specifically for irritable bowel syndrome, not celiac disease. Figure 8 below is the celiac disease test map used for the serology and histology component of the celiac disease risk estimation and decision-making expert system.
A CDSS that takes into account the need for an educational model, combining accurate language of signs, symptomatology and other associated diseases, that would be part of an EHR and the advances in celiac disease testing with the serology and histology component based on the accepted and thorough Mayo Clinic celiac disease testing algorithm, is the best option for a celiac disease risk estimation and decision-making expert system. Since the goal in modern health care education models is to identify, diagnose and treat diseases, a celiac disease risk estimation and decision-making expert system does not currently exist, is strongly needed, and would result in a prevention of misdiagnosis and underdiagnosis, all while enhancing the learning experience for future and current clinicians.
CHAPTER 3

METHODS

The CDSS was developed using the software Exsys Corvid version 6.1.0, which uses Java applets, allowing flexibility for the user, where it can be accessed from any location and any device that can connect to the Internet using a web browser. Exsys Corvid provides an automated experience that emulates interacting with a human expert in the fact that it directly delivers knowledge as opposed to information. A decision-making knowledge base is derived from variables and clinical outcomes input as rules. This results in a problem-solving tool at the expert level, educating users to perform at this clinical level, but also assists actual experts in arriving at an accurate diagnosis.

Key features of Exsys Corvid include a powerful inference engine to analyze rules and combine them to solve a problem. It has the ability to use both forward and backward chaining. Additionally, Exsys Corvid offers a confidence factor for using natural language. Data is entered as algebraic equations and answers to provide complete certainty with regard to symptomatology, serology and histology. The software has a confidence system that allows the creating of rules for symptoms that are the most accurate possibilities based on knowledge from clinical literature. A failsafe rule will be included to cover potential patients that may be asymptomatic at the time of assessment or have latent celiac disease, where a patient presents with no symptoms or has very minor symptoms, yet, their serology is positive for the disease. With the rate of underdiagnosis, this inclusion seems critical and having a confidence system within the inference engine makes this possible.
IF AND THEN data are the hierarchy of rules programmed into the CDSS using Exsys Corvid, which allows the inference engine to quickly obtain the logical response based on the input data and relationship to these rules. For example:

IF:

Testing for selective IgA deficiency: IGA / Immunoglobulin A (IgA), Serum
Normal or elevated IgA
AND: TTGA / Tissue Transglutaminase: (tTG) Antibody, IgA, Serum greater than 10 U/mL
THEN:
Proceed to biopsy

The CDSS is divided into components that function independently or in concert for an enhanced learning experience and diagnostic accuracy. The two parts are:

1) A symptom and manifestations section. This section uses common language that would appear in an EHR as symptoms and medical diagnoses and is cross-referenced with knowledge from clinical literature as to their relevance to celiac disease. This section is further divided into:
a) classic and non-classic symptoms and manifestations that have appeared in multiple peer-reviewed publications and many of which are summarized by the American College of Gastroenterology as the most recent guidelines for identifying, diagnosing and treating celiac disease.3,7,20,47-51
b) known symptoms and conditions that are unique to the >2 but <15 year old celiac disease population based on peer-reviewed literature.\textsuperscript{3,7,47-51}

c) the knowledge present in peer-reviewed literature on the <2 celiac disease population which is failure to thrive.

d) sIgA deficiency symptoms are included since there is a higher incidence present for deficiency in the celiac population and a general lack of consensus in understanding this connection with celiac disease diagnosis among healthcare practitioners exists. This is critical since TTG IgA is a gold standard toward diagnosis. If positive for an sIgA deficiency, this should avert the direction of the healthcare practitioner toward a different serological path. Symptoms and manifestations of sIgA deficiency appear in table 5 below and are included in this section of the CDSS.

Table 5: sIgA Deficiency Symptoms\textsuperscript{106,107}

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma of unknown cause</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Gastrointestinal inflammation (Ulcerative colitis, Crohn's disease can be causes)</td>
</tr>
<tr>
<td>Mouth infection</td>
</tr>
<tr>
<td>Otitis media</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Skin infections</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
</tr>
</tbody>
</table>

This section contains 13 classic symptoms and manifestations (pediatric to adult), 28 non-classic symptoms, manifestations and associations (pediatric to adult), 19 current conditions and diseases associated with celiac disease, four unique pediatric symptoms
and conditions specific to those age 2 to 15 years, and factors for failure to thrive in the under 2 years of age category. It also factors for family history of first-degree relatives with the disease and 12 sIgA deficiency symptoms. If no symptoms, conditions or diseases are selected, a rule will fire asking if there is suspicion of asymptomatic or silent celiac disease. This factors for the case in which the disease is suspected, but there are no symptoms, conditions or diseases present, and will instruct the user to start the serology component toward diagnosis. In total there are 80 points of navigation in the symptomatology section.

2) Serology and histology component. This section of the system walks the user through the complex path to celiac disease serology and biopsy, simplifying the process and is based on the Mayo Clinic celiac disease testing algorithm (Figure 8).

The opening of the CDSS provides the end user with a question asking where they would like to start in the system. A user may choose to start at the symptomatology section, following the decisions toward serology or start at the serology and histology section.

3.1 Building the CDSS

An example of variables and data types that will be input into Exsys Corvid to create the CDSS is found in table 6 below.

Table 6: Variables and Data Types

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy_Results</td>
<td>Static List</td>
</tr>
<tr>
<td>CELI_Test</td>
<td>Static List</td>
</tr>
<tr>
<td>Variable</td>
<td>Type</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>CELI Test REDO</td>
<td>Static List</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Confidence</td>
</tr>
<tr>
<td>Celiac disease very unlikely</td>
<td>Confidence</td>
</tr>
<tr>
<td>DAGL Test</td>
<td>Static List</td>
</tr>
<tr>
<td>IgA Test</td>
<td>Static List</td>
</tr>
<tr>
<td>IgA Test VALUE</td>
<td>Continuous (numeric)</td>
</tr>
<tr>
<td>Max_iga_Limit</td>
<td>Continuous (numeric)</td>
</tr>
<tr>
<td>Min_iga_Limit</td>
<td>Continuous (numeric)</td>
</tr>
<tr>
<td>Not celiac disease</td>
<td>Confidence</td>
</tr>
<tr>
<td>Notes</td>
<td>Collection</td>
</tr>
<tr>
<td>Patient_Age</td>
<td>Static List</td>
</tr>
<tr>
<td>Possible celiac disease</td>
<td>Confidence</td>
</tr>
<tr>
<td>Proceed_to_biopsy</td>
<td>Static List</td>
</tr>
<tr>
<td>TSTGP_Test</td>
<td>Static List</td>
</tr>
<tr>
<td>TTGA_Test</td>
<td>Static List</td>
</tr>
<tr>
<td>TTGA_Test VALUE</td>
<td>Continuous (numeric)</td>
</tr>
<tr>
<td>TTGG_Test</td>
<td>Static List</td>
</tr>
</tbody>
</table>

In the above example, notice the name of the variable and type of the variable.

There are seven variable types that can be input into the system:

1. **Static list** – a multiple choice type list with defined values during the CDSS development.

2. **Dynamic list** – a multiple choice type list with values defined during runtime of the system.

3. **Numeric** – a numeric value used in formulas or test expressions.

4. **String** – a value that can hold any text string.

5. **Date** – a date value that can be used in testing various comparison data.

6. **Collection** – a list of strings as values.

7. **Confidence** – a variable that is assigned a confidence value for degree of certainty.

Figure 9 below is a screenshot of how this appears as it is being entered into Exsys Corvid.
Figure 9: Corvid Serology Variables

Figure 10 and 11 below are images of the main logic block of the serology and histology section of the CDSS.

Figure 10: Serology Logic 1
Figure 11: Serology Logic 2

Figure 12: Serology Main Block Rule View

Figure 12 above is a screen capture of the rule view of the serology main logical block. Placing the cursor on any path brings up the rule view in a separate window.

Figure 13 below depicts the symptoms and manifestations main logic block.
Figure 13: Symptoms and Manifestations Main Logic Block

Confidence variables are implemented to provide a degree of certainty and are based on the peer-reviewed literature. In the case of well-known symptoms of celiac disease such as the classic symptoms and manifestations, some key non-classic symptoms and manifestations and diseases such as type 1 diabetes, a higher numerical value is assigned to reflect a strong recommendation with a high level of confidence to initiate celiac disease serology, starting with total sIgA. Based on the literature review, lower numerical values are assigned such as conditional recommendations with a high level of evidence and strong recommendations with a moderate level of evidence. These conclusions are included in the most recent clinical guidelines of the American College of Gastroenterology and the most recent World Gastroenterology Organization Global Guidelines for celiac disease, July 2016. The complete Main Serology and Static List Variables are located in Appendix A.
3.2 Validation

Validation included having the system analyzed by professionals in the field of celiac disease diagnosis and obtaining their responses to a 5-point Likert scale survey of 10 statements on the usability, relevance and accuracy of the system. The purpose of the Likert scale, developed 85 years ago by Psychologist Rensis Likert, is to provide statements that detail and define the content being measured. Modern research has revealed the scale’s validity in health sciences. Sjövall and colleagues state the Likert scale can minimize equivocal positron emission tomography (PET) scans.

A letter was sent by email to 22 physician experts in the field of celiac disease from various institutions (University of Chicago, Harvard, Rush University, Columbia University, Thomas Jefferson University, and Boston Medical Center), including medical residents at the Mayo Clinic (Appendix B). For interrater reliability calculations, Cronbach’s Alpha reliability coefficient was the statistical validation of the survey responses. Cronbach’s alpha ranges between 0 and 1 and is based on the following formula (Figure 14).

\[
\alpha = \frac{k \cdot \bar{c}}{\bar{v} + (k - 1) \cdot \bar{c}}
\]

- \( k \) = the number of items.
- \( \bar{c} \) = average covariance between item-pairs.
- \( \bar{v} \) = average variance.

Figure 14: Cronbach’s alpha reliability coefficient

Gliem and the UCLA Institute for Digital Research and Education state a Cronbach’s alpha reliability coefficient of 0.7 is considered acceptable, and provide the following information on results found in table 7.
<table>
<thead>
<tr>
<th>Result</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;.9</td>
<td>Excellent</td>
</tr>
<tr>
<td>&gt;.8</td>
<td>Good</td>
</tr>
<tr>
<td>&gt;.7</td>
<td>Acceptable</td>
</tr>
<tr>
<td>&gt;.6</td>
<td>Questionable</td>
</tr>
<tr>
<td>&gt;.5</td>
<td>Poor</td>
</tr>
<tr>
<td>&lt;.5</td>
<td>Unacceptable</td>
</tr>
</tbody>
</table>

Table 7: Cronbach's Alpha Scale\textsuperscript{11,12}

Table 8 below depicts the Likert scale collection tool.

Table 8: 5-Point Likert Scale Validation Chart

<table>
<thead>
<tr>
<th>Survey Statements</th>
<th>Strongly Disagree (1)</th>
<th>Disagree (2)</th>
<th>Neutral (3)</th>
<th>Agree (4)</th>
<th>Strongly Agree (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Due to the fact that the majority of people with celiac disease will never receive a diagnosis, there is a need to develop this CDSS system.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. The system is user friendly.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. It is better for the system to be available online and function in any web browser instead of being a stand-alone application.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The system is a good tool for training medical students or residents.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. The system is a good tool for continuing medical education.

6. The system is capable of guiding a healthcare professional through the diagnostic process.

7. The system contains an accurate list of symptoms based on the clinical literature.

8. The serology section accurately covers all options and decisions based on test results.

9. The system can foster improved awareness and education about celiac disease.

10. Your overall agreement with the system.
CHAPTER 4

RESULTS

4.1 System Execution

Using a standard web browser, the celiac disease risk estimation and decision-making system is accessed via a direct link and the user is met with a clean and easily understandable opening screen (figure 15).

![Welcome Screen](Image)

The user is given the option to enter either the symptom and manifestations section or the serology and histology section. Choosing to enter symptom and manifestations results in the following screen that requests the user choose any or none of the classic symptoms, manifestations and syndromes associated with celiac disease from pediatric to adult (figure 16).
The user also has the option to restart the system from any screen or simply navigate back to the previous screen. Once a selection is made and OK is clicked, the user is met with the following screen, which moves on to non-classic symptoms, manifestations and associations (figure 17).
Non-Classic Symptoms, Manifestations and Associations

- Alopecia
- Amenorrhea
- Aphthous Ulcers/Stomatitis
- Ataxia
- Cognitive Impairment
- Constipation
- Delayed Onset of Puberty / Delayed Menarche
- Dental Defects/Enamel Defects
- Depression
- Dyspepsia
- Fertility Problems (female and male)
- Headaches
- Heartburn/GERD
- Hyposplenia
- Irritability
- LFT Elevations
- Nausea/Vomiting
- Nutritional Deficiencies (example: B12, Folate, Zinc, Vitamin A, D E, K, etc.)
- Obesity
- Osteopenia/Osteoporosis/Metabolic Bone Disease
- Peripheral Neuropathy
- Pancreatitis
- Pulmonary Hemosiderosis
- Seizure Disorders
- Thyroid Disorders
- Urinary Stone Disease
- Refractory Vitamin D Deficiency
- Weight Gain/Overweight
- None of the above

Figure 17: Non-classic Symptoms
The next screen asks if lactose intolerance is present because celiac disease patients have a high prevalence of a positive H2-lactose breath test compared to healthy controls\textsuperscript{113} (figure 18).

![Lactose Intolerance Screen](image)

**Figure 18: Lactose Intolerance Screen**

The user is then met with a question about any first-degree relative that has (had) celiac disease (figure 19).

![Family History Screen](image)

**Figure 19: Family History Screen**

Navigating further progresses the user to sIgA deficiency symptoms screen seen in figure 20 below.
After making a selection the user reaches the current conditions and diseases screen below (figure 21).
Current Conditions and Diseases

- Atrial fibrillation
- Autoimmune hepatitis
- Budd Chiari syndrome
- Cancers - gliomas, breast, lung, lymphomas, ovarian, pancreatic
- Cardiovascular disease
- CIDP
- Epilepsy
- Immune thrombocytopenia purpura
- Juvenile idiopathic arthritis
- Microscopic colitis
- Multiple Sclerosis
- Nonalcoholic fatty liver disease
- Primary biliary cirrhosis
- Rheumatoid Arthritis
- Sarcoidosis
- Sjogren's syndrome
- Systemic lupus erythematosus
- Thromboembolic disease
- Type 1 Diabetes
- None of the above

Figure 21: Current Conditions and Diseases Screen
At this point in the system there is an option to select if the subject is pediatric <2 years of age or between the age of 2 to <15 years, or not. If <2 years is selected the user will see the failure to thrive screen (figure 22).

![Image](image1.png)

**Figure 22: Failure to Thrive Screen**

If >2 to <15 years is selected, the user will see specific symptoms identified for this population group (figure 23).

![Image](image2.png)

**Figure 23: Pediatric Presentation Screen**
Moving forward in the system with any of these options, including selecting not pediatric, takes the user to the diagnosis/recommendations screen.

**Diagnosis:**

*Strong recommendation with a high level of confidence to test for celiac disease using the serology component of this CDSS, starting with total IgA.*

The following are classic symptoms, manifestations or syndromes of celiac disease:  
*Flatulence/Gas (particularly postprandial)*

The following are non-classic symptoms, manifestations or associations of celiac disease:  
*Heartburn/GERD*

A high prevalence of celiac disease was observed in patients with a positive H2-lactose breath test compared to healthy controls.

There can be as high as a 22% increased risk for celiac disease if a first degree relative has the disease.

An αlglA deficiency has a rate of occurrence 10 to 15 times more frequent in celiac disease patients than their non-celiac counterparts, it is wise for physicians to measure total serum IgA first, because that should dictate the correct testing course of action. This CDSS will guide you through this process automatically if the patient is IgA deficient. The following are IgA deficiency symptoms:  
*Mouth infection*

Current conditions and or diseases have been selected that are associated with celiac disease:  
*Type 1 Diabetes*

Figure 24: Sample of Recommendation Screen

Figure 24 above states there is a strong recommendation with a high level of confidence to test for celiac disease using the serology component of the CDSS, starting with total IgA. This is based on a case in which specific symptoms were selected. Notice above that selections are categorized, and statements are made about specific selections elucidating the connection to celiac disease as a form of education. For example, since lactose intolerance was selected, the statement that a high prevalence of celiac disease is
observed in patients with a positive H2-lactose breath test compared to healthy controls appears.\textsuperscript{111} Since there is an elevated risk for an sIgA deficiency in celiac, the statement identifying this fact reinforces this knowledge.\textsuperscript{20} With enough patient sample run-throughs the practitioner should have developed an expanded knowledge base of symptoms, manifestations, associations, and conditions or diseases linked to celiac disease.

Using an example of a case study from Yasawy and colleagues, a 30 year old Palestinian female presents with palpitations and amenorrhea.\textsuperscript{114} The patient was previously evaluated for possible mitral value prolapse.\textsuperscript{114} Physical exam indicates she’s pale, with aphthous ulcers in her oral cavity.\textsuperscript{114} Gynecological exam reveals no abnormalities.\textsuperscript{114} Serology results indicate a hemoglobin of 8.8mg/mL with a deficiency of iron and folate present and sIgA is 102mg/dL.\textsuperscript{114} There is evidence of osteoporosis. Inputting this information into the celiac disease risk estimation and decision-making system results in the following diagnosis/recommendation (figure 25).
**Figure 25: Patient Recommendations**

Notice above how the presenting symptoms and conditions are reported as classic and non-classic, providing education of the symptomatology and recommending the start of the serology section.

Starting from the home screen, if serology and histology is selected the first screen is a request to test for selective IgA deficiency as seen in figure 26 below.
In this section the user is asked to put in numerical values of the recommended tests. Once the sIgA value is put in and OK is selected the user arrives at a screen requesting the age range of the subject being tested as seen in figure 27 below.
If a normal sIgA value is inserted for any age, the following screen appears, which is a recommendation to order a tissue transglutaminase (tTG) antibody, IgA blood test (figure 28).
In figure 28 above, note the reference values as they determine the path of the backward chaining. If the subject’s tTG IgA is 3, the following diagnostic screen appears (figure 29).

**Figure 28: TTGA Screen**

Order the following test:

**TTGA / Tissue Transglutaminase: (tTG) Antibody, IgA, Serum (U/mL)**

Reference Values:
- <4.0 U/mL (negative)
- 4.0-10.0 U/mL (weak positive)
- >10.0 U/mL (positive)

Reference values apply to all ages

In figure 28 above, note the reference values as they determine the path of the backward chaining. If the subject’s tTG IgA is 3, the following diagnostic screen appears (figure 29).

**Figure 29: Diagnosis Celiac Disease Unlikely**

*Diagnosis:*

*Celiac disease very unlikely*

**Exception:**

~10% of patients with celiac disease are seronegative
If celiac disease is highly suspected, consider CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood

With a normal sIgA, and a below 4.0U/mL tTG IgA result, celiac disease is very unlikely according to the testing algorithm of the Mayo Clinic. Of importance to note
is the caveat that while celiac disease is unlikely, if the practitioner feels strongly that risk is still present, genetic testing should be considered.

If a weak positive value is input into the system, the following screen appears, which recommends additional testing (figure 30).

![Figure 30: DAGL / EMA Screen](image)

Order the following tests:

**DAGL / Gliadin (Deamidated) Antibody, IgA, Serum**

**EMA / Endomysial Antibodies (IgA), Serum**

- NEGATIVE (EMA negative and d-gliadin < 20 Units)
- POSITIVE (EMA positive and/or d-gliadin >= 20 Units)

A negative selection results in the recommendation to run the following DNA tests (figure 31).

![Figure 31: HLA DQ2/8 Screen](image)

Order the following DNA tests:

**CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood**

- NEGATIVE
- POSITIVE for DQ2 or DQ8
A negative selection on the screen above results in the following diagnosis (figure 32).

![Figure 32: Diagnosis Not Celiac Disease]

However, if ‘positive’ were selected for the DAGL screen, the recommendation would be to proceed to a biopsy as seen in figure 33 below.

![Figure 33: Biopsy Results Screen]

Due to the former positive serology, if the biopsy is negative, the next screen alerts the practitioner of the possibility of future development of celiac disease as seen in figure 34.
Starting from the beginning of the serology section, if the user inputs an sIgA value that is considered below age-matched reference values the following tests would be recommended as seen in figure 35.

Notice above that there is the addition of tTG IgG and Gliadin Deaminated IgG in addition to both IgA counterparts. This is because of the fact that if just an IgA testing path were run, the chances of a false negative are high. Any positive result would fire the proceed to biopsy recommendation screen and any negative result will fire the celiac
disease is very unlikely screen that also includes the note for DNA testing if the practitioner wants to rule that out.

Of course, in straight forward cases of a normal sIgA and a positive tTG IgA, such as a score of 22 U/mL, the recommendation by the system would be to proceed directly to biopsy and positive or negative result would determine the outcome as previously stated.

Returning to the case study by Yasawy and colleagues, moving to the serology section of the system as recommended in figure 2, a total sIgA of 102 mg/dL is input into the system and that would present with the recommendation to order a tTG IgA. The case study indicates this value is 25114, which is considered positive and therefore this would fire the recommendation for a biopsy. In the case study the biopsy was positive and revealed total villous atrophy, resulting in the diagnosis of celiac disease.114 The system arrives at the same diagnosis.

4.2 Statistics

Thirteen experts in the field of gastroenterology and celiac disease responded to the Likert Survey (59.09%). There were no missing values. Likert survey results were analyzed using Cronbach’s alpha reliability coefficient, which was calculated using SPSS (Version 25). Cronbach’s alpha value is 0.813 (Cronbach’s alpha based on standardized variables 0.844) and is depicted in table 9 below, followed by the values if a scale statement was deleted. A Cronbach’s alpha score equal to or greater than 0.7 is considered to be of clinical value.111,112
Table 9: Reliability Statistics

<table>
<thead>
<tr>
<th>Cronbach's Alpha</th>
<th>Cronbach's Alpha Based on Standardized Items</th>
<th>N of Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>.813</td>
<td>.844</td>
<td>10</td>
</tr>
</tbody>
</table>

Item-Total Statistics

<table>
<thead>
<tr>
<th>Cronbach's Alpha if Item Deleted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
</tr>
<tr>
<td>Q2</td>
</tr>
<tr>
<td>Q3</td>
</tr>
<tr>
<td>Q4</td>
</tr>
<tr>
<td>Q5</td>
</tr>
<tr>
<td>Q6</td>
</tr>
<tr>
<td>Q7</td>
</tr>
<tr>
<td>Q8</td>
</tr>
<tr>
<td>Q9</td>
</tr>
<tr>
<td>Q10</td>
</tr>
</tbody>
</table>

Expert response distributions to the Likert scale statements are found below in table 10.

<table>
<thead>
<tr>
<th>Survey Statements</th>
<th>Strongly Disagree (1)</th>
<th>Disagree (2)</th>
<th>Neutral (3)</th>
<th>Agree (4)</th>
<th>Strongly Agree (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Due to the fact that the majority of</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (23.08%)</td>
<td>10 (76.92%)</td>
</tr>
</tbody>
</table>
people with celiac disease will never receive a diagnosis, there is a need to develop this CDSS system.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. The system is user friendly.</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (7.69%)</td>
<td>2 (15.38%)</td>
</tr>
<tr>
<td>3. It is better for the system to be available online and function in any web browser instead of being a stand-alone application.</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (38.46%)</td>
</tr>
<tr>
<td>4. The system is a good tool for training medical students or residents.</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (7.69%)</td>
<td>11 (84.62%)</td>
</tr>
<tr>
<td>5. The system is a good tool for continuing medical education.</td>
<td>0 (0%)</td>
<td>0 (%)</td>
<td>3 (23.08%)</td>
<td>9 (69.23%)</td>
</tr>
<tr>
<td>6. The system is capable of guiding a healthcare professional through the diagnostic process.</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>12 (92.30%)</td>
</tr>
<tr>
<td>7. The system contains an accurate list of symptoms based on the</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (76.92%)</td>
</tr>
</tbody>
</table>
8. The serology section accurately covers all options and decisions based on test results.

<table>
<thead>
<tr>
<th></th>
<th>0 (0%)</th>
<th>2 (15.38%)</th>
<th>2 (15.38%)</th>
<th>7 (53.84%)</th>
<th>2 (15.38%)</th>
</tr>
</thead>
</table>

9. The system can foster improved awareness and education about celiac disease.

<table>
<thead>
<tr>
<th></th>
<th>0 (0%)</th>
<th>0 (0%)</th>
<th>0 (0%)</th>
<th>8 (61.53%)</th>
<th>5 (38.46%)</th>
</tr>
</thead>
</table>

10. Your overall agreement with the system.

<table>
<thead>
<tr>
<th></th>
<th>0 (0%)</th>
<th>0 (0%)</th>
<th>0 (0%)</th>
<th>11 (84.62%)</th>
<th>2 (15.38%)</th>
</tr>
</thead>
</table>

Table 10: Expert Response Distributions
CHAPTER 5

DISCUSSION

Examining the expert responses reveals that 100% agreed on the following Likert survey statements about the system.

- Due to the fact that the majority of people with celiac disease will never receive a diagnosis, there is a need to develop this CDSS system.

- It is better for the system to be available online and function in any web browser instead of being a stand-alone application.

- The system is capable of guiding a healthcare professional through the diagnostic process.

- The system contains an accurate list of symptoms based on the clinical literature.

- The system can foster improved awareness and education about celiac disease.

- Your overall agreement with the system.

Additionally, 92.3% of experts agreed on the following Likert survey statements about the system.

- The system is user friendly.

- The system is a good tool for training medical students or residents.

While over 90% of experts agreed the system is a good tool for training medical students or residents, 77% agreed with the statement ‘the system is a good tool for continuing medical education’, with three experts scoring that statement as neutral.
Moreover, even though the serology section of the system is based on the accepted Mayo Clinic algorithm for properly diagnosing celiac disease, and the same rules are part of the American College of Gastroenterology’s recommendations for diagnosing celiac disease\textsuperscript{20}, two experts scored the statement ‘the serology section accurately covers all options and decisions based on test results’ with a disagree value of 2, and two other experts scored it as neutral.

These percent review values reveal this system was correctly designed and also magnifies the key point identified in the review of the relevant literature, in which is there is a lack of consensus on diagnostics and signs and symptoms of celiac disease among experts in the field, even in the presence of extensive publication and education of diagnostic guidelines by the American College of Gastroenterology.

When trying to find reasoning behind the expert opinion of the disagree score for the serology section, comments that were included with the reviews were “Why proceed with biopsy if TTG >10 times? Where is the place for EMA?” and the statement “The ESPGHAN has a guideline reference that allows skipping the biopsy in children who fulfill certain conditions.” When addressing these statements it is important to note the current clinical recommendation for the diagnosis of celiac disease set forth by the American College of Gastroenterology is an intestinal biopsy.\textsuperscript{20} However, in 2012 the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has recommended a non-biopsy path to diagnosis in pediatric cases that meet specific serology guidelines, which include the presentation of classic symptoms, a TTG IgA $> 10$ times the ULN (upper level of normal), a positive EMA IgA and positive genetic testing (HLA-DQ2/8).\textsuperscript{115} While Mills and Murray state that a duodenal biopsy should be the
main clinical diagnostic tool, they agree that as serology and genetic testing evolve, there may be a path to diagnosis that avoids a biopsy, but the data doesn’t support such a recommendation at this time.\textsuperscript{116} Mills and Murray state that there are potential risks to diagnosing celiac disease without a biopsy. TTG and EMA specificity has been based on populations with a high prevalence of celiac disease and not including a population of non-celiac counterparts.\textsuperscript{116} There is also a lack of transference of reference ranges for different TTG and EMA test kits processed at varying institutions and of standardization of TTG assays, making it challenging to identify or follow a single universal upper level of normal cutoff range for such a serious, life changing diagnosis.\textsuperscript{116} According to the most recent clinical guidelines for the diagnosis and management of celiac disease by the American College of Gastroenterology, data to validate a non-biopsy path to celiac disease diagnosis as recommended by ESPGHAN are lacking.\textsuperscript{20} In 2016, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published a clinical report on gluten-related disorders and stated that due to the fact that a strict lifelong gluten free diet is inconvenient, costly and can negatively impact quality of life, it is critical to confirm a celiac disease diagnosis prior to such an undertaking, and therefore, recommend a biopsy as the only method for an accurate diagnosis.\textsuperscript{117} NASPGHAN also states that there is a risk of missing other diagnoses that may occur in concert with celiac disease if a biopsy is not performed, including Helicobacter pylori gastritis.\textsuperscript{117}

Regarding the statement “where is the place for EMA”, EMA do indeed appear in the serology section of the system and do so based exactly on the Mayo Clinic diagnostic algorithm.\textsuperscript{103} If a TTG IgA result is between 4 and 10 U/mL, EMA IgA and DAGL IgA
should be ordered. Therefore, the EMA analysis is indeed present in the system and nine out of 11 reviewers agree with the Likert statement ‘the serology section accurately covers all options and decisions based on test results’ and two scored it as neutral.

Another expert statement used to validate the reduced score was “I don’t like the ‘proceed with biopsy’ when any test abnormal: in fact, DGP-IgA and TTG-IgG are notoriously very bad predictors of celiac.” Put in context, in the presence of a selective IgA deficiency, the system recommends ordering a TTG IgG and DGG IgG serum tests. If any result is positive, the system recommends proceeding to a biopsy. This is based on the Mayo Clinic celiac disease diagnostic testing algorithm. In a review of 1,414 IgA deficient adults from seven Swedish clinical immunology laboratories, Wang and colleagues state TTG-IgG is a reliable marker for celiac disease in IgA deficient celiac disease subjects. Moreover, a look back at table 1 reveals the sensitivity of a DGG IgG in adults is .967 (CI 884-995) and specificity 100 (CI .995-100) and sensitivity of DGP IgA is 0.874 (CI 0.79-0.92) and specificity of 0.972 (CI 0.92-0.99) in the pediatric population. Rashtak and colleagues concluded after reviewing data from 216 biopsy selected subjects that DGG IgG is a reliable test for biopsy recommendation. The recommendation of the system is to use these tests only if needed and let the biopsy determine the diagnosis. These serological tests are not intended to make a celiac disease diagnosis in the absence of a biopsy. Putting the clinical evidence together in this scenario from the Mayo Clinic, Wang and colleagues, Rostom and colleagues, Monzani and colleagues, and Niveloni and colleagues, clearly these serology markers are far from
being notoriously bad predictors of celiac disease with their intended use in the system.\textsuperscript{41-43,103,118}

Another statement included with a positive review of the system was “though this will increase the sensitivity of diagnosis of celiac disease, I wonder about the specificity of these recommendations. For example, if I input data for a hypothetical patient, who is a male adult, has abdominal pain, gastric reflux symptoms, and unexplained weight loss I would be concerned about malignancy more than celiac disease.” The goal of the symptomatology section is to foster education by including with great clinical accuracy, the symptoms, manifestations and associated conditions that are linked to celiac disease in the clinical literature and are accepted by the American College of Gastroenterology and the World Association of Gastroenterology as signs and symptoms of the disease. The effort is to reduce the accepted statistic that 83\% of those with celiac disease will never be diagnosed. Part of the overall goal is to increase the knowledge base of residents or practitioners that may not be adroit, so they can use their judgment to proceed. The serology component would be the definitive remover of non-celiac patients. This reviewer’s statement is in agreement with the governing goal of this section of the system with the mention that this system will increase the sensitivity of the diagnosis of celiac disease. To create a symptomatology section that removes the weight of risk in the potential celiac disease patient with just a few clear signs or symptoms would only increase the current rate of the undiagnosed. However, abdominal pain, gastric reflux symptoms, and unexplained weight loss are major signs that celiac disease risk should be evaluated.\textsuperscript{20} In the International Journal of General Medicine, Gikas and Triantafillidis state primary care physicians need to be highly suspicious of celiac disease as it is vastly
underdiagnosed, presents with an average of 10 years before diagnosis and can lead to intestinal malignancy, among other conditions. Therefore, even if gastrointestinal cancer is pursued and diagnosed, it is essential to identify if celiac disease is present as well. Furthermore, Lionetti and colleagues express concern that since most celiac disease cases elude diagnosis all over the world, increasing in-depth knowledge of associated signs and symptoms beyond that of just classic symptoms should be paramount to reduce the rate of undiagnosed, and believe the merits and downside of long-term serological screening in asymptomatic populations are needed for complete diagnostic protocols to be established. In a 45 year follow up study using serology collected from 9,133 healthy men at Warren Air Force Base, undiagnosed celiac disease resulted in a 4-fold increased mortality. In support of the opinion of Lionetti and colleagues, Kochhar and colleagues identified asymptomatic celiac disease in 1:179 of 1,610 blood donors in north India by only measuring anti-tissue glutaminase antibodies serology. Since this choice of serology isn’t complete, it stands to reason the potential of a greater number of asymptomatic celiac disease subjects in such a population with a different analysis.

Other statements included with the Likert results from experts include “this risk estimation system seems to be very useful! Thank you!” “In regards for its use in teaching medical school students, it would be a great tool to use with a series of cases. The serologic testing algorithm would be very helpful for residents, fellows, and providers.” “Extremely exhaustive work, congratulations on your efforts.” “Overall, it was useful, I think it could stand to be a bit more visually appealing, but medically the information was accurate.” “Well done with the system, it definitely adds value to celiac
disease clinical practice.” “The symptomatology section is the most in depth I have seen in one educational tool.”

Addressing the visual appearance of the system, examining the usability of a web-based CDSS, Graham and colleagues state in health care such a system needs to be designed in a logical way that is void of distractions, with a full focus on being completely accurate and useful. Thus, the celiac disease risk estimation and decision-making system was designed with a simple white interface. The system can be personalized for Universities, hospitals and continuing medical education companies as needed.

Future direction of the research is to test the system in an academic environment as part of the medical curricula for celiac disease in an effort to increase awareness and diagnostic prowess. Feedback by students and experts will be collected to further refine the system. Any advances in celiac disease diagnostic science will be input into the system. Experimentation on developing a symptomatology section with a high sensitivity and specificity will continue.
CHAPTER 6

SUMMARY AND CONCLUSIONS

Celiac disease can present as a clinical chameleon and be challenging to identify and diagnose. The development of tools to increase celiac disease education and awareness can help obtain an accurate diagnosis. CDSS provide the ability to guide the knowledgeable user toward a diagnosis. A celiac disease risk estimation and decision-making expert system was successfully developed using Exsys Corvid software and built upon evidence-based knowledge that acts as a training tool as well as a robust system for the clinical environment.

The first goal for this CDSS is that it takes into account the need for an education model, combining accurate language of signs, symptomatology and other associated diseases, with the serology and histology component based on the accepted and thorough Mayo Clinic celiac disease testing algorithm. The second goal is to make the CDSS easily accessible and user friendly, to remove any impediment to access, not require special software, and operate in a standard web browser. Driving these goals is the governing theme in the review of the literature that the average time to diagnosis is 10 years, and that 83% of the celiac disease population never receive a diagnosis.

The system was validated by 13 experts in the field of celiac disease using a 10 statement, 5-point Likert scale. This scale was analyzed using Cronbach’s alpha reliability coefficient, which was calculated using SPSS. Cronbach’s alpha revealed good internal consistency and reliability with a result of 0.813 (0.844 standardized variables).

One-hundred percent of the experts agreed with the system and that the CDSS is capable of guiding a healthcare professional through the diagnostic process, contains an
accurate list of symptoms based on the clinical literature, can foster improved awareness and education about celiac disease, that there is a need for this system, and that it should function online. Almost all of the experts (92.3%) agreed the system is a good tool for training medical students or residents.
BIBLIOGRAPHY


111. Gliem RR, Gliem JA. Calculating, interpreting, and reporting Cronbach’s alpha reliability coefficient for Likert-type scales. 2003.


APPENDIX A

LOGIC BLOCK: MAIN SEROLOGY AND STATIC LIST VARIABLES

A.1 Logic Block: Main Serology
Section = Serology_and_Histology
IgA_Test = Normal_or_elevated_IgA
TTGA_Test = less_than_4_UmL
--> [Celiac_disease_very_unlikely] = 10
--> [Notes.ADD] Exception:<b>Exception:</b><br>~10% of patients with celiac disease are seronegative br> If celiac disease is highly suspected, consider CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1

Medium-High Resolution DNA Typing, Blood
TTGA_Test = 4_to_10_UmL
DAGL_Test = NEGATIVE_EMA_negative_and_dgliadin__20_Units
--> [Notes.ADD].

CELI_Test = NEGATIVE
--> [Not_celiac_disease] = 10

CELI_Test = POSITIVE_for_DQ2_or_DQ8
--> Proceed_to_biopsy = Yes

DAGL_Test = POSITIVE_EMA_positive_andor_dgliadin__20_Units
--> Proceed_to_biopsy = Yes

TTGA_Test = greater_than_10_UmL
--> Proceed_to_biopsy = Yes

IgA_Test = IgA_greater_than_or_equal_to_1_mgdL_and_below_age_matched
TSTGP_Test = Any_result__test_abnormal
--> Proceed_to_biopsy = Yes

TSTGP_Test = All_results__tests_normal
--> [Celiac_disease_very_unlikely] = 10

--> [Notes.ADD] <b>Exception:</b><br>~10% of patients with celiac disease are seronegative<br>If celiac disease is highly suspected, consider CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1

Medium-High Resolution DNA Typing, Blood

IgA_Test = IgA_less_than_1_mgdL

--> [Notes.ADD] Selective IgA deficiency<br>For individuals with clinical symptoms suggestive of recurrent infections, suggest further evaluation for possible primary immunodeficiency: IGGS / IgG Subclasses, Serum IMM / Immunoglobulins (IgG, IgA, and IgM), Serum<br>

TTGG_Test = Any_result__test_abnormal
--> Proceed_to_biopsy = Yes

TTGG_Test = All_results__tests_normal
--> [Celiac_disease_very_unlikely] = 10

--> [Notes.ADD] <b>Exception:</b><br>~10% of patients with celiac disease are seronegative<br>If celiac disease is highly suspected, consider CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood
Logic Block: TTGA Test

Section = Serology_and_Histology \([\text{TTGA\_Test\_VALUE}] < 4\)

\(\rightarrow\) TTGA\_Test = less\_than\_4\_UmL

\([\text{TTGA\_Test\_VALUE}] \geq 4\) \& \([\text{TTGA\_Test\_VALUE}] \leq 10\)

\(\rightarrow\) TTGA\_Test = 4\_to\_10\_UmL

\([\text{TTGA\_Test\_VALUE}] > 10\)

\(\rightarrow\) TTGA\_Test = greater\_than\_10\_UmL

Logic Block: Symptoms and Manifestations

Section = Symptom_and_Manifestations \([\text{Classic\_symptom\_list.COUNT}] > 0\)

\(\rightarrow\) \([\text{Test\_based\_on\_Classic\_symptoms}] = 10\)

\([\text{Classic\_symptom\_list.COUNT}] = 0\) \& \([\text{Non\_Classic\_symptoms.COUNT}] > 0\)

\(\rightarrow\) \([\text{Test\_based\_on\_Nonclassic\_symptoms}] = 10\)

\([\text{Non\_Classic\_symptoms.COUNT}] = 0\) Lactose\_Intolerance = Yes

\(\rightarrow\) \([\text{Test\_based\_on\_other\_indicators}] = 10\)

First\_Degree\_Relative = Yes

\(\rightarrow\) \([\text{Test\_based\_on\_other\_indicators}] = 10\)

\([\text{sIgA\_Symptoms.COUNT}] > 0\)

\(\rightarrow\) \([\text{Test\_based\_on\_other\_indicators}] = 10\)

\([\text{Current\_disease\_list.COUNT}] > 0\)

\(\rightarrow\) \([\text{Test\_based\_on\_other\_indicators}] = 10\)

Pediatric = Pediatric\_2\_years\_of\_age Failure\_to\_Thrive = Yes

\(\rightarrow\) \([\text{Test\_based\_on\_other\_indicators}] = 10\)
Pediatric = Pediatric_2_to_15_years_of_age [Pediatric_disease_list.COUNT] > 0

--> [Test_based_on_other_indicators] = 10

[Test_based_on_other_indicators] = 0 No_symptoms = Yes

--> [Test_asymptomatic_based_on_suspicion] = 10

No_symptoms = No

--> [Test_NO_TEST] = 10

[Classic_symptom_list.COUNT] > 0

--> [Notes.ADD] The following are classic symptoms, manifestations or syndromes of
celiac disease:

[Non_Classic_symptoms.COUNT] > 0

--> [Notes.ADD] The following are non-classic symptoms, manifestations or associations
of celiac disease:

Lactose_Intolerance = Yes

--> [Notes.ADD] A high prevalence of celiac disease was observed in patients with
a positive H2-lactose breath test compared to healthy controls.

First_Degree_Relative = Yes

--> [Notes.ADD] There can be as high as a 22% increased risk for celiac disease if a
first degree relative has the disease.

[slgA_Symptoms.COUNT] > 0

--> [Notes.ADD] An slgA deficiency has a rate of occurrence 10 to 15 times more
frequent in celiac disease patients than their non-celiac counterparts, it is wise for
physicians to measure total serum IgA first, because that should dictate the correct testing
course of action. This CDSS will guide you through this process automatically if the
patient is IgA deficient. The following are IgA deficiency symptoms:

\[ \text{Current\_disease\_list.COUNT} > 0 \]

--> [Notes.ADD] Current conditions and or diseases have been selected that are associated with celiac disease:

\[ \text{Pediatric = Pediatric\_2\_years\_of\_age} \]

Failure to Thrive = Yes

--> [Notes.ADD] Failure to thrive in this pediatric population is a sign of celiac disease.

\[ \text{Pediatric = Pediatric\_2\_to\_15\_years\_of\_age} \]

[Pediatric\_disease\_list.COUNT] > 0

--> [Notes.ADD] Pediatric symptoms have been selected that are associated with celiac disease:

\[ \text{Test\_asymptomatic\_based\_on\_suspicion} = 10 \]

--> [Notes.ADD] If no symptoms are present but celiac disease is suspected, note that asymptomatic celiac disease or silent celiac disease should be ruled out.

Command Block: Command Block 1

1 DERIVE CONF

2 DERIVE [Notes]

3 RESULTS Servlet=Celiac\_CORVID\_Results\_Default.html

Variables:

[Biopsy\_Results]

Static List Variable Prompt: Biopsy Results Static List Values:

NEGATIVE

POSITIVE
Flags:

Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line Before Ask, display:
TEXT "Proceed to biopsy" FORMAT: FONT=SansSerif SIZE=12 TEXT " "
[CELI_Test]
Static List Variable
Prompt: CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1 Medium-High Resolution DNA Typing, Blood Static List Values:
NEGATIVE
POSITIVE_for_DQ2_or_DQ8
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line Before Ask, display:
TEXT "Order the following DNA tests:" FORMAT: FONT=SansSerif SIZE=12 TEXT "
[CELI_Test_REDO]
Static List Variable
Prompt: <b>Biopsy results inconsistent with serology</b><br>Redo CELI / Celiac-Associated HLA-DQ Alpha 1 and DQ Beta 1
Medium-High Resolution DNA Typing, Blood Static List Values:
NEGATIVE
POSITIVE_for_DQ2_and_DQ8
Flags:
Always obtain a value: False Display with results: False
Never Ask User: False Display with results: False Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line
[Celiac_disease]
Confidence Variable Prompt: Celiac disease Calculation Mode: Sum
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False

Display:
Ask with: Edit Box
Arrange: One item per line

[Celiac_disease_very_unlikely]

Confidence Variable
Prompt: Celiac disease very unlikely Calculation Mode: Sum

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False

Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False

Display:
Ask with: Edit Box
Arrange: One item per line

[Classic_symptom_list]

Collection Variable Prompt: Severe Symptoms
Flags:

Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Display:
Ask with: Edit Box
Arrange: One item per line

[Classic_Symptoms]
Static List Variable
Prompt: Classic Symptoms, Manifestations and Syndromes (Pediatric to Adult) Static
List Values:
Abdominal_Pain_particularly_postprandial
Bloating_particularly_postprandial
Dermatitis_Herpetiformis
Diarrhea
Downs_Syndrome
Edema_hypoproteinemia
Fatigue/Lethargy
FlatulenceGas_particularly_postprandial
Iron_Deficiency_Anemia
Severe_Itchy_Rash
Steatorrhea
Turner’s_Syndrome
Weight_Loss_unexplained
None_of_the_above

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Check Boxes
Selecting last value clears all others

Arrange: One item per line

[Current_disease_list]

Collection Variable

Prompt: Current disease list

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box Arrange: One item per line

[Current_Diseases]

Static List Variable

Prompt: Current Conditions and Diseases Static List Values:

Atrial_fibrillation

Autoimmune_hepatitis
Budd-Chiari syndrome

Cancers_gliomas_breast_lung_lymphomas_ovarian_pancreatic

Cardiovascular_disease

CIDP

Epilepsy

Immune_thrombocytopenia_purpura

Juvenile_idiopathic_arthritis

Microscopic_colitis

Multiple_Sclerosis

Nonalcoholic_fatty_liver_disease

Primary_biliary_cirrhosis

Rheumatoid_Arthritis

Sarcoidosis

Sjogren’s_syndrome

Systemic_lupus_erythematosi

Thromboembolic_disease

Type_1_Diabetes

None_of_the_above

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Check Boxes
Selecting last value clears all others
Arrange: One item per line

[DAGL_Test]

Static List Variable
Prompt: DAGL / Gliadin (Deamidated) Antibody, IgA, Serum
<br>EMA / Endomysial Antibodies (IgA), Serum
Static List Values:
NEGATIVE (EMA negative and d-gliadin < 20 Units)
POSITIVE (EMA positive and/or d-gliadin >= 20 Units)
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line Before Ask, display:

TEXT "Order the following tests:" FORMAT: FONT=SansSerif SIZE=12 TEXT " "

[Failure_to_Thrive]

Static List Variable

Prompt: Is there a Failure to Thrive? Static List Values:

Yes

No

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip
redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line

[First_Degree_Relative]

Static List Variable

Prompt: Does any First Degree Relative have (had) Celiac Disease? Static List Values:

Yes

No

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False
Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line

[IgA_Test]

Static List Variable

Prompt: Testing for selective IgA deficiency: IGA / Immunoglobulin A (IgA), Serum

Static List Values:

Normal_or_elevated_IgA

IgA greater than or equal to 1 mg/dL and below age matched

IgA less than 1 mg/dL

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned
Display:

Ask with: Radio Buttons

Arrange: One item per line

[IgA_Test_VALUE]

Numeric Variable

Prompt: Test for selective IgA deficiency: IGA / Immunoglobulin A (IgA), Serum (mg/dL)

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: Same line as Prompt

Servlet ASK Template to use: Celiac_CORVID_Question_Iga_Test_Value.html

[Lactose_Intolerance]
A.2 Static List Variables

Prompt: Lactose Intolerance Static List Values:

Yes
No

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False

Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned

Display:
Ask with: Radio Buttons
Arrange: One item per line

[Max_Iga_Limit]

Numeric Variable Prompt: Max_Iga_Limit

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Display:
Ask with: Edit Box
Arrange: One item per line
[Min_IgA_Limit]
Numeric Variable Prompt: Min_IgA_Limit
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False

Display:
Ask with: Edit Box
Arrange: One item per line

[No_symptoms]
Static List Variable
Prompt: While none of the preceding symptoms are present, is silent or asymptomatic celiac disease still suspected? Static List Values:
Yes
No

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:

Ask with: Radio Buttons

Arrange: One item per line

[Non_Classic_symptoms]

Collection Variable

Prompt: Moderate symptoms

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[NonClassic_Symptoms]

Static List Variable

Prompt: Non-Classic Symptoms, Manifestations and Associations Static List Values:
Alopecia
Amenorrhea
Aphthous_Ulcers/Stomatitis
Ataxia
Cognitive_Impairment
Constipation
Delayed_Onset_of_Puberty_Delayed_Menarche
Dental_Defects/Enamel_Defects
Depression
Dyspepsia
Fertility_Problems_female_and_male
Headaches
Heartburn/GERD
Hyposplenia
Irritability
LFT_Elevations
Nausea/Vomiting
Nutritional_Deficiencies_example_B12_Folate_zinc_Vitamin_A_D_E_K_etc
Obesity
Osteopenia/Osteoporosis_Metabolic_Bone_Disease
Peripheral_Neuropathy
Pancreatitis
Pulmonary_Hemosiderosis
Seizure Disorders
Thyroid Disorders
Urinary Stone Disease
Refractory Vitamin D Deficiency
Weight Gain Overweight
Weight Gain/Overweight
None of the above

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Check Boxes
Selecting last value clears all others
Arrange: One item per line
[Not_celiac_disease]
Confidence Variable Prompt: Not celiac disease Calculation Mode: Sum

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Display:
Ask with: Edit Box
Arrange: One item per line

[Notes]
Collection Variable Prompt: Notes
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[Patient_Age]

Static List Variable Prompt: Patient Age Static List Values:

Less_than_5_months

5_months_to_less_than_9_months

9_months_to_less_than_15_months

15_to_less_than_24_months

2_years_to_less_than_4_years

4_years_to_less_than_7_years

7_years_to_less_than_10_years

10_years_to_less_than_13_years

13_years_to_less_than_16_years

16_years_to_less_than_18_years

18_years_or_older

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line
[Pediatric]
Static List Variable Prompt: Is the patient Static List Values:
Pediatric_<2_years_of_age
Pediatric_2_to_15_years_of_age
Not_pediatric
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line

[Pediatric_disease_list]

Collection Variable

Prompt: Pediatric disease list

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[Pediatric_Presentation_215_years]

Static List Variable

Prompt: Pediatric Presentation (>2 and <15 years of age) Static List Values:

Abdominal_Distension

Personality_Disorders

Short_Stature

Thin_Extremities

None_of_the_above

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True
Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Check Boxes

Arrange: One item per line

[Possible_celiac_disease]

Confidence Variable

Prompt: Possible celiac disease - Follow-up patient for future development of celiac disease Calculation Mode: Sum

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line
[Proceed_to_biopsy]

Static List Variable Prompt: Proceed to biopsy Static List Values:

Yes

No

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line

[Section]

Static List Variable

Prompt: Where would you like to start? Static List Values:

Symptom_and_Manifestations
Serology_and_Histology

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line Before Ask, display:
TEXT "Welcome to the Celiac Disease Risk Estimation and Decision Making Expert System " FORMAT: FONT=Serif SIZE=14 STYLE=
[slgA_Deficiency_Symptoms_question]
Static List Variable
Prompt: slgA Deficiency Symptoms Static List Values:
Asthma_of_unknown_cause
Bronchitis
Bronchiectasis
Chronic_diarrhea
Conjunctivitis
Gastrointestinal_inflammation_Ulcerative_colitis_Crohns_disease_can_be_causes
Mouth_infection
Otitis_media
Pneumonia
Sinusitis
Skin_infections
Upper_respiratory_tract_infections
None_of_the_above

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:

Ask with: Check Boxes

Arrange: One item per line

[sIgA_Symptoms]

Collection Variable Prompt: sIgA Symptoms

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[Test_asymptomatic_based_on_suspicion]

Confidence Variable

Prompt: Test for celiac disease using the serology component of this CDSS, starting with total IgA. Calculation Mode: Sum
Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False

In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[Test_based_on_Classic_symptoms]

Confidence Variable

Prompt: Strong recommendation with a high level of confidence to test for celiac disease using the serology component of this CDSS, starting with total IgA Calculation Mode: Sum

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False
Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: One item per line

[Test_based_on_Nonclassic_symptoms]

Confidence Variable

Prompt: There is a strong recommendation with a moderate level of confidence to test for celiac disease using the serology component of this CDSS, starting with total IgA. Calculation Mode: Sum

Flags:

Always obtain a value: False

Display with results: False

Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip
redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Display:
Ask with: Edit Box
Arrange: One item per line
[Test_based_on_other_indicators]
Confidence Variable
Prompt: Test for celiac disease using the serology component of this CDSS, starting with total IgA. Calculation Mode: Sum
Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Display:
Ask with: Edit Box
[Test_NO_TEST]
Confidence Variable
Prompt: Do not proceed to celiac disease testing. Calculation Mode: Sum

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False

Display:
Ask with: Edit Box
Arrange: One item per line

[TSTGP_Test]
Static List Variable
Prompt: TSTGP / Tissue Transglutaminase (tTG): Antibodies, IgA and IgG Profile,
Serum DGLDN / Gliadin (Deamidated) Antibodies:
Evaluation, IgG and IgA, Serum Static List Values:
Any_result__test_abnormal
All_results__tests_normal

Flags:

Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned

Display:

Ask with: Radio Buttons
Arrange: One item per line
Before Ask, display:
TEXT "Order the following tests:" FORMAT: FONT=SansSerif TEXT " "
[TTGA_Test]
Static List Variable
Prompt: TTGA / Tissue Transglutaminase: (tTG) Antibody, IgA, Serum
Static List
Values:
less_than_4_UmL
4_to_10_UmL

greater_than_10_UmL

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False
Display with results: False
Initialize: False
Check for PARAM data passed in Applet call: False
In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False
Use backward chaining to derive value: True
Use External Source to get value: False
Any number of values can be assigned
Display:
Ask with: Radio Buttons
Arrange: One item per line

[TTGA_Test_VALUE]
Numeric Variable
Prompt: TTGA / Tissue Transglutaminase: (tTG) Antibody, IgA, Serum (U/mL)

Flags:
Always obtain a value: False
Display with results: False
Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False
In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Display:

Ask with: Edit Box

Arrange: Same line as Prompt Before Ask, display:

TEXT "Order the following test:" FORMAT: FONT=SansSerif SIZE=12 STYLE=Plain
TEXT " "

Servlet ASK Template to use: Celiac_CORVID_Question_TTGA_Test_Value.html

[TTGG_Test]

Static List Variable

Prompt: TTGG / Tissue Transglutaminase: (tTG) Antibody, IgG, Serum DGGL / Gliadin (Deamidated): Antibody, IgG, Serum Static List Values:

Any_result__test_abnormal

All_results__tests_normal

Flags:

Always obtain a value: False

Display with results: False
Never Ask User: False

Display with results: False

Initialize: False

Check for PARAM data passed in Applet call: False

In backward chaining, stop after first value is set: False In backward chaining, skip redundant rules: False

Use backward chaining to derive value: True

Use External Source to get value: False

Any number of values can be assigned

Display:

Ask with: Radio Buttons

Arrange: One item per line Before Ask, display:

TEXT "Order the following test:" FORMAT: FONT=SansSerif SIZE=12 TEXT " "

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Dear Doctor (personalized):

My name is Robert Pastore. I am a PhD candidate at Rutgers University. Dr. Joseph Murray is on my dissertation committee and he recommended you to please review a new celiac disease risk estimation and decision-making expert system I developed.

The goal of the system is to use evidence-based knowledge that acts as a training tool as well as a robust system for the clinical environment. It takes into account the need for an educational model, combining accurate language of signs, symptomatology and other associated diseases and manifestations that would be part of an electronic health record.

Here is a bullet point summary of the symptomatology section:

• Total of 80 points of navigation through the symptomatology section -
• Built upon 13 classic symptoms and manifestations (pediatric to adult)
• 28 non-classic symptoms, manifestations and associations (pediatric to adult)
• 19 current conditions and diseases associated with celiac disease
• 4 unique pediatric symptoms and conditions specific to age 2 to 15 years
• Factors for failure to thrive in the <2 year old population
• Factors for family history (first degree relatives) with celiac disease
• Includes 12 sIgA deficiency symptoms
• Factors for asymptomatic celiac disease or silent celiac disease

The serology component contains advances in celiac disease testing based on the accepted and thorough Mayo Clinic celiac disease testing algorithm.

Here is a link to the system for your examination and experimentation - http://www.exsyssoftware.com/CORVID61/corvidsr?KBNAME=../726364294/Celiac_v2.CVR

Dr. Murray and I would greatly appreciate if you would take the time to provide your opinion using the attached 5-point Likert scale of 10 statements about the system and kindly email your completed document back to me at your convenience.

I would be honored if you could please take the time to participate in this research. My main goal is to drastically reduce the number of the undiagnosed well below the current estimation of 83%. That motivates me on a daily basis. If this system can increase the knowledge of just one medical resident, so they are more adroit in celiac disease signs, symptoms and serology, I will feel validation.

Respectfully,
Robert Pastore, MS, CNS, PhD candidate
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Biomedical Informatics, Nanomedicine and Clinical Informatics
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