Celiac Disease Diagnosis Among Primary Care Nurse Practitioners: A Quality Improvement Project

CELIAC DISEASE DIAGNOSIS AMONG PRIMARY CARE NURSE PRACTITIONERS: A QUALITY IMPROVEMENT PROJECT

by

Morgan Reimann

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As members of the DNP Project Committee, we certify that we have read the DNP project prepared by Morgan Reimann entitled "Celiac Disease Diagnosis Among Primary Care Nurse Practitioners: A Quality Improvement Project" and recommend that it be accepted as fulfilling the DNP project requirement for the Degree of Doctor of Nursing Practice.

Lori Martin-Plank Date: 10/26/2017
Lori Martin-Plank, PhD, FNP-BC, NP-C, GNP-BC, FAANP

Luz Wiley Date: 10/26/17
Luz Wiley, DNP, RN, APRN-BC

Joseph Hepworth Date: 10/26/17
Joseph Hepworth, PhD

Final approval and acceptance of this DNP project is contingent upon the candidate's submission of the final copies of the DNP project to the Graduate College.

I hereby certify that I have read this DNP project prepared under my direction and recommend that it be accepted as fulfilling the DNP project requirement.

Lori Martin-Plank Date: 10/26/2017
DNP Project Chair: Lori Martin-Plank, PhD, FNP-BC, NP-C, GNP-BC, FAANP

STATEMENT BY AUTHOR

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SIGNED: __Morgan Reimann_____

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DEDICATION

To my loving parents who have made this doctoral journey possible for me. Thank you for always supporting me and fostering growth and self-confidence in me.

To my kind-hearted husband who has encouraged me to relish life no matter what obstacles I face. Thank you for being supportive of me always.

TABLE OF CONTENTS

TABLE OF CONTENTS – *Continued*

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

INTRODUCTION: Celiac disease (CD), an inflammatory condition of the small bowel, is now recognized as the most common of the autoimmune disorders (Kenrick & Day, 2014). Unfortunately, due to poor awareness among primary care providers (PCPs) this disease remains highly underdiagnosed despite its increasing prevalence (Catassi & Fasano, 2008). Aims of this quality improvement project were to examine current knowledge and practices of nurse practitioners in the primary care setting that influence the screening and diagnosis of CD.

METHODS: A 32-item survey was sent out to nurse practitioner primary care providers (NP-PCPs) in the Dallas-Fort Worth Metroplex over a four-week period. The survey assessed demographic characteristics, knowledge and clinical practices of nurse practitioners as it relates to CD diagnosis. Data was analyzed using SPSS and descriptive statistics.

RESULTS: Eighteen valid responses were received for analysis. The majority of respondents reported having no familiarity with the American College of Gastroenterology (ACG) and National Institute for Health and Care Excellence (NICE) guidelines. Two thirds of the respondents reported their education did not properly prepare them to accurately diagnose celiac disease. The vast majority also reported they do not test patients, pediatric or adult, using any celiac related blood test. The same results were true for patients being sent for intestinal biopsy. Although able to list typical symptoms of CD, many respondents were unaware of atypical symptoms. Most also omitted family history as important when considering celiac related testing.

CONCLUSIONS: Overall NP-PCPs are not aware of and therefore do not follow clinical guidelines related celiac disease. It is clear that NP-PCPs need to be made aware of the prevalence of this disease and should be directed to follow evidence-based practice guidelines in

their primary care practices. One step for doing this includes providing better education for NP-PCP students. Educators should include lectures or discussions about CD in their curriculum and provide students with resources such as the NICE and ACG guidelines. For practicing NPs, free continuing education can be offered. Lastly, clinicians who are aware of the high rates of underdiagnosis can present CD related information at conferences and meetings.

INTRODUCTION

Overview of Celiac Disease

Celiac disease (CD) is an immune disorder in which the small intestine is permanently unable to properly digest gluten, a protein found in wheat, rye and barley, leading to villous atrophy (Paul & Basude, 2013). Damage to the intestine ultimately leads to malabsorption of essential vitamins and nutrients and increases risk for numerous health problems (Mavrinac, Ohannessian, Dowling, & Dowling, 2014). Common symptoms of CD include diarrhea, weight loss, anemia, fatigue and abdominal pain and bloating. Although serological testing for celiac-specific antibodies indicates whether there is a possibility of CD, diagnosis is confirmed with a duodenal mucosal biopsy (Rewers, 2005). The only effective treatment is a gluten-free diet, which reverses mucosal inflammation and damage and leads to recovery from symptoms (Norstrom, Lindholm, Sandstrom, Nordyke, & Ivarsson, 2011).

Background Knowledge

Celiac disease is the most common human genetic autoimmune condition, estimated to affect nearly one in 141 Americans (Rubio-Tapia, Ludvigsson, Brantner, Murray, & Everhart, 2012). Previously thought to develop in infancy, this chronic systemic disease is now known to develop at varying ages with increasing diagnostic rates in adulthood (Murray et al., 2003). In fact, prevalence rates have increased nearly fourfold in the United States over the past ten to twenty years (Lebwohl et al., 2013). Barriers to recognizing CD include atypical and silent presentations, which can only be illuminated by careful observation and risk assessment (Fasano & Catassi, 2001). Furthermore, false negative results may occur when patients or their providers are unaware that both serology and biopsy should be performed while the patient is on a gluten-

containing diet. Due to these and other barriers, the average time to diagnosis can be delayed for several years. In fact, Norstrom et al. (2011) found a diagnostic delay of 9.7 years from onset of symptoms and 5.8 years from the first doctor visit.

Current research links CD to other autoimmune disorders such as thyroid disease and type I diabetes. For example, Sharma et al. (2016) found the prevalence of CD to be much higher in patients with autoimmune thyroid disease (AITD) than in the general population and suggests patients with AITD be screened for celiac disease. Similarly, Kylokas et al. (2016) found markedly higher rates of CD among adults with type I diabetes, especially in men. Research also supports associations between CD and higher rates of anxiety and migraines (Dimitrova et al., 2013; Hauser, Janke, Klump, Gregor, & Hinz, 2010).

In 2013 the American College of Gastroenterology (ACG) published a clinical practice guideline for the diagnosis and management of CD. The document aims to guide providers in recognizing, screening for and diagnosing patients with CD using current evidence based practice, as summarized in Table 1. In addition to this resource, the 2015 National Institute for Health and Care Excellence (NICE) guideline provides recommendations for clinicians on when to investigate and test patients for CD, as summarized in Table 2. It is unclear, however, if providers are using resources such as these in practice as evidenced by the number of missed CD cases.

TABLE 1. *ACG 2013 Recommendations on Who to Test for Celiac Disease*

Offer serological testing to:
• Patients with symptoms, signs or laboratory evidence of malabsorption such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain and bloating. • Patients with symptoms, signs or laboratory evidence for which CD is a treatable cause. • Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD. • Patients with Type I diabetes mellitus if there are any digestive symptoms or signs or laboratory evidence suggestive of CD.

TABLE 2. *NICE 2015 Recommendations on Who to Test for Celiac Disease*

Offer serological testing to patients who have a first-degree relative with celiac disease and to patients with any of the following:
• Diarrhea, chronic or intermittent • Faltering growth • Irritable bowel syndrome • Persistent, recurrent or unexplained nausea, vomiting, abdominal pain or bloating • Sudden or unexpected weight loss • Unexplained iron deficiency, B12 or folate deficiency • Autoimmune thyroid disease (preferably at the time of diagnosis) • Type I diabetes (preferably at the time of diagnosis) • Prolonged fatigue • Severe or persistent mouth ulcers

The ACG and NICE guidelines are similar in the fact that they both recommend serological testing in individuals with signs, symptoms and laboratory evidence suggestive of CD. Both guidelines also agree on offering serological tests to patients with first-degree relatives with confirmed CD. The guidelines differ in two ways: 1) The signs and symptoms mentioned in the ACG guidelines are slightly more general; and 2) Although the ACG guideline mentions first-degree relatives with CD and patients with type I diabetes, only the NICE guideline recommends offering serological testing to these individuals. According to the ACG guidelines the individuals must also be exhibiting signs and symptoms.

Local Problem

Celiac disease was once considered to be a rare condition occurring mostly in children of Celtic or Northern European descent. However, in recent decades it has been uncovered that CD occurs in adults as well as children and is prevalent in all areas of the world including the United States (Kang, Kang, Green, Gwee, & Ho, 2013). In fact, research suggests that 1 per 100 to 200 individuals in the United States has CD; unfortunately, only 1 in 5 to 7 individuals with CD is accurately diagnosed as having CD (Fowell, Thomas, Surgenor, & Snook, 2006; Rubio-Tapia et al., 2012). This issue expands to all areas of the United States including Texas. In informal discussions with several different medical providers in Texas it was noted that most of these providers were unaware of the current CD screening guidelines and were not actively screening for CD in their practices.

A study conducted by Zipser, Farid, Baisch, Patel and Patel (2005) discovered that primary care providers (PCPs) diagnosed only 11% of the 2,440 CD patients surveyed (8% of those confirmed by biopsy). Diagnosis of CD was categorized under PCP if they suspected CD before referral to a gastroenterologist. In addition to this, gastroenterologists were only able to diagnose 65% of patients with CD (Zipser et al., 2005). Coupled with underdiagnosis, there is a significant delay in the time it takes providers to diagnose CD. In fact, many individuals with CD are not diagnosed until the later decades of life with a delay in diagnosis ranging from one to seven years (Matthias et al., 2011; Rampertab, Pooran, Brar, Singh, & Green, 2006). As a case point, Fuchs et al. (2014) found that 32% of the 825 study participants with CD experienced a diagnostic delay of greater than 10 years. The diagnosis was considered delayed when the interval between first symptoms and diagnosis was greater than 10 years. Left undiagnosed and

untreated, CD can lead to such conditions as severe malabsorption, anemia, infertility, lymphomas and osteoporosis (Machado et al., 2013; Viljamaa et al., 2006).

Multiple factors likely play a role in the underdiagnosis of CD in the United States including a lack of recognition by PCPs of the diverse manifestations and atypical disease presentations. Gastrointestinal symptoms now represent the "typical" presentation, however, atypical and silent forms also exist and represent nearly 50% of newly diagnosed CD patients (Fasano & Catassi, 2001; Kinos et al., 2012). Some of the atypical symptoms of CD include skin rashes, fatigue, joint pain, infertility, hair loss, osteoporosis and headaches (Admou et al., 2012). Primary care providers, including nurse practitioners (NPs), play a vital role in the detection and accurate diagnosis of CD in adults and children presenting with all categories of CD symptoms. Primary care providers have the unique opportunity of caring for patients from infancy to adulthood and are well suited to recognize atypical symptoms from growth failure in infancy to infertility in adulthood. Improving awareness of the clinical spectrum of CD among NPs and increasing the use of reliable screening tools are ways to foster early recognition of CD. Aside from improved patient outcomes, benefits of accurate diagnosis include reductions in medical costs and utilization of medical services over time (Green et al., 2008).

Aims of the Project

The specific aims of this quality improvement project are: 1) to critically appraise the existing literature regarding the assessment and diagnosis of CD among primary care providers; 2) to identify current practice among local NP-PCPs related to assessment and diagnosis of CD; and 3) to provide recommendations for aligning practice among NP-PCPs with that of current clinical practice guidelines. To accomplish aims 2 and 3, a needs assessment will be conducted

to determine the knowledge and practice of NP-PCPs in this, the Dallas-Fort Worth Metroplex, geographic area. Findings will be analyzed to identify gaps between current practice and clinical guidelines. Recommendations will be made to close any gaps and align NP-PCP practice with current clinical guidelines for optimal patient outcomes. For example, priorities and resource allocations may need to be rearranged to improve the health of individuals with CD and reduce inequities. Examining NP-PCPs routines, use of clinical practice guidelines and knowledge about CD at the local level will help uncover gaps in care and/or knowledge. This information can then be used to implement strategies to improve diagnostic rates and care for individuals with CD.

Key Concepts

Atypical Symptoms

Atypical symptoms of CD involve more than just the gastrointestinal tract and can include the dermatologic, musculoskeletal, pulmonary, hepatic, renal, reproductive, autoimmune and neurological systems. Examples include osteoporosis, recurrent abortions, dermatitis herpetiformis, dental enamel hypoplasia, polyneuropathy and psoriasis (Fasano & Catassi, 2001).

Biopsy

A biopsy is the removal of cells or tissues for examination by a pathologist. A diagnosis of CD is confirmed upon finding distinguishing histological features on biopsy of the small intestine (NICE, 2015).

Case-Finding Approach

Case finding is defined as the systemic identification of people with a specific disease, in a predetermined target group, using tests, procedures or examinations that can be applied rapidly (World Health Organization, 2017). The ACG and NICE guidelines provide support for adopting

a case-finding approach by highlighting criteria patients should meet in order to undergo serological testing and biopsy (Table 1 & 2).

Celiac Disease Diagnosis

The process of diagnosing CD involves three steps 1) recognition of individuals who meet certain criteria for CD screening, 2) screening those individuals using serological tests and 3) performing a biopsy to confirm CD if the serological tests indicate CD.

Population-Wide Screening

Population wide screening seeks to promote healthy behavior in order to achieve an overall reduction of risk in the entire population. For example, offering mammography screening in women over the age of forty. Although serological screening of the general population would identify most cases of unrecognized CD, this type of screening is not currently recommended due to the lack of evidence supporting this method as a cost-effective strategy (Strong et al., 2005).

Primary Care Setting

A primary care setting is defined as an outpatient practice that provides care for the public in the form of diagnosing acute and chronic illnesses as well as providing health promotion, disease prevention, health maintenance and patient education (American Academy of Family Physicians, 2015).

Sackett's Evidence Hierarchy

Sackett's evidence hierarchy consists of levels I-V based on type of evidence. Level I is large randomized controlled trials (RCTs) with clear cut results, level II is small RCTs with

unclear results, level III is cohort and case-control studies, level IV is historical cohort or case-control studies and level V is case studies with no controls.

Screening

Screening for CD, as it relates to this project, involves performing certain serological tests such as immunoglobulin A (IgA) anti-transglutaminase (TTG) testing or deamidated gliadin peptide (DGP) IgG testing.

Typical Symptoms

Typical symptoms of CD are those that relate to the gastrointestinal tract and malabsorption. Typical symptoms are often recognized in the first two years of life (Iwanczak, Matusiewicz, & Iwanczak, 2013). Some typical CD symptoms include chronic diarrhea, anorexia, abdominal distention, abdominal pain, muscle wasting, iron deficiency anemia and failure to thrive (Iwanczak et al., 2013).

SYNTHESIS OF EVIDENCE

In order to present a comprehensive state of knowledge about recognition, screening and diagnosis of CD in the primary care setting, a literature review was performed. PubMed, Embase, and CINAHL searches were conducted, from 2003 to 2016 respectively, limited to the English language and using the mesh terms ‘celiac disease’ or ‘coeliac disease,’ ‘primary care providers’ or ‘primary care,’ ‘diagnosis,’ ‘underdiagnosis,’ ‘misdiagnosis,’ ‘guidelines’ and ‘screening’ or ‘screening tools.’ Abstracts were initially reviewed to determine the appropriateness of articles for inclusion. Relevant full-text articles were pursued resulting in 19 articles. The findings of each article were organized using an evidence appraisal table (Appendix

C) and findings were compared. The following national organization websites were also used as resources: National Institutes of Health (NIH), NICE and ACG.

In relation to the literature review below, most evidence reviewed falls under Sackett's Evidence Hierarchy level 2 and 3. Level 2 is defined as small-randomized controlled studies with unclear results and level 3 is defined as cohort and case-control studies (Burns, Rohrich & Chung, 2011).

Primary investigative studies differ in their recommendations for screening of CD by medical providers. Celiac disease does meet most of the World Health Organization (WHO) criteria for population-wide screening, however, the NIH Consensus Development Conference on CD (2004) determined there is insufficient evidence to support population wide screening (Strong et al., 2005). Due to these conclusions, the ACG (2013) advises clinicians to use a case-finding approach, as mentioned previously (Rubio-Tapia et al., 2013). A case-finding approach has been suggested by researchers since before 2007 (Ch'ng, Jones, & Kingham, 2007; Shamir, Hernell, & Leshno, 2006).

Secondary to the wide variability in CD related findings and the inability to develop algorithms that cover the complexity of the disease, Catassi and Fasano (2010) developed a quantitative approach called the "4 out of 5" rule. Using this approach, patients are diagnosed with CD if they meet "4" of the following "5" criteria: (1) typical CD symptoms; (2) positive serum CD disease IgA class autoantibodies at high titer; (3) human leukocyte antigen (HLA)-DQ2 or DQ8 genotypes; (4) response to a diet containing no gluten; and (5) duodenal CD enteropathy on biopsy (Castassi & Fasano, 2010). However, if the HLA genotype is not routinely performed, only "3" of the "4" criteria will suffice (Castassi & Fasano, 2010). This algorithm

allows patients who have signs and symptoms of CD, but refuse biopsy to be classified as having CD.

Screening for CD has been made easier and more accurate with advances in serological testing; however, many providers are not aware that patients must be on a gluten-containing diet for accurate blood test results. If a patient is on a gluten free diet they should consume two slices of wheat bread per day for two to eight weeks before a serologic test or biopsy is performed (Ludvigsson et al., 2014). Blood tests can detect the presence of specific IgA antibodies; however in 2% of patients with CD these tests will be falsely negative and IgG based tests are required (NICE, 2014). Although these tests have a high sensitivity and specificity for CD, duodenal biopsies remain the only definitive test and require a referral by the PCP to a specialist.

Although celiac disease meets WHO criteria for nation-wide screening, the majority of evidence supports a case finding approach (Rubio-Tapia et al., 2013). Several of the guidelines and research articles support serological screening of individuals with certain medical conditions associated with CD, such as irritable bowel syndrome (IBS) and iron deficiency anemia (IDA) (Mohseninejad, Feenstra, van der Horst, Woutersen-Koch, & Buskens, 2013; National Institute for Health and Care Excellence, 2015; Pelkowski & Viera, 2014). A recent cost effective analysis conducted by Mohseninejad et al. (2013) further supports serological testing in individuals with IBS.

Gaps and deficiencies in the literature include the absence of any articles including NP-PCPs in provider studies, and the fact that many of the studies were conducted outside of the United States. Unfortunately, evidence is also lacking on the accuracy of diagnosis among populations that are the most difficult to diagnose--asymptomatic patients with no risk factors for

CD. Only one of the studies reviewed focused on populations of special interest (patients with type I diabetes mellitus).

In summary, evidence clearly indicates CD is underdiagnosed by PCPs and variability in recommendations for CD screening is apparent (Barbero, McNally, Donohue, & Kagnoff, 2014; Spencer et al., 2017; Zipser et al., 2005). There appears to be a consensus on implementing a case finding approach, however, specific recommendations for exactly who to serologically test differs from one resource to the next. Both the NICE and ACG guidelines provide a diagnostic algorithm that can be used as a recourse for PCPs. While some researchers believe there should be more of a focus on screening patients with first-degree relatives who have a certain medical history, the ACG guidelines have a narrower focus. Testing for specific IgA antibodies appears to be standard across the board. No studies included NP-PCPs in their provider panel indicating a need for further research that involves these types of providers.

THEORETICAL FRAMEWORK

Theoretical frameworks offer a systematic approach to identifying logical and precisely defined relationships among variables. The Plan, Do, Study, Act (PDSA) method, also known as the Deming wheel, represents a theoretical framework that can be applied to the purpose, aims and objectives of this project (Appendix A). This framework involves a systematic series of steps used to acquire valuable knowledge for the continual improvement of an outcome or process. The PDSA cycle provides a way to assess change by following four simple steps: developing a plan, setting the plan in motion, studying the results, and making conclusions about whether the plan was successful and how improvements can be made (Agency for Healthcare Research and Quality, 2015).

The first step in the PDSA cycle is to develop a plan, therefore, ideas were formulated about how data could be collected to determine awareness of the presentations and diagnosis of CD among NP-PCPs in the Dallas-Fort Worth area. Ultimately, a survey was developed with research questions and objectives in mind. Moving forward into the Do stage, the survey was sent to local NP-PCPs after review by the University of Arizona Institutional Review Board (IRB). This step involved a local primary care nurse practitioner organization board member who posted the survey link with an announcement to recruit organization followers and members to take the survey. The remaining steps, Study and Act, were implemented once surveys were returned. The Plan, Do, Study, Act framework was chosen for its simplicity, structure for iterative assessment, wide acceptance in healthcare improvement and applicability to needs assessment.

Study Questions

The project was designed to answer the following questions:

1. Where do NP-PCPs report they obtained the majority of their knowledge regarding CD?
2. To what extent are NP-PCPs familiar with the various aspects of clinical practice guidelines for the diagnosis of CD?
3. To what extent are NP-PCPs following the various components of practice guidelines for the diagnosis of CD?
4. Are NP-PCPs aware of the typical symptoms that would suggest a diagnosis of CD?
5. Are NP-PCPs aware of the atypical symptoms that would suggest a diagnosis of CD?
6. How much experience do NP-PCPs have caring for patients with CD?

How many CD patients on average are NP-PCPs diagnosing either with gluten autoantibody blood tests or biopsy over a period of one year?

METHODS

Quality Improvement Project Design

The purpose of this quality improvement project was to determine the current knowledge and practices of NP-PCPs in relation to the diagnosis of CD. A needs assessment involving an online survey was utilized, with both multiple choice and short answer questions.

Data Collection

Qualtrics, a reliable provider of web-based survey solutions, was used to design a 29-question electronic needs assessment survey (Appendix B), developed by this author. These survey questions were designed with the aims of the project in mind and were formulated from the perspective of the respondent. The survey included questions regarding NP demographics, knowledge of CD symptoms, knowledge of guidelines for diagnosis and years of experience with CD patients. Present diagnostic practices of the NP-PCPs were investigated, including whether or not the NP-PCP is aware of current ACG and NICE guidelines. Unnecessary questions were omitted to prevent confusion. Placement of questions within the survey was also considered to optimize responses. Face validity was established by having three experts evaluate whether the survey captured the topic under investigation. After this, the survey was refined once more before being distributed to a convenience sample.

North Texas Nurse Practitioners (NTNP), a local organization, was used as a resource for participant recruitment. The NTNP network currently has 106,860 members and many followers. An executive board committee member posted the survey link with an announcement containing

the study abstract to NTNP members as well as followers. To increase response rates a second announcement was posted two weeks after sending out the initial survey link to encourage those who had not yet responded to do so.

Human Subjects Considerations

Potential risks for human subjects in this research project were considered. All identifiable information was excluded and confidentiality was upheld using anonymous data files in order to encourage complete and accurate information by responders (Alcser, Antoun, Bowers, Clemens & Lien, 2011). Response to the survey implied consent. A right of individuals to refuse participation was respected without coercion. Approval from the University of Arizona Institutional Review Board (IRB) was obtained.

RESULTS

Setting and Sample

The survey was posted to the NTNP website for both members and followers to participate in. The sample consisted of 21 NPs, regardless of experience. Three of these were removed from the sample due to responses indicating the participants were not NP-PCPs.

Data Analysis

Survey Data was uploaded to the Statistical Package for the Social Sciences (SPSS) for analysis using descriptive statistics, including measures of central tendency where appropriate. Manual checks were performed after data collection to identify any missing data and screening for outliers was conducted to prevent coding errors. No missing data and no outliers were found. Data was backed up periodically to ensure archived files did not get lost. Analysis of freeform questions was accomplished by summarizing survey responses.

Outcomes

Respondent Demographics

The majority of the respondents were female (94.4%) ranging in age from 25 to 73 years (mean 49.89, standard deviation 11.7). Most participants had a Master of Science in Nursing (72.2%), practicing as a Family Nurse Practitioner for 0 to 5 years (44.4%). Demographic data is summarized in Table 3.

TABLE 3. *Demographic Summary Table*

Gender	Female Male	94.4% (n = 17) 5.6% (n = 1)
Age	Mean Range	49.89 25 - 73
Education	MSN DNP PhD	72.2% (n = 13) 11.1% (n = 2) 16.7% (n = 3)
Years' Experience	0 – 5 years 6 – 10 years 11 – 15 years 16 or more years	44.4% (n = 8) 16.7% (n = 3) 22.2% (n = 4) 16.7% (n = 3)
Gender	Female Male	94.4% (n = 17) 5.6% (n = 1)
Age	Mean Range	49.89 25 - 73
Education	MSN DNP PhD	72.2% (n = 13) 11.1% (n = 2) 16.7% (n = 3)
Years' Experience	0 – 5 years 6 – 10 years 11 – 15 years 16 or more years	44.4% (n = 8) 16.7% (n = 3) 22.2% (n = 4) 16.7% (n = 3)

Respondents Knowledge Related to Celiac Disease

The majority of knowledge related to CD came from NP education (50%) and personal investigation (38.9%). Although a higher percentage of individuals chose NP education as their

primary source of knowledge, 61.90% asserted their education did not prepare them to properly diagnose patients with celiac disease. Figure 2 and 3 below represents this data.

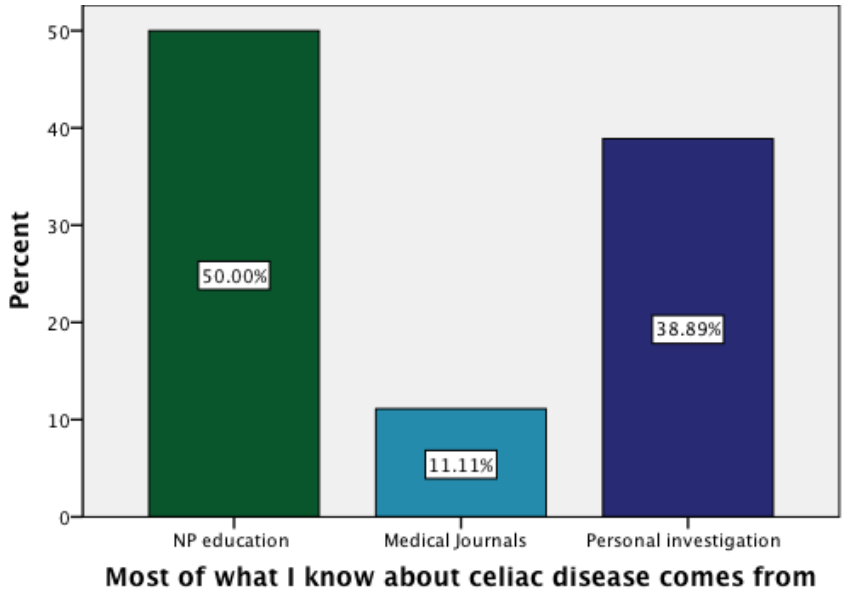


FIGURE 1. Percentages of Respondents Who Chose NP Education, Medical Journals or Personal Investigation as Their Primary Source of Knowledge Related to Celiac Disease

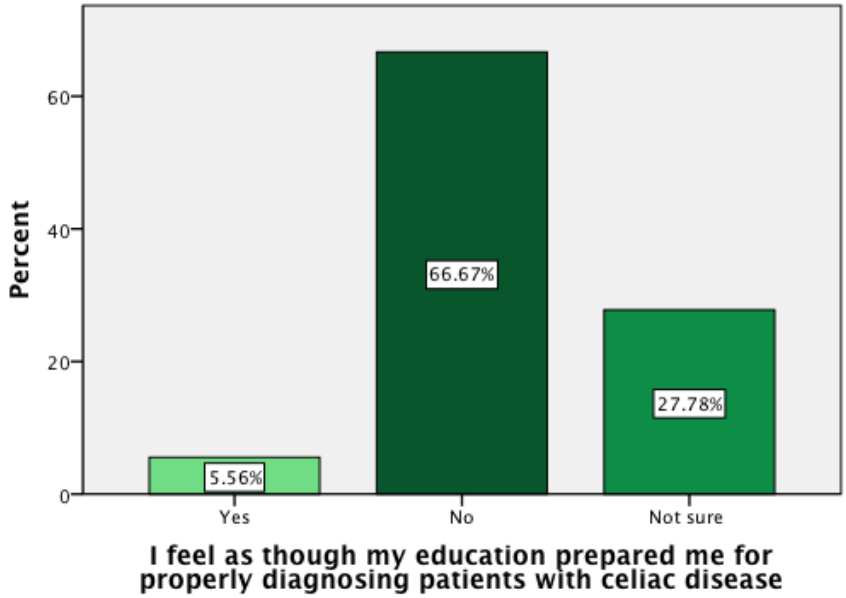


FIGURE 2. Percentages of Respondents Who Believe Their Education Did or Did Not Prepare Them to Properly Diagnose Patients with Celiac Disease.

Familiarity of Guidelines

In relation to familiarity with the ACG and NICE guidelines, percentages were the same. For both guidelines, 61.1% reported no familiarity and the remaining respondents reported only minimal familiarity. All responders who selected *minimal familiarity* with the ACE guideline also chose indicated they had minimal familiarity with the NICE guideline. If the responder chose *unfamiliar* they were unfamiliar with both guidelines. Other guidelines mentioned included the American Diabetes Association (ADA) and the American Association of Medical Endocrinologists (AACE). Table 4 represents a cross tabulation between highest level of education and familiarity of ACE guideline. The cross tabulation for the NICE guideline was identical.

TABLE 4. *Cross Tabulation Comparing the Relationship Between Familiarity of ACE Guidelines and Highest Level of Nursing Degree Obtained.*

		What is your highest nursing degree earned?			
		MSN	DNP	PhD	Total
Are you familiar with the ACE clinical guidelines for the management and diagnosis of CD?	No familiarity	8	1	2	11
	Minimal Familiarity	5	1	1	7
	Total	13	2	3	18

Knowledge of typical and atypical symptoms. The majority of respondents (72.2%) reported they are aware of the typical symptoms of celiac disease. Five of the 18 participants reported having no knowledge of the typical symptoms of celiac disease. Responders who reported knowing typical symptoms included atypical symptoms as part of their answer and two incorrectly reported constipation as a typical symptom of the disease. Interestingly, 88.9% reported they were not aware of atypical symptoms, yet several of them listed atypical symptoms under the typical symptoms of celiac disease. Only three respondents reported knowing atypical

symptoms and correctly listed at least one of these types of symptoms. Table 4 above represents a summary of typical celiac disease symptom (one, two and three) respondent results.

TABLE 5. *Percent of Responders that Reported Knowing or Not Knowing Typical Symptoms of Celiac Disease*

		Frequency	***Percent***
Valid	Yes	2	11.1
	Not sure	16	88.9
	Total	18	100.0

TABLE 6. *Typical Symptom Survey Results*

"What are three typical symptoms of celiac disease?"

		Frequency	***Percent***
Symptoms			
	Abdominal bloating	2	4.8
	Abdominal pain	7	16.7
	Abnormal stools	1	2.4
	Bloating	8	19.0
	Bloating with certain food	1	2.4
	Diarrhea	8	19.0
	Fatigue	1	2.4
	Rash	2	4.8
	Abdominal cramps	2	4.8
	Constipation	2	4.8
	Indigestion	1	2.4
	Gas	1	2.4
	Headache	1	2.4
	Malnutrition	1	2.4
	Weight loss	1	2.4
	Nausea	1	2.4
	Pain	1	2.4
	Unable to eat wheat	1	2.4
	Total	42	100.0

TABLE 7. *Percent of Responders Who Reported Knowing or Not Knowing Atypical Symptoms of Celiac Disease*

		Frequency	***Percent***
Valid	Yes	2	11.1
	Not sure	16	88.9
	Total	18	100.0

TABLE 8. *Atypical Symptom Survey Results*

"What are three atypical symptoms of celiac disease?"

		Frequency	*Percent*
Symptoms			
	Depression	1	11.1
	Fatigue	1	11.1
	Rash	2	22.2
	Weight loss	2	22.2
	Nausea	1	11.1
	Diarrhea/constipation	1	11.1
	Fatty stools	1	11.1
	Total	9	100.0

Respondent experience with celiac disease. One half (50%) of participants reported having no experience taking care of patients with celiac disease and 33.3% had only 1-5 years experience. The remaining percentages were the same (5.56%) for 6 to 10 years, 11 to 15 years and 16 or more years.

Average number of celiac disease diagnoses. Data results related to diagnostic testing revealed that the vast majority of PCPs had never tested adults (72.2%) or children (94.4%) using any celiac related blood test. Even more respondents reported never sending adult patients to a gastroenterologist for biopsy (77.8%). Only a small percentage of the PCPs (11.1%) send one to five pediatric patients a year for biopsy.

Guideline adherence. More than half of the PCPs (61.1%) reported never performing the TTG IgA blood test in patients suspected of having celiac disease. Only 22.2% of respondents reported they always perform the test. One PCP reported using a stool sample to check for antibodies. Table 9 represents a cross tabulation comparing highest level of nursing degree obtained and performance of the TTG IgA blood test in patients suspected of having CD.

TABLE 9. *Cross Tabulation Comparing Highest Level of Nursing Degree Obtained and TTG IgA Blood Testing.*

		What is your highest nursing degree earned?			
		MSN	DNP	PhD	Total
When I suspect a patient may have celiac disease I perform the TTG IgA blood test	Always	3	0	1	4
	Sometimes	1	1	1	3
	Never	9	1	1	11
Total		13	2	3	18

Approximately 44% of PCPs reported they always encourage a gluten free diet and refer patients despite negative serologies if CD is strongly suspected. Despite the fact that intestinal biopsy is the gold standard for diagnosing CD, only 38.9% of PCPs refer their symptomatic patients to a gastroenterologist. Similarly, only 33.3% refer asymptomatic patients with positive serology results for biopsy before initiating a gluten free diet. Less than half of PCPs (38.9%) reported always performing a gluten free challenge in patients suspected of having celiac disease. Similar percentages (22.2%) never initiated a gluten free challenge or did so depending on small biopsy performance or results. Of the 18 respondents, 44.4% reported never testing patients with a first-degree relative diagnosed with CD who shows signs and symptoms or laboratory evidence of celiac disease.

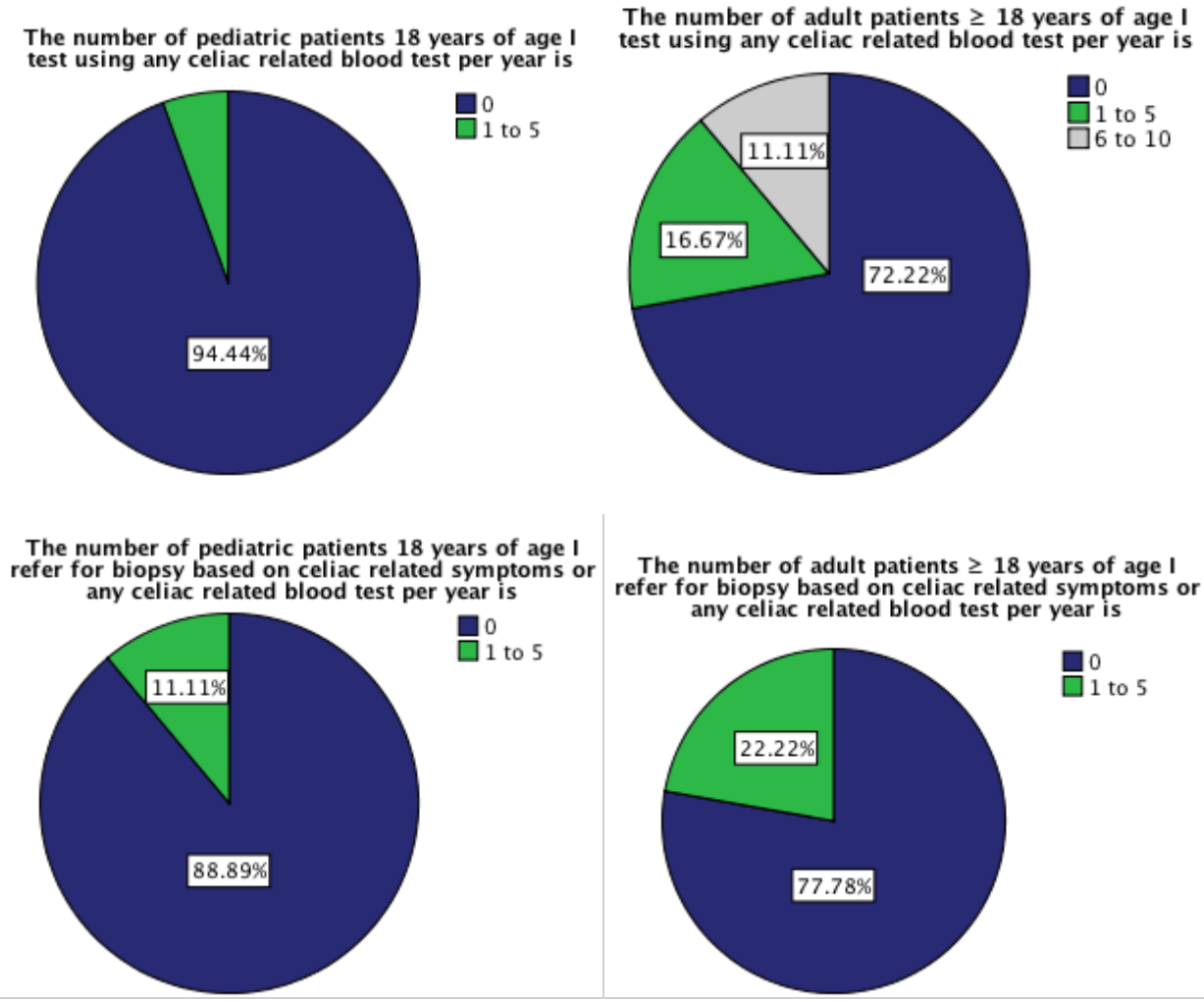


FIGURE 3. Responders Experience with Treating Celiac Disease Patients

DISCUSSION

Data analysis indicates the need for better education related to correct assessment and diagnosis of celiac disease. The majority of PCPs reported their education did not prepare them to properly diagnose celiac disease. In addition to this, most of the participants reported no familiarity with the ACG or NICE guidelines. Although the majority of primary care providers were able to identify at least three typical symptoms of CD, many of them were only able to list one atypical symptom. In addition to this, the majority of PCPs are not following the CD

guidelines. The lack of knowledge and lack of evidence based practice among PCPs has led and will continue to lead to an underdiagnosis of CD unless these issues are addressed.

Unclear terms and definitions may be attributing to the confusion around symptoms as well as assessment and diagnosis of celiac disease. For example, literature is unclear in distinguishing typical vs atypical symptoms of celiac disease. Additionally, much of the literature refers to diagnosing CD with an IgA blood test; however, the gold standard for diagnosis is a small intestinal biopsy. This in turn confuses PCPs and leads to a misunderstanding of guidelines.

Research studies regarding the underdiagnosis of CD among PCPs are limited therefore further research is warranted. In order to build a stronger evidence base it would be beneficial for future studies to focus on all primary care providers including physicians and physicians' assistants. It would also benefit to research whether or not the clinical practice guidelines are clear enough for providers to truly understand and implement.

Although this research has offered insight into the knowledge and practice of NP-PCPs in regards to celiac disease certain limitations were unavoidable. First, because of the time limit, this research was conducted on a small sample of the population who were members or followers of the NTNP association. Therefore, in order to generalize the results for larger groups the study should have involved more time and effort in recruiting survey takers. Response rates may have been better if the survey had been emailed or written surveys had been handed out at meetings instead of posted to an announcements board. Limiting respondents to NP-PCPs only represents a small portion of primary care providers and therefore results cannot be generalized to other primary care providers.

Important Implications for Practice and Education

Survey data analysis indicates the need for better education of NP-PCPs in regards to celiac disease. The majority of NP-PCPs surveyed reported most of their knowledge related to CD was obtained in their master or doctoral programs. Thus, educational programs can help improve diagnostic rates by providing NP students with an understanding of the issues surrounding CD, including underdiagnosis. Courses where the content would be beneficial include primary care and health assessment courses and could be included with other content related to gastroenterology or autoimmune disorders. It would be most beneficial to present the content in more than one course in order to increase retention rates among students (Kang, 2016). Considering the fact that CD is now acknowledged as the most common autoimmune disorder it deserves a spot among other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (Kenrick & Day, 2014). Emphasizing the prevalence of CD may bring to light the significance of this disease among others. A 20- to 30-minute lecture should be allocated to cover CD content and could replace a less common disease. Another option would be to assign students the task of researching CD on their own and then have them present their findings in discussion groups. This approach would allow students to learn about CD without taking time away from lectures. The University of Arizona does offer content on CD, but the information is limited to only a few slides. The content should be more expansive and provide clear and updated information on how to recognize, screen for and diagnose celiac disease. Lectures should touch on the atypical symptoms and silent presentation of celiac disease, as many providers are unaware of these disease features. Considering the fact that the majority of

survey takers did not follow guidelines related to CD, educators should provide students with resources such as the NICE and ACG guidelines.

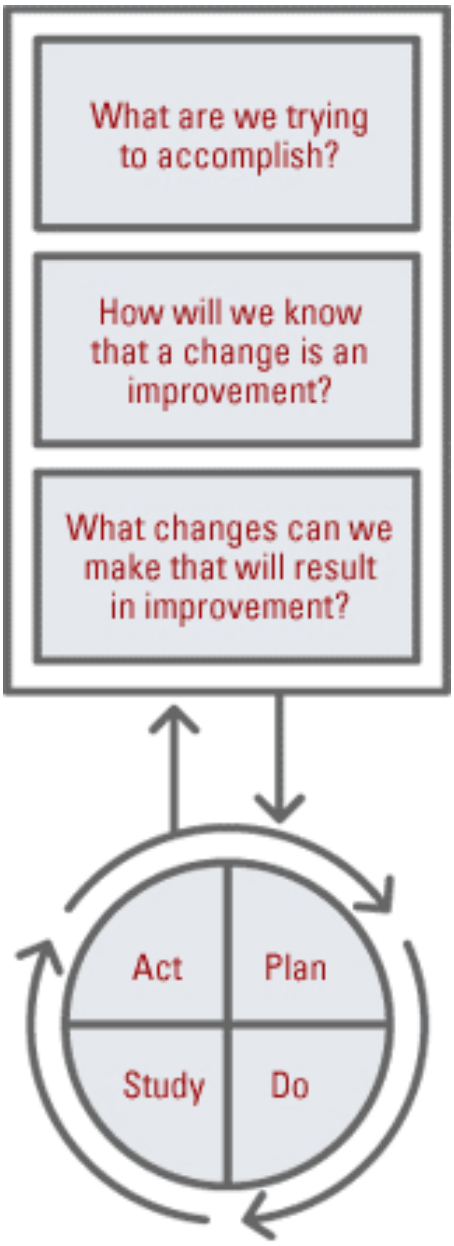
For NP-PCPs who already practice, free CD continuing medical education (CME) can be offered. In addition to this, clinicians who are aware of the high rates of underdiagnosis can advocate for patients by presenting CD related information at conferences and meetings. Furthermore, NP associations, like the one used for this project, can post important CD information to their news page. At the very least, those who are aware of the issues surrounding CD should speak to their co-workers in the medical field about these issues. A few other suggestions include providing patient brochures in offices, posting CD information to social media, working with local CD support groups and sharing CD related webinars.

Due to its prevalence and alarming rate of underdiagnosis, it is important for clinicians to be aware of CD symptoms, including atypical symptoms, and clinical practice guidelines. According to the guidelines, providers should be using the IgA TTG blood test as their first choice in all patients over the age of two who are suspected of having celiac disease. However, clinicians need to ensure that the patient is on a gluten containing diet before testing. Furthermore, although false negative test results are rare (1-2%), they can occur due to factors such as patient age less than two years, laboratory error, reduction or elimination of gluten from the diet, selective IgA deficiency and use of corticosteroids (Rashid & Lee, 2016). If the blood test is negative and the provider has a strong suspicion of CD, he or she should discuss the option for intestinal biopsy with the patient. Another reason the provider may want to discuss biopsy is if the patient already commenced a gluten free diet prior to conduction of serological testing. If the patient does not agree to a biopsy at the very least providers should encourage a gluten free

dietary trial. Clinicians should also place importance on a family history of CD and consider other related comorbidities. Celiac disease prevalence has increased fourfold over the last 10 to 20 years, therefore underdiagnosis is only going to become a greater issue if it remains unaddressed.

APPENDIX A:

PDSA MODEL FOR QUALITY IMPROVEMENT



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APPENDIX B:

SURVEY QUESTIONS

SURVEY QUESTIONS

1. What is your gender?

    a. Female

    b. Male

    c. Prefer not to answer

2. What is your age? _____

3. How many years have you been practicing as a primary care provider?

    a. 0 to 5 years

    b. 6 to 10 years

    c. 11 to 15 years

    d. 16 or more years

4. What best describes your role in primary care practice?

    a. Family Nurse Practitioner

    b. Pediatric Nurse Practitioner

    c. Adult-Gerontology Primary Care Nurse Practitioner

    d. Other (please explain) _____

5. What is your highest nursing degree earned?

    a. Master of Science in Nursing

    b. Doctor of Nursing Practice

    c. Certificate

    d. Other (please explain) _____

The following questions pertain to your knowledge of and practice related to celiac disease:

6. Most of what I know about celiac disease comes from

a. NP education

b. Medical journals

c. Personal investigation

d. CME/Other (please explain) _____

7. I feel as though my education prepared me for properly diagnosing patients with celiac disease

a. Yes

b. No

c. Not sure

8. How many years of experience do you have taking care of patients with celiac disease?

a. 0 years

b. 1 to 5 years

c. 6 to 10 years

d. 11 to 15 years

e. 16 or more years

For the next few questions we are interested in your current awareness of celiac disease. We realize that if there was a need you could and would look up this information, but for now just respond to the questions as written and proceed.

9. Off the top of your head, do you know what the typical symptoms of celiac disease are?

a. Yes

b. Not sure

10. If yes, what are three typical symptoms of celiac disease (fill in the blank)

a. _____

b. _____

c. _____

11. Off the top of your head do you know what the atypical symptoms of celiac disease are?

a. Yes

b. Not sure

12. If yes, what are three atypical symptoms of celiac disease (fill in the blank)

a. _____

b. _____

c. _____

13. The number of adult patients ≥ 18 years of age I test using any celiac related blood test per year is

a. 0

b. 1 to 5

c. 6 to 10

d. 11 to 15

e. 16 or more

14. The number of adult patients ≥ 18 years of age I refer for biopsy based on celiac related symptoms or any celiac related blood test per year is

a. 0

b. 1 to 5

c. 6 to 10

d. 11 to 15

e. 16 or more

15. The number of pediatric patients < 18 years of age I test using any celiac related blood test per year is

a. 0

b. 1 to 5

c. 6 to 10

d. 11 to 15

e. 16 or more

16. The number of pediatric patients < 18 years of age I refer for biopsy based on celiac related symptoms or any celiac related blood test per year is

a. 0

b. 1 to 5

c. 6 to 10

d. 11 to 15

e. 16 or more

17. Are you familiar with the American College of Gastroenterology (ACG) Clinical Guidelines for the diagnosis and management of celiac disease? Please answer this question using a 5-point scale ranging from one to 5 with one indicating no familiarity, 2 being a very low degree of familiarity and 5 being extremely familiar. _____

1----------2----------3----------4----------5

unfamiliar minimal familiarity some familiarity moderately familiar extremely familiar

18. Are you familiar with the National Institute for Clinical Excellence (NICE) Clinical Guidelines for the diagnosis and management of celiac disease? Please answer this question using a 5-point scale ranging from one to 5 with one indicating no familiarity, 2 being a very low degree of familiarity and 5 being extremely familiar. _____

1----------2----------3----------4----------5
unfamiliar minimal familiarity some familiarity moderately familiar extremely familiar

19. Are you aware of and familiar with any other Clinical Guidelines for the diagnosis and management of celiac disease? If so, please indicate what those guidelines are:
    Guideline (please specify): _____
20. Please indicate your familiarity of this guideline using a 5-point scale ranging from 1 to 5 with 1 being a very low degree of familiarity and 5 being extremely familiar. _____

1----------2----------3----------4----------5
unfamiliar minimal familiarity some familiarity moderately familiar extremely familiar

21. When I suspect a patient may have celiac disease I perform a blood test
    a. Always
    b. Sometimes
    c. Never
22. If you always or sometimes perform a blood test, what blood test(s) do you perform?_____
23. When I suspect a patient may have celiac disease I ensure they are on a gluten containing diet before I perform the TTG IgA or alternate blood test
    a. Always
    b. Sometimes

c. Never

24. Even if celiac serologies are negative, if I strongly suspect celiac disease, I refer the patient for intestinal biopsy

    a. Always

    b. Sometimes

    c. Never

25. I refer to a gastroenterologist before performing any serological screening tests if I suspect a patient may have celiac disease

    a. Always

    b. Sometimes

    c. Never

26. In symptomatic patients, to establish the diagnosis of celiac disease I refer to a gastroenterologist for a biopsy before initiating a gluten free diet

    a. Always

    b. It depends on the TTG IgA, DGP IgG or IgA EMA results

    c. Never

    d. Other (please explain) _____

27. In asymptomatic patients, who have positive markers by screening I refer for a biopsy before initiating a gluten free diet

    a. Always

    b. It depends on the TTG IgA, DGP IgG or IgA EMA results

    c. Never

d. Other (please explain) _____

28. I perform a gluten free challenge in patients suspected to have celiac disease

a. Always

b. Never

c. If a small bowel biopsy is not performed or if biopsy results are not definitive

d. Other (please explain) _____

29. I test patients with a first-degree relative who has a confirmed diagnosis of celiac disease if they show signs or symptoms or laboratory evidence of celiac disease

a. Always

b. Sometimes

c. Never

APPENDIX C:

RESULTS OF LITERATURE REVIEW: EVIDENCE APPRAISAL

Author / Article	Qual: Concepts or phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/tools)	Findings
Zipser, R. D., Farid, M., Baisch, D., Patel, B., & Patel, D. (2005). Physician awareness of celiac disease: a need for further education. *Journal of General Internal Medicine, 20*(7), 644-646. doi: 10.1111/j.1525-1497.2005.0107.	What do internists and family physicians know about CD? Is there a need for further education for PCPs regarding CD? How often are PCPs diagnosing CD?	Qualitative study design	PCPs N = 132 Patients N = 2,440	Surveys Questionnaires	Patient surveys indicated only 11% were diagnosed by PCPs versus 65% diagnosed by gastroenterologist Physician surveys showed only 35% of PCPs had ever diagnosed CD, only 32% knew onset of symptoms of CD in adulthood is common, 54% knew that fatigue is a symptom, 24% knew depression and irritability are symptoms, only a small percentage knew that diabetes, anemia, and osteoporosis are associated with CD

Catassi, C., Kryszak, D., Louis-Jacques, O., Duerksen, D. R., Hill, I., Crowe, S. E., . . . Fasano, A. (2007). Detection of Celiac disease in primary care: a multicenter case-finding study in North America. *American Journal of Gastroenterology, 102*(7), 1454-1460. doi: 10.1111/j.1572-0241.2007.01173.x	Would performing active case finding strategies in primary care increase the frequency of CD diagnosis? Variables: - Active case finding strategy (independent variable) - Frequency of CD diagnosis (dependent variable)	Multicenter Prospective Study	N = 976 Women = 737 Men = 239 Median Age = 54.3 yrs	Marsh Classification Patient recrutement Inclusion and exclusion criteria Questionnaires Serological testing Anti-tTG antibodies were measured using an ELISA method, if elevated EMA performed, if positive pt asked to get a biopsy Statistical analysis	Diagnosis of CD occurred in 22 of the 976 patients, the majority of which were women The most frequent reason for CD screening was secondary to bloating, thyroid disease, IBS, unexplained chronic diarrhea, chronic fatigue and constipation The prevalence of CD in the overall screened sample was 2.25% (95% CI 1.32–3.18) Diagnostic rates significantly increased during the study period to 8.6 per thousand visits (95% CI 5.0–12.1, $P < 0.001$) and to 11.6 per thousand visits (95% CI 6.8–16.4, $P < 0.001$), calculated on either 2,568 subjects (overall study population) or 1,902 subjects; excluding the 666 individuals that were eligible for the study but refused the serological screening test Most frequent risk factors for undiagnosed CD: - Thyroid disease - Positive family history - Persistent GI complaints

Korponay-Szabo, I. R., Szabados, K., Pusztai, J., Uhrin, K., Ludmany, E., Nemes, E., . . . Maki, M. (2007). Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. *BMJ, 335*(7632), 1244-1247. doi: 10.1136/bmj.39405.472975.80	Does screening for coeliac disease by rapid detection of IgA antibodies to tissue transglutaminase in primary care improve diagnostic accuracy and rates?	Quantitative study	N = 2690	District nurses used to screen all 6 yr olds in their care due to start school in 2005 Whole blood from finger prick w/ results in 5-10 min If positive referred for small bowel biopsy 80ul of blood obtained for laboratory determination of IgA antibodies to endomysium and transglutaminase in plasma	Antibodies to transglutaminase detected in 28 children by onsite rapid testing - 25 of these children underwent biopsy and were found to have CD CD was newly diagnosed in 32 of the screened children (24 girls/8boys) None of the 32 children diagnosed w/ CD had been judged chronically ill or sent to a gastroenterologist by their PCP, however 27 of the 32 pts showed had clinical problems commonly seen with undiagnosed CD (underweight, iron deficiency anemia, autoimmune thyroid disease) Indicates that this rapid method for testing is an efficient way to find new cases and can be performed by PCP/nurses

Van der Windt, D. A., Jellema, P., Mulder, C. J., Kneepkens, C. M., & van der Horst, H. E. (2010). Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA, 303*(17), 1738-1746. doi: 10.1001/jama.2010.549	Objective: summarization of evidence on performance of diagnostic tests for identifying CD in adults complaining of abd. symptoms in the primary are setting	Systematic Review MEDLINE (beginning Jan 1996), EMBASE (Jan 1947-Dec 2009), manual search for references	133 full articles retrieved 16 studies included (N = 6085)	Primary care was setting of interest Diagnostic studies selected if 1. Cohort or nested case-control design 2. Enrolled adults presenting with non-acute abd. Symptoms 3. CD prevalence of 15% or less 4. Tests used included GI symptoms and serum antibody tests Quality Assessment of Diagnostic Accuracy Studies tool Data extraction	Conclusion: IgA antitissue transglutaminase antibodies and IgA antiendomysial antibodies have high sensitivity and specificity for diagnosing CD in adult pts presenting to their PCPs with abdominal pain Diarrhea: sensitivity (0.27 – 0.86), specificity (0.21 – 0.86) IgA antiendomysial antibodies sensitivity (0.90) and specificity (0.99) 95% CI

Viljamaa, M., Collin, P., Huhtala, H., SievÄNen, H., MÄKi, M., & Kaukinen, K. (2005). Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Alimentary Pharmacology and Therapeutics, 22*(4), 317-324. doi: 10.1111/j.1365-2036.2005.02574.x	Is celiac disease screening in risk groups justified?	Prospective cohort study design conducted in Finland	N = 53 (53% women) Median age = 51 years	Comparisons made to 3 different control groups 1. 44 randomly selected symptoms detected, biopsy proven CD pts 2. 54 untreated CD pts 3. 110 individuals without known CD diagnosis QOL and GI symptoms assessed using questionnaires Dietary adherence assessed using interview/dietary recall	Median age of CD diagnosis was 39 yrs in both screen and symptom detected pts Most screen detected individuals were tested secondary to family hx of CD Adherence to gluten free diet occurred in 96% of screen detected pts and 93% of symptoms detected pts Dietary compliance not associated with age of diagnosis, follow-up time, age, family hx of CD, GI symptoms or QOL in both groups QOL did not differ in screen detected vs. symptoms detected vs. non-celiac controls –untreated pts w/ CD >GI symptoms and <QOL Laboratory results did not differ significantly between groups Osteoporosis found more commonly in symptom-detected pts In conclusion: excellent dietary compliance in screen detected CD pts after long-term tx, therefore active screening seems to be reasonable

Verkasalo, M. A., Raitakari, O. T., Viikari, J., Marniemi, J., & Savilahti, E. (2005). Undiagnosed silent coeliac disease: a risk for underachievement? Scandinavian Journal of Gastroenterology, 40(12), 1407-1412. doi: 10.1080/00365520510023792	What are the complications of untreated celiac disease in a well-defined cohort of Finnish adults? Is there a need for population based screening?	Cohort study	N = 2,427	Subjects attending a follow-up visit of the study "Cardiovascular Risk in Young Finns" completed a questionnaire on their social situation, health, diet, and family life Each subject underwent a physical examination in which they were tested for CD using IgA-endomysium and IgA-transglutaminase antibodies	21 subjects had CD No differences in age, gender, weight, stature, medical diagnosis, physical activity, or alternative medications between groups (silent vs. no CD) Those with silent CD had lower serum HDL-cholesterol and fewer had a university degree or worked in a managerial/professional position Conclusion: possible association between untreated CD and depressive/disruptive behaviors in teenagers/adults Limitations: no intestinal biopsies performed to confirm CD diagnosis

Sanders, D. S., Patel, D., Stephenson, T. J., Ward, A. M., McCloskey, E. V., Hadjivassiliou, M., & Lobo, A. J. (2003). A primary care cross-sectional study of undiagnosed adult coeliac disease. *European Journal of Gastroenterology and Hepatology, 15*(4), 407-413. doi: 10.1097/01.meg.0000050023.34359.20	What is the prevalence of CD in the general population? What is the prevalence of CD in those with irritable bowel syndrome, iron deficiency anemia, fatigue, and other celiac related conditions?	Primary-care based cross-sectional study in UK	N = 1,200 Male (447) Female (753)	Random selection of patients attending one of five practices in South Yorkshire Health study questionnaires- hx of anemia, osteoporosis, type I dm Rome II symptom based diagnostic criteria was used for IBS assessment IgG/IgA antigliadin antibodies and endomysial antibody (EMA) used for initial CD testing- if + offered smll bowel biopsy	23 had positive IgA antigliadin antibody or IgA EMA results and were referred for biopsy (22 underwent procedure) 12 were confirmed to have CD Prevalence of CD in this primary care population is 1%; consistent with US statistics Prevalence of CD among those with IBS was 3.3% Three of the 64 pts with iron deficiency anemia has CD also 5 of the 12 CD pts had a normal health questionnaire

Mohseninejad, L., Feenstra, T., van der Horst, H. E., Woutersen-Koch, H., & Buskens, E. (2013). Targeted screening for Coeliac Disease among irritable bowel syndrome patients: analysis of cost-effectiveness and value of information. *European Journal of Health Economics, 14*(6), 947-957. doi: 10.1007/s10198-012-0441-4	What is the cost effectiveness of screening for CD in patients with diarrhea/mixed type IBS in terms of cost per QALY in the Netherlands?	Cost effectiveness analysis	N = 75,000 6,251 which would undergo biopsy- 4,380 cases of CD	Decision model used to reflect possible trajectories over the life span of a cohort of IBS pts Sensitivity analysis performed (one-way, probabilistic)	Conclusion: results indicated screening for CD in IBS/mixed pts is a cost effective way of improving QOL/health for pts compared to having no structured testing strategy
Green, P. H., Neugut, A. I., Naiyer, A. J., Edwards, Z. C., Gabinelle, S., & Chinburapa, V. (2008). Economic benefits of increased diagnosis of celiac disease in a national managed care population in the United States. *Journal of Insurance Medicine, 40*(3-4), 218-228.	To estimate the rate of CD diagnosis in the U.S. Evaluate the economic benefits of diagnosis	Retrospective cohort study	N = 10.2 million managed care members	4 different study cohorts used to compare direct standardized relative value based medical costs and utilization of certain health care services	Increased rates of celiac disease diagnosis leads to a reduction in standardized RVU-based medical costs and utilization of healthcare services
Ress, K., Harro, M., Maaroos, H. I., Harro, J., Uibo, R., & Uibo, O. (2007). High prevalence of coeliac disease: need for increasing awareness among physicians. *Dig Liver Dis, 39*(2), 136-139. doi: 10.1016/j.dld.2006.07.012	Objective: To determine if the awareness of CD is low in primary care providers and to determine the prevalence of CD in a population of schoolchildren of Estonia	Cross sectional study	N = 1160 (636 female & 564 male)	Tissue transglutaminase antibody immunoassay	Five subjects had antibodies, four agreed to have a biopsy which showed CD The prevalence in Estonia is comparable to areas in other parts of the world There is a need for increased awareness among PCPs

Norstrom, F., Lindholm, L., Sandstrom, O., Nordyke, K., & Ivarsson, A. (2011). Delay to celiac disease diagnosis and its implications for health-related quality of life. *BMC Gastroenterol, 11*, 118. doi:10.1186/1471-230X-11-118	To determine how the delay in CD diagnosis has developed during recent decades and how this affects the burden of disease in terms of health-related quality of life (HRQoL) Consider the differences in findings with respect to age and sex	Cross-sectional questionnaire survey	CD subjects N = 1, 031 General population survey N = 27, 809 Randomly selected members from the Swedish Society of Celiacs in 2009 with a CD diagnosis based on medical expertise Divided into equal-sized age and sex strata	HRQoL measured with EQ-5D descriptive system and then translated to QALY scores General adult population survey used as comparison	Mean delay from the onset of symptoms indicative of CD to diagnosis was 9.7 years, median delay was 4 years Mean delay from first visit to a doctor due to CD-related symptoms to diagnosis was 5.8 years, median delay 1 year For each five year age group except for those younger than 20, no age group had a shorter mean delay than 6 years During recent decades mean delay from onset of CD-related symptoms to diagnosis has increased from 1 year for those diagnosed before 1980 and 5 years for those diagnosed from 2005-2009 Anxiety/depression within the EQ-5D descriptive system differed most negatively for untreated CD patients when compared to the general population EQ VAS scores also improved after diagnosis Females had lower QALY scores than males for CD population pre-treatment and today

Popp, A., Jinga, M., Jurcut, C., Balaban, V., Bardas, C., Laurila, K., . . . Maki, M. (2013). Fingertip rapid point-of-care test in adult case-finding in coeliac disease. *BMC Gastroenterology, 13*, 115. doi:10.1186/1471-230X-13-115	Would a fingertip rapid point-of-care test help in case finding of CD?	Primary-care based cross-sectional study in Romania	N = 148 18 children, 130 adults, median age 36 years	170 first-degree relatives of 70 index cases were invited to participate Biocard Celiac Test, AniBiotech, Vantaa, Finland was the PCOT used Screened for presence of CD IgA-class antiendomysial antibodies, if positive sample further evaluated for TG2-IgA using ELISA, if positive endoscopy with small-bowel biopsy recommended	12 out of 148 first degree healthy relatives had positive POCTs, all of these also were EMA positive 100% specificity for POCT against reference standard for serum CD autoantibody 10 of 13 antibody positive 1st degree relatives agreed to undergo biopsy and of these all but one showed celiac mucosal lesions POCT was positive in 8 out of 9 biopsy proven CD subjects Supports use of POCT in correctly identifying individuals, even with silent CD, who should undergo confirmatory duodenal biopsies

Wakim-Fleming, J., Pagadala, M. R., Lemyre, M. S., Lopez, R., Kumaravel, A., Carey, W. D., & Zein, N. N. (2013). Diagnosis of celiac disease in adults based on serology test results, without small-bowel biopsy. *Clinical Gastroenterology & Hepatology, 11*(5), 511-516. doi:10.1016/j.cgh.2012.12.015	Aimed to estimate the frequency at which adult patients with positive serology tests are referred for small bowel biopsies Identify factors that improve the diagnosis of celiac disease	Retrospective data analysis	N = 2, 477	Retrospective analysis of data from subjects who received serology tests for CD between 2005-2007 Results analyzed for total levels of IgA, IgA against hTTG, IgA & IgG against gliadin and dilution titers of IgA against EMA Samples analyzed by pathologist who specialize in detecting mucosal changes associated with CD	Adult symptomatic patients with CD can be detected in the absence of a small-bowel biopsy by testing serum for IgAhTTG greater than 118 U or 21 to 118 U in combination with an EMA dilution titer of 1:160 or greater Lack of small-bowel biopsy in patients with abnormal serum celiac antibody levels is likely contributing to the underdiagnosis of CD
Rubio-Tapia, A., Kyle, R. A., Kaplan, E. L., Johnson, D. R., Page, W., Erdtmann, F., . . . Murray, J. A. (2009). Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology, 137*(1), 88-93. doi:10.1053/j.gastro.2009.03.059	Is undiagnosed CD associated with excess mortality? Has the prevalence of CD dramatically increased over the past 50 years?	Cohort study conducted in the U.S.	Sera obtained from 1948 to 1954 Warren Air Force Base (WAFB) cohort total = 9, 133 Present day cohort (similar years of birth) total = 5,558 Present day cohort (similar age at sampling) total = 7, 210	Serum from 3 cohorts tested for tissue transglutaminase antibodies (tTGA) by enzyme-linked immunosorbent assay, if abnormal serum was tested for endomysial antibodies by indirect immunofluorescence Testing had a sensitivity of 97% and specificity of 100% Undiagnosed CD was found in 1 in 121 persons for the present day cohort and 1 in 652 persons for the WAFB cohort	Prevalence of undiagnosed CD was 4.5 higher in the younger present day cohort and 4 times higher in the older present day cohort compared to the WAFB cohort Undiagnosed CD was found to be associated with close to a 4-fold increased risk of mortality compared to those with no serological evidence of CD In the past 50 years the prevalence of CD appears to have increased dramatically in the U.S.

Locke, G. R., 3rd, Murray, J. A., Zinsmeister, A. R., Melton, L. J., 3rd, & Talley, N. J. (2004). Celiac disease serology in irritable bowel syndrome and dyspepsia: a population-based case-control study. *Mayo Clinic Proceedings, 79*(4), 476-482. doi: 10.4065/79.4.476	Is undiagnosed CD associated with IBS or dyspepsia in a Minnesota community?	Qualitative	N = 260	Self-report bowel disease questionnaire Subjects examined by clinicians and medical charts reviewed Measured antiendomysial antibodies and tissue transglutaminase (TTg) IgA antibodies using validated assays	Dyspepsia found in 34 subjects, 50 had IBS, and 15 had both Two of 24 subjects with dyspepsia were seropositive for TTg, 2 of 50 were positive in IBS subjects Celiac disease did not explain the presence of IBS or dyspepsia in this community
Hadithi, M., von Blomberg, B. M., Crusius, J. B., Bloemena, E., Kostense, P. J., Meijer, J. W., . . . Pena, A. S. (2007). Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Annals of Internal Medicine, 147*(5), 294-302.	What is the accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease?	Prospective cohort study	Total: 463 Celiac disease or gluten-sensitive enteropathy: 16	Serologic tests performed on patients after undergoing a small bowel biopsy IgA, IgG and TGA tested using ELISA EMA tested for by indirect immunofluorescence assay CD diagnosed if biopsy results showed Marsh III and clinical resolution after initiation of GF diet- no follow-up biopsy performed	TGA & EMA tests either alone or in combination were specific and, compared to the other four serum antibody tests, were the most sensitive. HLA-DQ2 or HLA-DQ8 tests were 100% sensitive Either TGA & EMA or HLA-DQ typing should be performed, combining the two does not improve performance Data confirms that the absence of HLA-DQ2 and/or HLA-DQ8 virtually excludes the diagnosis of CD

Hopper, A. D., Cross, S. S., Hurlstone, D. P., McAlindon, M. E., Lobo, A. J., Hadjivassiliou, M., . . . Sanders, D. S. (2007). Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ, 334*(7596), 729. doi:10.1136/bmj.39133.668681.BE	To find an effective diagnostic method of detecting all cases of CD in patients undergoing gastroscopy without performing a duodenal biopsy	Retrospective cohort study	N = 2, 000	Data from 1, 464 patients undergoing gastroscopies and a duodenal biopsy were analyzed in order to devise a clinical decision tool Clinical decision tool included pre-endoscopy serological testing and identification of high risk patients in order to target patients needing a duodenal biopsy	Clinical decision tool showed a sensitivity of 100% with no missed CD diagnoses Confidence interval 5% Limitations: Performed in a secondary care, not a primary care setting
Berti, I., Della Vedova, R., Paduano, R., Devetta, M., Caradonna, M., Villanacci, V., . . . Ventura, A. (2006). Coeliac disease in primary care: evaluation of a case-finding strategy. *Digestive & Liver Disease, 38*(7), 461-467. doi:10.1016/j.dld.2005.12.007	What is the feasibility and cost-effectiveness of a case-finding approach for early detection of celiac disease among primary care providers?	Case finding approach	N = 1, 041 adults & 447 children Total = 1, 488 69 PCPs & 60 pediatricians enrolled	Enrollment criteria established Serum IgA anti-human-tTG antibodies assayed IgG anti-human-tTG when indicated Blind assay of serum IgA anti-endomysium Intestinal biopsy using Marsh's classification Pre and post-study questionnaire to assess knowledge of PCPs in regards to CD	31 participants were diagnosed with CD (19 adults, 12 children) No CD diagnoses by the participating doctors prior to the study, however, 29 patients were diagnosed the year after the study by the same PCPs Prevalence of confirmed CD increased in both the adults and children Approximate cost per new diagnosis of CD was roughly 923.25 euros (983.99 in US dollars) Researchers concluded that a case-finding approach is both feasibly and is more cost-effective than population wide screening Also increased awareness of CD among PCPs

Bakker, S. F., Tushuizen, M. E., Stokvis-Brantsma, W. H., Aanstoot, H. J., Winterdijk, P., van Setten, P. A., . . . Simsek, S. (2013). Frequent delay of coeliac disease diagnosis in symptomatic patients with type 1 diabetes mellitus: clinical and genetic characteristics. *European Journal of Internal Medicine, 24*(5), 456-460. doi:10.1016/j.ejim.2013.01.016	Aim of the study was to investigate clinical and genetic characteristics of patients with both celiac disease and type I diabetes in order to help with better detection of celiac disease in patients with type I diabetes	Retrospective cross sectional study	N = 118	Identification of pts with CD and type I DM by internists, pediatricians and gastroenterologists Recruitment of patients with both diagnoses to participate through advertisements in journals Participants interviewed by a single investigator Serum for typing of HLA-DQA1 & DQB1 Mann-Whitney *U* test Fisher's exact test	Majority of pts diagnosed with type I DM before CD Peak incidence of CD diagnosis was 10 years and 45 years Women diagnosed with CD at a younger age than men Age of onset of type I DM among men and women was equal Delay of CD diagnosis frequently found in adult type I DM patients

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