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Best Practice for Screening Adult Patients with Psoriasis for Polyautoimmunity: Celiac Disease, Rheumatoid Arthritis and Crohn's Disease

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Best Practice for Screening Adult Patients with Psoriasis for Polyautoimmunity:
Celiac Disease, Rheumatoid Arthritis and Crohn's Disease

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Abstract

The purpose of this quality improvement project was to determine if screening primary care patients with psoriasis will improve early detection of celiac disease (CD), rheumatoid arthritis, and Crohn's disease (CrD). The aim of this project is to assess the utility of early screening in patients with psoriasis in order to facilitate earlier diagnosis of CD, RA and CrD, which would consequently initiate earlier treatment and improve long-term patient outcomes. Genetic and population-based studies suggest that individuals with psoriasis have a greater risk of also having CrD, CD or RA, than do individuals without psoriasis. The literature also suggests that health care providers would be prudent to evaluate psoriatic patients in a prospective manner for these AI disorders in order to improve the patient's long-term health outcomes.

Based on the literature, the DNP project investigator developed a non-psychometric patient questionnaire to capture data including the signs and symptoms of CD, CrD and RA and three referral algorithms (one each per CD, CrD and RA). Over two weeks at a Northern Virginia dermatology clinic, the patient questionnaire was delivered to 261 adult patients, of which 34 were identified as psoriatic or newly diagnosed.

Findings indicated 100% provider compliance documentation for all 34 patients noting that the patient a) had been screened, and b) if referral was or was not indicated. Frequency data indicated that the most reported symptom was a history of vitamin D deficiency (38.24%). Thirty percent of psoriatic patients reported having a first-degree relative with celiac disease, Crohn's disease or rheumatoid arthritis. The most frequently reported symptoms were for rheumatoid arthritis: daily joint or muscle pain > 6 weeks (29.41%), daily tender or swollen joints > 6 weeks (23.53%), and weakness or fatigue > 6 weeks (23.53%). The most reported GI symptom was abdominal distention and/or bloating after eating (14.71%). The least reported symptoms, at 2.94% each, were abdominal pain after eating, painful bowel movements, and running a fever in the past 4 weeks. This quality improvement project highlights the need to evaluate adult patients with psoriasis for polyautoimmunity and familial autoimmunity and is consistent with the literature that recommends screening for these polyimmune relationships.

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Chapter 1

Background and Significance

1.1 Introduction

Autoimmune (AI) diseases refer to a collection of diseases where the immune system mistakenly directs the body to attack its own healthy organs, tissues, and blood, rather than the foreign organisms the immune response was designed to combat. The result is impaired function of the targeted organ or system. The National Institute of Health ([NIH], 2005) has identified more than 80 clinically distinct autoimmune disorders, while the American Autoimmune Related Disease Association ([AARDA], 2011) recognizes greater than 100 known autoimmune diseases. Psoriasis, a chronic, inflammatory skin disease, is known to be the most prevalent AI disease in humans (Raychaudhuri, 2014), affecting approximately 2-5% of the world population and as many as 7.5 million Americans (NIH, 2005).

Psoriasis belongs to a subset of AI diseases classified as Immune-Mediated Inflammatory Diseases (IMIDs) (Rahman, Inman, El-Gabalawy & Krause, 2010). The concept of IMIDs describes a group of seemingly unrelated clinical disorders that share common inflammatory pathways. While all IMIDs are AI diseases, the reverse is not also true; all AI diseases are not IMIDs. Central to the disease process in IMIDs is the imbalance and dysregulation of cytokine production (Rahman et al., 2010; Kuek,

Hazleton & Astor, 2007; Williams & Meyers, 2002). Cytokines play a pivotal role in normal immune function. When these molecules are inappropriately expressed, chronic inflammatory conditions arise. Celiac Disease (CD), Rheumatoid Arthritis (RA) and Crohn's Disease (CrD) also belong to this subset.

Another relatively new concept in the autoimmune field is polyautoimmunity, which is defined as the coexistence of more than one AI disease, or IMID, in a single individual (Rojas-Villarraga, Amaya-Amaya, Rodriguez-Rodriguez, Mantilla, & Anaya, 2012; Anaya, 2014). Research suggests that individuals with one autoimmune disease typically will develop an additional one or more separate, and distinct, autoimmune diseases over the course of their lifetime (Cooper, Bynum & Somers, 2009). Recent population-based studies, as well as studies that have identified common genes associated with multiple AI disorders, lend credibility to this idea that polyautoimmunity is not random, and that there is a true association between different AI disorders. Specifically, studies suggest that individuals with psoriasis have a greater risk of also having another IMID, such as CrD, CD or RA, than do individuals without psoriasis (Augustin, Reich, Glaeske, Schaeffer & Radtke, 2010; Bhatia, Millsop, Debbanch, Koo, Linos & Liao, 2014; Birkenfeld, Dreiher, Weitzman & Cohen, 2009; Cohen, Dreiher & Birkenfeld, 2009; Damasiewicz-Bodzek & Wielkoszynski, 2008; Einarsdottir et al., 2009; Li, Han, Chan & Qureshi, 2013; Makredes, Robinson, Bala & Kimball, 2009; Qui, Z., Zhang, X. Qui, Zhou & Li, 2013; Radtke et al., 2015; Tsai et al., 2011; Tsoi et al., 2013; Wolf et al., 2008; Wu, Nugyen, Poon & Herrington, 2012).

Although these advances in research have fostered a greater understanding of autoimmunity in the health care community, AI diseases continue to be one of the most

clinically difficult to recognize categories of disease. According to the AARDA (2011), it can take patients an average of five years and four health care professionals to obtain a correct diagnosis. Diagnostically, IMIDs remain a challenge for both patients and health care providers. The initial presentation of symptoms may be vague and confused with other disease processes (AARDA, 2011). Additionally, health care professional education provides minimal training about AI diseases, contributing to a poor understanding of autoimmunity among primary health care providers. As a result, despite the proven genetic component in AI disease, health care practitioners do not typically inquire whether patients have a personal or family history of autoimmune diseases, or screen for additional autoimmune diseases in the autoimmune patient. Lastly, there are very few standardized tests for many of the 80-100 AI diseases (AARDA, 2011). These gaps of knowledge represent lost opportunity for the patient whose disease process remains unchecked and whose associated AI co-morbidities also go unaddressed.

Despite the differences in heterogenic expression and clinical characteristics among the IMIDs' psoriasis, CrD, CD and RA, the shared genetic and pathophysiologic mechanisms suggest a common origin, and as health care providers, it is imperative to capitalize upon this information. The potential links between these diseases a) must not be ignored and b) must be further studied. The purpose of this project is to conduct a substantive review of the literature and conduct screening of primary care patients with psoriasis to determine early detection of celiac disease, rheumatoid arthritis, and Crohn's disease.

1.2 Scope of problem

Autoimmune diseases. Autoimmune diseases, to include the immune-mediated inflammatory diseases, can affect virtually every site in the body, including the nervous, gastrointestinal, and endocrine systems, as well as skin and other connective tissue, eyes, blood and blood vessels. These diseases are chronic conditions, for which there currently is no cure. Autoimmune and immune-mediated inflammatory diseases follow a progressive path, with more end-organ destruction over the passage of time. Symptoms tend to increase in severity as the disease progresses and as more tissue destruction occurs (San Jose Functional Medicine, 2012). While many of these diseases have low prevalence as a single occurring health disease, collectively autoimmune diseases are the third most common category of disease in the United States after cancer and heart disease (NIH, 2005) affecting approximately 5-8% of the population or approximately 23.5 million Americans. For reasons unknown, their prevalence is rising, while paradoxically, they continue to remain under detected and under diagnosed (NIH, 2005; AARDA, 2011).

Early diagnosis and treatment is key to staving off disease progression and improving patient outcomes. However, it is also recognized that there is often a delay in diagnosis due to the fact that symptoms are often vague, misdiagnosed, and treated symptomatically. The delay in diagnosis and treatment can unfortunately, lead to poorer clinical outcomes associated with accrued joint and organ damage.

Researchers have been uncertain exactly what triggers an autoimmune response, but certain modifiable and non-modifiable factors that play a role in autoimmunity have been identified (AARDA, 2011; NIH, 2005). Modifiable factors include an individual's

genetic predisposition toward autoimmunity, while non-modifiable factors could be anything from viruses, bacteria, medications, pollutants, or hormones. Autoimmune disorders present disproportionately, and predominately, in the female population, are the second highest cause of chronic disease (AARDA, 2011) and have been among the top ten leading causes of death for women in every age group up to 64 years of age (NIH, 2005).

        Incidence and Prevalence. In the United States alone, these AI diseases affect approximately 5-8% of the population, or 14 to 23.5 million individuals (NIH, 2005). However, the current data about the prevalence of these diseases in the United States is misleading, since most autoimmune disorders are asymptomatic for years before a clinical pattern emerges. Due to the silent nature of AI disease onset, one can logically extrapolate that the true numbers of individuals with autoimmune disorders is actually much higher than the statistics suggest. Many patients with AI disorders remain undiagnosed and therefore, have simply not been included in the current numbers. Furthermore, according to the AARDA (2011), the prevalence of autoimmune disorders as reported by the National Institute of Health, 14 to 23.5 million individuals was quite deflated, since the statistic only accounted for 24 of the 80 recognized autoimmune diseases. The AARDA (2011) estimates that the actual number of individuals that have autoimmune diseases is closer to 50 million.

        There is no doubt that the actual burden of these autoimmune diseases to society, and to individuals, is enormous. Individually, these chronic and progressively deteriorating disorders have caused emotional and financial challenges associated with

lost productivity; decreased quality of life; co-morbid mental illnesses, particularly depression and anxiety; and the disruption of social and family structures (NIH, 2002).

Costs. Quantifying the societal cost burden of AI disease has proven to be a problematic task, as well. AARDA (2011) and NIH (2002) both agree that the lack of epidemiological data on autoimmune disorders has made it difficult to calculate the full direct and indirect cost to the overall health care system due to autoimmune disease. In 2001, the National Institutes of Allergy and Infectious Diseases (NIAID) Director, Dr. Anthony Fauci estimated that annual autoimmune disease treatment costs were greater than $100 billion. Again, this number most likely underrepresents the true cost burden of disease, as the annual costs of only seven autoimmune diseases (Crohn's disease, ulcerative colitis, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis and scleroderma), have been estimated to total from $51.8-$70.6 billion annually (AARDA, 2011).

Psoriasis. In 2010, the Centers for Disease Control and Prevention (CDC) initiated a public health agenda for psoriasis in order to better characterize the burden of psoriasis on the United States population, and to expand the existing knowledge base. Examining data from the 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys, key indicators such as prevalence, severity, disparities, health-related quality of life and selected comorbidities were analyzed. The initiative found that the overall prevalence of psoriasis in the United States is approximately 3.1%, affecting 6.7 million adults aged 20 and greater (Hemlock, Lee-Han, Hirsch, Baird, & Bartlett, 2014). Those with psoriasis tend to have a higher mean age, are more often of non-Hispanic white background, suffer from frequent mental distress, depression, arthritis,

and obesity (Hemlock et al., 2014).   The National Foundation of Psoriasis (2008) further reports that psoriasis is clearly linked with systemic comorbidities, such as cardiovascular disease and events, hypertension, diabetes, as well as other immune-related diseases. Psoriasis has also been associated with an increased risk for lymphoma, the strongest risk was for Hodgkin's lymphoma, particularly with increased severity of psoriasis (Gelfand et al., 2006).

A systematic review of the economic burden of psoriasis was published in 2015 (Brezinski, Dhillon & Armstrong). The review concludes that patients with psoriasis incur annual health care costs that are significantly greater than those of the general population and may amount to $135 billion annually. In the United States, the economic burden of psoriasis is substantial because this disease results in considerable negative physical, psychiatric, and social consequences. The direct psoriasis costs ranged from $51.7 billion to $63.2 billion, the indirect costs ranged from $23.9 billion to $35.4 billion, and medical comorbidities were estimated to contribute $36.4 billion annually in 2013. Patients with psoriasis would pay a lifetime cost of $11,498 for relief of physical symptoms and emotional health (Brezinski et al., 2015).

Celiac Disease. Celiac disease is one of the recognized immune-mediated inflammatory diseases, which is caused by a permanent intolerance to the ingestion of gluten-containing cereals, wheat, rye, and barley, in genetically pre-disposed individuals (Catassi et al., 2007). Population based studies indicate that the prevalence of CD is approximately 0.5-1% in Western European and American populations (Tonutti & Bizzaro, 2014), and the frequency of CD is substantially increased in patients who have a first-degree family member affected with CD (Rubio-Tapia, Hill, Kelly, & Calderwood,

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2013). In patients with CD, the chronic intestinal damage over time carries risk for

adverse health consequences and increased mortality, including an increased risk for

malignancies such as small-bowel adenocarcinoma, cancer of esophagus, B-cell and T-

cell non-Hodgkin lymphomas, and in particular intestinal T-cell lymphomas (Rubio-

Tapia et al., 2013). The evidence also suggests that a consequence of untreated CD and

chronic malabsorption of nutrients is an increased prevalence of low bone mineral

density, risk for fractures, and micronutrient deficiencies including iron, folic acid,

vitamins B12 and B6, copper, zinc, and carnitine (Ludvigsson et al., 2014; Rubio-Tapia

et al, 2013). Women with CD have an increased risk of infertility, spontaneous abortions,

preterm deliveries, and delivery of low birth weight infants (Rubio-Tapia et al., 2013). It

is estimated that 83% of Americans who have celiac disease are undiagnosed or

misdiagnosed with other conditions (Fasano et al., 2003). The time from onset of

symptoms to celiac disease diagnosis averages 10 years in the US (Green & Jabri, 2003).

While prevalence is of CD is on the rise, the economic implications of CD are

only just emerging. A 2010 population-based study using administrative data for a cohort

of celiac disease cases and matched controls from Olmsted County, Minnesota were used

to compare direct medical costs one year pre- and post-coeliac disease diagnosis. The

study found that average total costs for patients were reduced by $1,764 in the year

following diagnosis, with a pre-diagnosis cost of $5023 versus a post-diagnosis cost of

$3259 (Long et al., 2010). While additional economic studies are necessary, these results

highlight the importance of early diagnosis and treatment, which may prevent

complications and reduce the economic burden of the disease.

Rheumatoid Arthritis. RA is characterized by inflammation of the synovial

tissue, which if left untreated, progresses to permanent structural damage and long term disability (Emery et al., 2002). Epidemiological studies of RA indicate a population prevalence of 0.5-1.0% in Northern European and North American countries (El-Gabalawy, Guenther, & Bernstein, 2010). According to the CDC (2016), an estimated 1.5 million (0.6%) of US adults aged greater than 18 years had RA in the year 2005. Data from the past decade indicate that the incidence of RA in women appears to be rising after four decades of decline (CDC, 2016; El-Gabalawy et al., 2010).

Unchecked disease progression in the RA patient increases the incidence of death due to infection, renal failure, non-Hodgkin's lymphoma (Emery et al., 2002) (Johns Hopkins Arthritis Center, 2016) and cardiovascular disease (John's Hopkins Arthritis Center, 2016). Cardiovascular disease, including ischemic heart disease and stroke, accounts for approximately one-third to one-half of RA-related deaths, and infection is responsible for approximately one-fourth of RA associated deaths (CDC, 2016). Those with RA who remain untreated are twice as likely to die as compared to those without RA of the same age (CDC, 2016; Johns Hopkins Arthritis Center, 2016). Additional risks associated with RA are anemia, osteoporosis and depression (Johns Hopkins Arthritis Center, 2016) and the possibility of partial or total joint replacement surgeries (Kumar, Karthik, Gayathri, & Sivasudha, 2016). Approximately 90% of patients with RA have some form of disability within two decades of onset (Emery et al., 2002).

In 2012, there were 9,100 hospitalizations with RA listed as the principal diagnosis (Birnbaum et al., 2010). Women and people aged 45 years and older accounted for the majority of these stays. A study utilizing administrative claims databases covering privately insured and Medicare and Medicaid beneficiaries in the US during the

year 2005 were used to estimate the comprehensive cost of RA patients to society and individual stakeholders (Birnbaum et al., 2010). According to the study, total hospital charges amounted to $374 million, with a mean charge of $41,000 per person. Direct out-of-pocket medical costs for patients were estimated to be $8.4 billion, while indirect costs were estimated to be $10.9 billion, including earning losses, disability payments and decreased productivity. Finally, the cost of quality of life deterioration and premature mortality were calculated to be approximately $39.2 billion (Birnbaum et al., 2010). Early detection and treatment of RA improve the long term patient outcomes and economic burden of this disease (Emery et al., 2002).

Crohn's Disease. Crohn's disease is a chronic, relapsing inflammatory bowel disease (IBD) that may potentially affect any portion of the gastrointestinal tract from the mouth to the anus. This condition is characterized by progressive bowel damage associated with impaired functioning (Peyrin-Biroulet, Loftus, Colombel, & Sandborn, 2010). The highest prevalence for CrD has been found for Europe, 322 per 100,000 people and in North America, 319 per 100,000 people (Laass, Roggenbuck, & Conrad, 2014). According to the Crohn's & Colitis Foundation of America ([CCFA], 2016), Crohn's disease may affect as many as 700,000 Americans. CrD is not gender-biased; men and women are equally likely to be affected. Further, the disease may appear at any age, although CrD is more prevalent among adolescents and young adults between the ages of 15 and 35 (CCFA, 2016).

Patient's with CrD may suffer from cardiovascular, hepatic, biliary, pancreatic, and digestive co-morbidities, as well as metabolic issues and psychiatric problems (San Roman & Munoz, 2011) since symptoms have a substantial impact on quality of life.

Blockage of the intestine due to swelling and scar tissue is the most common complication of Crohn's (CDC, 2014). Patients with CrD are at risk for early small bowel and colorectal cancer (Baumgart & Sandborn, 2012). Studies also link extraintestinal inflammatory symptoms with CrD in the eyes, skin or joints (Lichtenstein, Hanauer, & Sandborn, 2009), as well as ankylosing spondylitis, non-drug induced osteoporosis, and other inflammatory-mediated immune diseases (Baumgart & Sandborn, 2012). With initiation of corticosteroid therapy, up to 38% of CrD patients will require surgery within one year (Lichtenstein et al., 2009). Mortality risk has been calculated as over 50% greater than the general population (Canavan, Abrams, & Mayberry, 2007).

In addition to associated co-morbidities and quality of life issues, the economic burden on the individual and the United States is substantial. A systematic literature review of the costs of CrD in Western industrialized countries was conducted for the year 2006 (Yu, Cabanilla, Wu, Mulani, & Chao, 2008). Findings indicated that direct medical costs per year were $18,022-$18,932 per patient in the United States. Hospitalizations accounted for 53-66% of these direct medical costs, with a per-hospitalization rate of $37,459. The total economic burden of CrD was estimated to be between $10.9 and 15.5 billion in the United States (Yu et al., 2008).

Summary. By the numbers alone, it is clear that autoimmune disorders, on both a collective and individual level, should constitute a national, if not global, health crisis and that additional scrutiny to this category of diseases needs to be made. It is critical that new methods for facilitating earlier diagnosis of these diseases be developed. Earlier identification of diseases would lead to the initiation of treatments earlier in the course of

disease, with the hopes to stave off as much organ destruction as possible, reducing the long-term consequences, and costs, of the diseases.

1.3 Analysis of Current Practice

General Discussion. Obtaining a diagnosis for a particular autoimmune disease is typically a long and stressful process for most patients. Many of the initial signs and symptoms, such as fatigue, joint and muscle pain, fever or weight change (NIH, 2005) are vague and suggestive of many diagnoses. Practitioners end up treating the symptoms, without further regard for the etiology of these symptoms, while the disease continues to progress unchecked.   Patients are often required to see multiple practitioners and specialists before they have been able to get answers and a definitive diagnosis. According to the AARDA (2011), patients, on average, spent five years seeking a diagnosis; 46% of patients report being told that they were "constant complainers" or "too concerned with their health" (p. 9).

Diagnosis of an autoimmune disorder begins with a meticulous health history, including a careful family history, which might point to a familial tendency toward autoimmunity.   The general concept of shared autoimmunity within families, or the "kaleidoscope of autoimmunity (Somers, Thomas, Smeeth & Hall, 2009, p. 749)" has gained acceptance among researchers, and should be a cornerstone of autoimmunity identification.   A careful social history should also be documented, which may help to identify the patient's environmental or occupational exposures. Additionally, a complete physical evaluation has assisted the practitioner in more fully understanding the patient's issues (U.S. Department of Health and Human Services, Office on Women's Health, 2010).

Laboratory testing remains fundamental to the diagnosis of AI disease in today's healthcare setting (Castro & Gourley, 2010). Unfortunately, no one specific test exists to diagnose autoimmunity. Multiple tests may be run to help support a diagnosis of autoimmunity, such as the complete blood count (CBC), comprehensive metabolic panel (CMP), inflammatory markers, autoantibodies, flow cytometry, cytokine analysis, and HLA typing (Castro & Gourley, 2010). Additionally, non-specific tests, such as the erythrocyte sedimentation rate (ESR), serum complement markers, ferritin, fibrinogen, albumin and C-reactive protein (CRP), help to indicate a state of inflammation and allows the practitioner to evaluate disease activity (Castro & Gourley, 2010). However, possessing the knowledge about which tests are available for the 80-100+ AI diseases, and how to interpret them, continues to be a challenge for practitioners today.

In today's health care arena, AI diseases are managed as individual entities, via disease-specific profiles, as opposed to a general immune-related profile (Rahman et al., 2010). Guidelines have been developed to help practitioners with the diagnosis and treatment of psoriasis, CD, RA and CrD. The standards of care and current diagnostic approaches for these four IMIDs will be discussed below.

Psoriasis. Psoriasis commonly presents in the primary care setting (Krueger & Bowcock, 2005) and is a chronic, inflammatory, papulo-squamous skin disease. Hyperplasia of skin epithelial cells lead to well-circumscribed, raised, red lesions, with loosely adherent silvery white scales. Common locations are the knees, elbows and scalp. Approximately 10-30% of patients also develop psoriatic arthritis (PsA), a painful joint condition (Aldredge, 2015).

While a plethora of guidelines exist to direct the management and treatment of psoriasis, no published diagnostic criteria have been developed. Diagnosis is dependent primarily on the practitioner's recognition of characteristic skin and lesion patterns, using a subjective, qualitative assessment of the patient's skin (Menter et al., 2008; Raychaudhuri, Maverakis, & Raychaudhuri, 2014). A timely and proper diagnosis, therefore, is based wholly upon the practitioner's general knowledge of psoriatic morphology and phenotype.

Johnson and Armstrong (2012) published a set of clinical and histologic diagnostic guidelines for psoriasis, specifically for non-dermatologist practitioners. The authors acknowledge that while no established criteria exist for skin-limited psoriasis, trained health care providers should be able to diagnose psoriasis based on clinical history and skin examination. The guidelines (Johnson & Armstrong, 2012) do not offer absolute criteria for diagnosing psoriasis, however, they provide a set of recommendations that providers should take into consideration during the assessment and diagnosis of psoriasis.

Among these recommendations is to obtain a complete clinical, family and social history (Armstrong & Johnson, 2012). Clinical history should include onset of lesions, triggering factors, and associated symptoms (itch, pain, sensitivity, irritation). Family history should be discussed due to genetics and heritability of this IMID. Social factors should also be discussed, due to the association of psoriatic exacerbations with stress, smoking and alcohol. Finally, the provider must conduct a full skin examination to include the nails, scalp and intertriginous areas. Health care providers should take special notice of the characteristic morphology of the erythema, scaling and induration of lesions

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(Armstrong & Johnson, 2012).   Although not included in the Armstrong and Johnson guidelines, psoriasis classification can include the following morphologies, which may present differently in patients and often, present with overlapping clinical findings: plaque, inverse, erythrodermic, pustular, guttate, nail disease and psoriatic arthritis (Menter et al., 2008).

Histopathology and skin biopsy, while an option for the diagnosis of psoriasis, is not routinely practiced or required. However, if a question remains on the diagnosis, histopathology can be beneficial in distinguishing psoriasis from other inflammatory skin diseases (Armstrong & Johnson, 2012).

Celiac Disease.   Celiac disease is a chronic, immune-mediated inflammatory disease that manifests with a range of clinical symptoms in individuals who are genetically susceptible. The consumption of gluten-containing foods triggers an immune reaction, and a subsequent, inflammatory state of the duodenal mucosa (Tonutti & Bizzaro, 2014). The immune response is directed against both the exogenous gluten antigen and the autoantigen, tissue transglutaminase (tTG), which is a gluten byproduct created in the small intestine (Kagnoff, 2006).

Clinical manifestations of CD can vary widely, and there is no concrete consensus regarding which symptoms, laboratory abnormalities or associated diseases require further evaluation for CD.   Generally speaking, diagnosis begins with a health care provider's strong suspicion of CD based on the clinical exam and initial laboratory results.

According to the guidelines developed by the American College of Gastroenterology, individuals with signs, symptoms or laboratory evidence suggestive of

malabsorption, such as chronic diarrhea, weight loss, iron deficiency anemia (IDA) or elevated liver enzymes, and/or steatorrhea, postprandial abdominal pain, and bloating, should be tested for CD (Rubio-Tapia et al., 2013). Guidelines from the British Society of Gastroenterology (Ludvigsson et al., 2014) state that CD can be suspected in patients with mild gastrointestinal symptoms, associated conditions, or those at genetic risk, to include symptomatic first-degree relatives of patients with CD, as well as symptomatic individuals with Down's Syndrome and Turner's Syndrome (Ludvigsson et al., 2014). However, since the clinical picture of CD varies, and since many patients only have minor symptoms, it can be challenging for health care providers to make that first connection, from symptoms to suspicion.

Further confusing the diagnostic process is the fact that CD has been classified into multiple phenotypes: classic, atypical, silent, latent and refractory (Kagnoff, 2006). "Classic" CD is the most commonly described form, and patients present due to gastrointestinal symptoms. Whereas "classic" CD is the most commonly described form, "atypical" CD is actually the most prevalent form. Patients have little to no GI issues, but they become identified for other reasons, such as IDA, osteoporosis or infertility. "Silent" CD describes the cohort of patients who are asymptomatic, but who diagnose positive for CD as a result of serology or biopsy done for another reason. "Latent" CD refers to patients who previously have been diagnosed with CD, who responded to a gluten-free diet (GFD) and who retain normal mucosal histology. "Refractory" CD represents patients with true CD, who no longer respond to a GFD. (Kagnoff, 2006; Tutonni & Bizarro, 2014).

Regardless of how a patient comes to the attention of the practitioner as potentially having CD, the next steps in diagnosis are well agreed upon. The first step in diagnosis is serology, followed by a biopsy, which is considered to be the gold standard for CD diagnosis (Green & Jabri, 2003; Kagnoff, 2006; Ludvigsson et al., 2014; Rubio-Tapia et al., 2013; Tonutti & Bizzaro, 2014). The Immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody is the preferred serological test for individuals over the age of 2 years. Both the sensitivity and specificity of the IgA-tTG for untreated CD is approximately 95% (Kagnoff, 2006; Rubio-Tapia et al., 2013). If IgA deficiency is a concern, occurring in 1.7%-2.6% of patients with celiac disease (Green & Jabri, 2003), total serum IgA should be included in the panel and both IgA and IgG-based testing may be initiated to include the IgG-deamidated gliadin peptides (DGPs) (Green & Jabri, 2003; Rubio-Tapia et al., 2013). With known IgA deficiency, both IgG-DGPs and IgG-tTG serology may be tested. Finally, if serology is negative, but suspicion for CD is high, intestinal biopsy should be pursued (Green & Jabri, 2003; Kagnoff, 2006; Ludvigsson et al., 2014; Rubio-Tapia et al., 2013; Tonutti & Bizzaro, 2014).

The intestinal biopsy remains the gold standard in diagnosis because results reflect the varying degrees by which mucosal villi have been affected over the course of the disease. The Marsh-Oberhuber classification of architectural changes in the intestine outline three categories of lesion: "Type 1" describes an infiltrative lesion, "type 2" an infiltrative-hyperplastic lesion, and "type 3" reports mild, moderate and total levels of villous atrophy (Tonutti & Bizzaro, 2014). Multiple samples should be taken from the second or third portion of the duodenum and at least one sample from the duodenal bulb (Tonutti & Bizzaro, 2014).

In the setting where results from the aforementioned tests are not clear, or for patients already on a GFD, individuals can be genotyped for the gene pairs that encode HLA class II heterodimer HLA-DQ2 or HLA-DQ8. Almost all patients with CD have either DQ2 (~95% of CD patients) or DQ8 (the remaining ~5% of CD pts) and the absence of both of these DQ alleles provide a negative predictive value for the disease of close to 100% (Kagnoff, 2006; Green, 2003; Ludvigsson et al., 2014).

Rhe**umatoid Arthritis**.   The three major pathways for this immune-mediated inflammatory disease include bone degradation, cartilage and synovial destruction, which lead to severe disability and premature mortality (Aletaha et al., 2010). While the precise etiology and pathophysiology of RA is not completely understood, at least 16 different cytokines, autoantibodies and other mediators are implicated in the disease process (Kumar et al., 2016). The initial immune response, the pre-articular phase, begins with the generation of autoantibodies against own tissue components. During the transition phase, the introduction of autoantibodies and autoantigens in the articular joints becomes evident, causing joint destruction to occur symmetrically to joints all over the body, although the distal interphalangeal and cervical spine is typically spared (Kumar et al., 2016). Permanent structural damage occurs early in the disease course of RA and early intervention with disease modifying anti-rheumatics drugs (DMARDs) treatment is critical toward slowing the progression of joint damage, improving quality of life and long term outcomes for patients (Emery et al., 2002).

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) collaborated to update the classification criteria for RA that was last published in 1987 (Cohen & Emery, 2010).   The criteria were developed to

help researchers classify newly presenting patients and to help determine which patients would benefit from early treatment (Aletaha et al., 2010). The expert panel identified the following mandatory criteria: pattern and extent of joint involvement, serology (rheumatoid factor (RF) and anti-cyclic citrullinated protein (ACPA)), acute-phase response (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and duration of symptoms (Aletaha et al., 2010; Neogi et al., 2010). Two criteria were deemed essential. First, the patient must present clinically with joint swelling in at least one joint, indicating synovitis, and second, there must also be an absence of another condition that could explain the patient's symptoms. Differential diagnoses include multiple disorders such as psoriatic arthritis, systemic lupus erythematous (SLE), osteoarthritis and gout. The authors of the classification criteria suggest that if it is unclear to the provider which relevant differential diagnoses to consider, a rheumatologist should be consulted (Aleteha et al., 2010).

The remaining four criteria each contribute differently to the probability of developing RA and were weighted accordingly during the criteria development (Aleteha et al., 2010). The table below shows the criteria and scoring, with a required score of 6 or greater to be classified as having definite RA.

Table 1.1 The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

Target population (who should be tested?) Patients who:
   1) Have at least 1 joint with definite clinical synovitis (swelling),
   2) With the synovitis not better explained by another disease.

Classification criteria for RA (score-based algorithm): add score of categories A-D: a. A score of $\geq$ 6/10 is needed for classification of a patient as having definite RA.
A. Joint Involvement

1 large joint	0
2-10 large joints	1
1-3 small joints (with or without large joint involvment	2
4-10 small joints	3
> 10 joints (at least 1 small joint)	5
B. Serology	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result required for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

(Reproduced from Aletaha et al., 2010)

Although not included in the new classification criteria, radiograph imaging is

used to assess the structural damage associated with RA, and continues to be the best

method for collecting data on joint erosions and bone density. Other markers

traditionally used by providers to diagnose RA, such as the assessment of morning

stiffness and the metacarpal "squeeze test" (Emery et al., 2002), have also been excluded

from the classification criteria.

One point must be elucidated about the classification criteria. These criteria were

deliberately labeled "classification," as opposed to "diagnostic" criteria, in order to

provide a standardized approach for determining which patients presenting with

undifferentiated synovitis, would have the highest probability of persistent or erosive RA

(Aletaha et al., 2010). As such, the authors acknowledge that the criteria may in fact be

used as a tool for diagnosis, but that easier-to-use tools are in development through

another joint effort by ACR/EULAR for primary care providers.

Crohn's Disease. Crohn's disease is a chronic, progressive, destructive

inflammatory bowel disease (IBD) of the GI tract, manifesting anywhere from the mouth

to the anus. Ulcerative colitis (UC) is the second disease included in the IBD

classification. By comparison to CrD, which is intermittent inflammation and can attack

all bowel wall layers, UC is a continuous inflammation that it is limited to only the

innermost layer of the intestinal linings in the colon and rectum (CCFA, 2016).   Both

IBDs are characterized by periods of disease activity interspersed with periods of

remission. Symptoms of both CrD and UC may include fever, bloating, cramping,

nausea, vomiting, severe diarrhea, bloody stool, abdominal pain, weight loss and fatigue.

CrD patients may also have mucous in their stool (Laass et al., 2014).   Patients can have

symptoms for many years prior to diagnosis (Burgmann et al., 2006; Pimentel et al.,

2000).

The rationale for defining early Crohn's disease is to modify the clinical course of

the disease and intervene prior to the onset of bowel damage in the form of stricture,

fistula, or abscess. However, approximately one-fifth of adult patients already have

evidence of structuring or penetrating intestinal complications at diagnosis (Peyrin-

Biroulet et al., 2010). CrD is a seronegative IMID, meaning there is no direct serological

test for detecting disease activity. And presently, there is no gold standard for CrD

diagnosis. Diagnosis integrates patient information and physical exam with objective

data from a combination of laboratory, radiologic, endoscopic and histologic findings

(Laass et al., 2014; Peyrin-Biroulet et al., 2010; Van Assche et al., 2009; (Baumgart &

Sandborn, 2012).   Genetic testing is not currently recommended (Lichentstein, 2009;

Peyrin-Biroulet, 2010; Van Assche et al., 2009).

The most common presenting CrD symptom is chronic diarrhea, defined as a

decrease in fecal consistency for more than 4 to 6 weeks (Laass et al., 2014). Abdominal

pain is seen in about 70% of patients before diagnosis, and approximately 60% of

patients experience weight loss (Van Assche et al., 2009). In approximately 10% of

patients, the presenting complaint is a perianal fistula (Van Assche et al., 2009).

Providers must take a complete medical history itemizing symptoms and inquire about

family history, as first-degree relatives of patients with IBD have a 10-15 fold risk for

also having IBD (Laass et al., 2014). A full history should also include information about

recent travel, food intolerances and medications. Attention should be paid to proven risk

factors including smoking and recent infectious gastroenteritis (Van Assche et al., 2009).

Physical examination includes general well-being, vital signs, body weight, BMI,

abdominal tenderness or distention, palpable masses, perineal and oral inspection, rectal

digital examination (Van Assche et al., 2009; Laass et al., 2014) plus signs of

extraintestinal disease. Extraintestinal manifestations might present as joint pain,

swelling, redness or stiffness, erythema nodosu, or redness of the eye (Laass et al., 2014).

Clinical laboratory testing continues the inflammatory status assessment, although

of and by themselves, labs are not enough to differentiate CrD from UC or enteric

infection. The initial lab investigations support GI inflammation and are used as an

adjunct to diagnosis (Van Assche et al., 2009). Patients should be assessed for anemia,

fluid depletion and signs of malnutrition or malabsorption via the complete blood count

(CBC). Anemia and thrombocytopenia represent the most common changes in CBC

evaluation of patients with CrD (Van Assche et al., 2009). CRP and ESR are non-

specific acute phase inflammatory markers that should be evaluated. Fecal calprotectin

or lactoferrin provides an estimation of fecal inflammation by measuring for the presence

of fecal leukocytes (Lichtenstein et al., 2009). Fecal calprotectin has a positive predictive

value of 85-90% in distinguishing IBD from irritable bowel syndrome (IBS). Stool cultures are beneficial for ruling out infectious colitis caused by viral, bacterial or parasitic sources (Laass et al., 2014; Van Assche et al., 2009; Lichentenstein et al., 2009). Providers must also consider lactose intolerance and celiac disease in their list of differential diagnoses.

Upper or lower GI endoscopy is used to confirm the diagnosis of CrD, assess disease location, and obtain tissue for pathological examination (Laass et al., 2014; Van Assche et al., 2009). However, the initial symptoms frequently determine the order of subsequent testing. For example, colonoscopy, intubation of the terminal ileum, is the most appropriate initial test for patients presenting with predominant diarrhea, and is used to establish the diagnosis of ileocolonic CrD. On the other hand, imaging studies may be more appropriate for those presenting with abdominal pain. Magnetic resonance enterography is the initial test used to evaluate the small intestine. Wireless video endoscopy, or video capsule endoscopy (VCE), may also be useful for detecting small bowel involvement (Laass et al., 2014; Van Assche et al., 2009).

1.4 Statement of Problem/Purpose

In adult patients aged 18 years and greater with psoriasis, does screening for celiac disease, rheumatoid arthritis, and crohn's disease improve early detection for these autoimmune disorders? The Population (P) in this question is adult patients aged 18 years and greater in primary care and outpatient settings. The Intervention (I) is the development and implementation of a simple screening tool in adults patients with psoriasis for celiac disease, rheumatoid arthritis and crohn's disease. There is no Comparison (C) for this background-type question. The Outcome (O) is demonstrating

improved early detection of celiac disease, rheumatoid arthritis and crohn's disease in

adult patients with psoriasis.   Table 1.1 contains the definitions of population, setting,

intervention, and outcome as defined by Melynk & Fineout-Overholt (2011).   The

purpose of this project is to conduct a substantive review of the literature to determine if

screening primary care patients with psoriasis will improve early detection of celiac

disease, rheumatoid arthritis, and Crohn's disease.

Table 1.2 PICO Definitions

Population of Interest	Setting	Current Practice	Intervention	Outcome
In adult patients over ages 18 with psoriasis	Primary care or outpatient settings	No screening	Screening for celiac disease, rheumatoid arthritis and Crohn's disease	Improved early detection of celiac disease, rheumatoid arthritis and Crohn's disease as measured by: a provider documentation for screening those with psoriasis for celiac disease, rheumatoid arthritis and Crohn's disease.

1.5 Project Questions

The project was guided by the following clinical questions:

What is autoimmunity? What is polyautoimmunity? What are IMIDs?

Why is it so difficult for patients with autoimmune diseases to become diagnosed?

Is there evidence that suggests that individuals with one autoimmune disease are

more at risk for developing another autoimmune disease?

Is there evidence that suggests that individuals with psoriasis have a greater risk

of developing celiac disease, rheumatoid arthritis or Crohn's disease?

What are the current, accepted approaches for diagnosing psoriasis, celiac disease, rheumatoid arthritis and Crohn's disease?

Would screening patients with psoriasis for celiac disease, rheumatoid arthritis and Crohn's disease improve early detection for these diseases?

1.6 Definitions

Adult Patients – Adult patients refer to men and women over the age of 18 years seeking health care in a primary care setting.

Celiac Disease - Celiac disease is an autoimmune disease that causes an inflammatory reaction to ingested gluten, a protein found in wheat, rye, and barley. When a person has celiac disease, gluten causes the immune system to react in a way that can cause intestinal inflammation—irritation or swelling—and long-lasting damage (NIH, 2015).

Crohn's Disease - Crohn's disease is an autoimmune disease characterized by chronic, relapsing inflammation to any portion of the gastrointestinal tract from the mouth to the anus. Also known as one of the inflammatory bowel diseases (IBD), this condition is caused by an abnormal response to the body's immune system which results in progressive bowel damage associated with impaired functioning (Peyrin-Biroulet et al., 2010; CDC, 2014).

Early Detection - Early detection refers to a screening program that detects disease in asymptomatic persons or in symptomatic persons not yet recognized to have disease. Relative to background conditions, screening identifies the affected individual at an earlier time point in the natural history of disease (Weissfeld, 2001).

Health Screening - Health screenings include specific technology (survey

questionnaire, physical observation or measurement, laboratory test, radiological procedure, etc.) that are used to help identify persons with unrecognized disease or unrecognized risk factors for disease (Weissfeld, 2001).

Rheumatoid Arthritis – Rheumatoid arthritis is an autoimmune disease characterized by chronic, systemic inflammation of the synovial tissue. If left untreated, RA progresses to permanent structural damage and long-term disability (CDC, 2016; Emery et al., 2002).

Primary Care Providers - A primary care provider (PCP) is a health care practitioner who is responsible for monitoring an individual's overall health care needs. The PCP's role is to provide preventative care and teach healthy lifestyle choices, identify and treat common medical conditions, assess the urgency of medical problems and direct the patient to the best place for their care, and make referrals to medical specialists when necessary (She, 2012).

1.7 Chapter Summary

Research suggests (Cooper, Bynum & Somers, 2009) that individuals with one autoimmune disease typically will develop an additional one or more separate, and distinct, autoimmune diseases over the course of their lifetime. Further, links have been drawn between psoriasis and celiac disease, rheumatoid arthritis and crohn's disease (Augustin, Reich, Glaeske, Schaeffer & Radtke, 2010; Ali & Warren, 2013; Wu, Nugyen, Poon & Herrington, 2012; Guerin, Zhang, Gauthier, Day & Khan, 2012; Hsu & Armstrong, 2012; Makredes, Robinson, Bala & Kimball, 2009; Birkenfeld, Dreiher, Weitzman & Cohen, 2009; Tsai, Wang, Hung, Tsai, Schenkel, Zhang & Tang, 2011). Regrettably, practitioners may overlook the associations between these autoimmune

diseases, prolonging the diagnostic process (Somers et al., 2009).   The purpose of this project is to conduct a substantive review of the literature to determine if screening primary care patients with psoriasis will improve early detection of celiac disease, rheumatoid arthritis, and Crohn's disease. The aim of this project is to assess the utility of early screening in patients with psoriasis in order to facilitate earlier diagnosis of CD, RA and CrD, which would consequently initiate earlier treatment and improve long-term patient outcomes.

The next step in the evidenced-based practice process is the literature search and analysis. The evidence will be organized using an evidence table. This process is explained in detail in chapter II.

Chapter 2

Literature Review

2.1 Introduction

The goal of this chapter is to appraise and synthesize the evidence for conducting the DNP project for changes in practice. The discussion that follows describes the literature search process, and an objective summary and analysis of fourteen research articles. The purpose of this content is to convey the current state of knowledge, and significance of, the relationship between psoriasis and the three IMIDs of interest (celiac disease, rheumatoid arthritis, and Crohn's disease) to healthcare providers and decision makers.

2.2 Search Methodology

Evidence-based practice mandates that clinical decisions be driven by the most current research studies, the clinical experience of the practitioner, and patient preferences (Melnyk & Fineout-Overholt, 2011). Evidence-based research begins with a question of interest, followed by the systematic collection, appraisal and synthesis of evidence. The following information presents the search strategy employed for the question: in adult patients aged 18 years and greater with psoriasis, does screening for celiac disease, rheumatoid arthritis, and Crohn's disease improve early detection for these autoimmune disorders?

This is a background-type PICO question and according to Melnyk and Fineout-Overholt (2011), the following types of studies are appropriate for review, in descending order of level of evidence: synthesis of cohort study or case control studies, single cohort studies or case-control studies, meta synthesis of qualitative or descriptive studies, single qualitative or descriptive studies, and expert opinion. A search of databases was performed, accessed through the University of South Carolina's online library. The Cumulative Index for Nursing and Allied Health Literature (CINAHL), PubMed-Medline, Medline OVID, Cochrane Library, Web of Science, Essential Evidence Plus, Nursing Resource Center, Health Source: Nursing/Academic Edition, Dissertations and Thesis, Annual Reviews, as well as Google Scholar were included in the search. Reference lists of acceptable papers were also manually examined for additional resources.

The main search terms were "psoriasis" and "autoimmunity." Limitations were set for the years 2006-2016, in order to review the most up-to-date research and evidence on the topic, and for English-only papers, to eliminate language barriers. Additional cross-searching terms utilized were "co-autoimmunity," "co-existence," "association," "pan autoimmunity," "immune mediated inflammatory diseases," or "IMIDs," and "screening." Finally, "psoriasis" was searched specifically against the three AI disorders of interest for this project: "celiac disease," "Crohns disease," and "rheumatoid arthritis."

A total of fourteen papers were selected. Levels of evidence were appraised using the Scottish Intercollegiate Guidelines Network (SIGN) rating system (Appendix A). The rating scale ranges from 1++, the highest level of evidence, reserved for high quality meta-analysis, systematic reviews of RCTs, or RCTs with a very low risk of bias,

to 4, reserved for expert opinion, the lowest level of evidence. Four retrospective cohort studies with control groups were found (level of evidence 2+). Four case-control studies (level of evidence 2+), one cross-sectional study (level of evidence 3), two meta-analysis of genetic studies (level of evidence 1+), one meta-analysis of population based studies (level of evidence 1+), one prospective cohort study (level of evidence 2+), and one expert review paper (level of evidence 4) were included.

2.3 Analysis of the Evidence

Evidence was organized in table format with the following headings: brief reference, type of study/quality ratings, methods, threats to validity/reliability, findings and conclusions (Appendix B). The table was developed to consolidate methodological and outcome summaries from the selected articles and used for the purpose of synthesis and analysis. Each evidence-based, peer reviewed article was systematically appraised on the individual level, followed by an overall summary of findings. The four genetic studies are presented first, followed by the population-based studies. For the purposes of this literature review, when studies include multiple AI disorders, only the four AI diseases directly related to this study, psoriasis, celiac disease, rheumatoid arthritis, and Crohn's disease, will be discussed.

2.4 Genetic Studies.

Four of the fourteen research articles included in this review can be classified as genetic studies. What follows is a brief discussion to foster a basic understanding of single nucleotide polymorphisms (SNPs), the main concept in each of the studies.

From a top down perspective, all cells in the body contain a nucleus, which then contains 23 pairs of chromosomes. Each tightly packed chromosome unravels to reveal a

double helix of deoxyribonucleic acids, or DNA. The DNA double helix is composed of

a long sequence of nucleotide base pairings, adenine (A), thymine (T), guanine (G) and

cytosine (C). These nucleotide bases link in a very specific way: A always pairs with T,

and C always pairs with G. Distinct sequences of these nucleotides organize the

chromosomes into sub-units, which are genes. Genes provide the cell with the

instructions that dictate cell function (National Human Genome Research Institute, 2015).

A SNP is defined as a single nucleotide base change in a DNA sequence that

occurs in a significant proportion (more than 1 percent) of a large population (University

of Utah Health Sciences, 2016). To make an analogy, 99% of the population has a

sequence for "Mari*e*," while approximately 1% has a sequence for "Mari*a*." Today's

challenge for researchers is to identify SNPs, or the "Maria's," that correlate with a

particular effect in patients. Genetic association studies, such as the ones to follow,

compare the frequency of genotypes at genetic marker loci, usually single-nucleotide

polymorphisms (SNPs), in individuals with and without a given disease trait from a given

population. The objective of these association studies is to determine whether a

significant statistical association exists between the disease trait and the genetic marker

(Clarke, Anderson, Peterson, Cardon, Morris & Zondervan, 2011). Reliable SNPs could

serve as predictive gene markers that inform decisions about numerous aspects of

medical care, including specific disease diagnosis, predisposition to disease, and the

effectiveness of various drugs and adverse reactions to specific drugs (University of Utah

Health Sciences, 2016).

Association of SNP Gly307Ser (rs763661) with Psoriasis, CD & RA. Qiu,

Khang, X. Qiu, Zhou and Li (2013) conducted a meta-analysis to evaluate the

relationship between the non-synonymous single nucleotide polymorphism (SNP) Gly307Ser (rs763361) in the CD226 gene that has been reported to be associated with several AI diseases, including psoriasis, celiac disease, and rheumatoid arthritis. Whether the presence of this t allele rs763361 confers a risk for multiple AI diseases remains under investigation. This study was rated a 1+.

The authors conducted a comprehensive search of the U.S. National Library of Medicine's PubMed and Embase databases for studies that fulfilled the following inclusion criteria: (1) were based on case-control design, (2) evaluated the association of the Gly307Ser (rs763361) polymorphism with multiple autoimmune disorders, (3) disease diagnosis followed the diagnosis criteria of the World Health Organization (WHO), (4) genotype frequencies were provided, (5) authors provided sufficient data for estimating an odds ratio and their 95% confidence interval (CI), and (6) papers were published with full text articles (Qui, Z., Zhang, X. Qui, Zhou & Li, 2013). Seven published studies met the inclusion criteria, covering 7,876 cases and 8,558 controls. The sample sizes varied from 90 to 2,838 and included two European, two Asian, one South American and three Estonian studies. The studies utilized three different genotyping methods, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan genotyping and SNPlexTM (Qui, et al., 2013).

Qui et al. (2013) used STATA 12.0 software for statistical analysis and estimated the association between CD226 Gly307Ser (rs763361) polymorphism and multiple AI diseases using crude odds ratio (OR) with 95% CIs. As is appropriate for meta-analyses, the authors assessed the degree of inconsistency in the studies' results, or between-studies heterogeneity, using Q-test and I^2 statistics. The DerSimonian and Laird random-effect

model calculated pooled estimates in case of significant heterogeneity. In cases without

obvious heterogeneity, the Mantel-Haenszel fixed-effect model estimated a summary OR.

The evaluation of the association of CD226 Gly307Ser (rs763361) polymorphism

with multiple AI diseases demonstrated an overall OR 1.19 (95% CI: 1.12-1.27,

$P_{heterogeneity}$=0.136), indicating that a significantly increased multiple AI disease risk was

found to be associated with the t allele rs763361 (Qui et al., 2013). The authors also

conducted a subgroup analysis by ethnicity, where increased risks were found for South

Americans (OR=1.31, 95% CI=1.17-1.48, $P_{heterogeneity}$ = 0.644), Asians (OR=1.23, 95%

CI=1.11-1.38, $P_{heterogeneity}$ = 0.690), and Europeans (OR=1.13, 95% CI=1.04-1.24,

$P_{heterogeneity}$ = 0.085) (Qui et al, 2013).

Although heterogeneity was detected in both the overall comparison and in the

subgroup analyses, none were notable ($P_{heterogeneity}$ = 0.136, I^2=29.3% in overall

comparsion; $P_{heterogeneity}$ = 0.644, I^2=0.0% in South Americans; $P_{heterogeneity}$ = 0.690,

I^2=0.0%; $P_{heterogeneity}$ = 0.085, I^2=46% in Europeans). Meta-regression analysis was

performed to explore sources of heterogeneity across studies when statistical

heterogeneity was detected. Publication year was closely related to the heterogeneity in

allele comparison (I^2=11.9%, P=0.036), while racial descent, study sample size,

genotyping methods, and controls' source did not indicate any modifying effect of the

factor (P>0.05) (Qui et al, 2013).

Further, Begg's test suggested no significant publication bias and the Hardy-

Weinberg equilibrium was demonstrated by using the Fisher's exact test (p < 0.10).

Finally, the authors conducted a sensitivity analysis to assess the stability of results. The

sensitivity analysis indicated that no individual study significantly affected the pooled

OR, and that results were statistically robust. The authors, however, acknowledged limitations to this study. First, this study lacked the original information for the individuals in the included studies; as such, data could not be stratified by other variables, such as gender, and mean age at onset (Qui et al, 2013). The lack of original data also means that the authors would not have been able to validate each case for the meta-analysis. Therefore, the possibility of diagnoses misclassification in the original studies cannot be completely excluded. Second, races other than South American, Asian, European and Estonian were not represented in this meta-analysis. Third, the authors note that while their publication bias showed no significance, it cannot be completely ruled out due to exclusion of relevant publications that were not indexed by their selected databases, PubMed and Embase (Qui et al, 2013).

The results of this meta-analysis, that a significantly increased multiple AI disease risk was found to be associated with the t allele rs763361, highlight the evolving comprehension of co-autoimmunity. It further supports the concept that susceptibility to AI diseases may be due to a complex interaction of multiple genes, some of which seem to be shared among many of these AI diseases, including psoriasis, celiac disease and rheumatoid arthritis.

15 New Psoriasis Susceptibility Loci. Tsoi et al. (2013) conducted a meta-analysis of three GWAs and two independent datasets genotyped on the "Immunochip," to include a total of 10,588 cases (patients with psoriasis) and 22,806 controls. The "Immunochip" is a custom-designed SNP array whose function is to fine-map genome-wide significant ($P<5\times10^{-8}$) susceptibility loci and to explore replication of thousands of SNPs representing additional promising signals. Tsoi et al. and other investigators of 12

distinct autoimmune and inflammatory diseases designed the chip in 2009 (Parkes,

Cortes, Van Heel & Brown, 2013).

The Immunochip consists of 196,524 SNPs compiled from variants identified in

previous GWAS of 12 different IMIDs. Each disease-focused group involved in the chip

design were then allowed to submit approximately 3000 additional SNPs in order to

evaluate signals that were deemed promising or that had not quite met genome-wide

significance in previous studies (Tsoi et al, 2013). The main objective of this study was

to increase understanding of the genetic architecture of psoriasis, identify new genetic

determinants of psoriasis, and to relate them to other AI diseases (Tsoi et al., 2013). This

study has been rated a 1+.

The authors performed a meta-analysis from five datasets that were genotyped on

the Immunochip. These datasets included three existing GWAS (Kiel, CASP and

WTCCC2) and two independent European descent case-control datasets, the Psoriasis

Association Genetics Extension (PAGE) and the Genetic Analysis of Psoriasis

Consortium (GAPC) (Tsoi et al., 2013).   Prior to meta-analysis, a number of quality

control steps were taken by the authors in order to identify and remove DNA samples and

markers that could introduce bias into the study. SNPs with a call rate below 95% were

excluded. Using the HapMap 3 samples as a reference, the authors performed principal

component (PC) analysis to identify and remove samples with non-European ancestry.

Samples with extreme inbreeding coefficients or heterozygosity values were also

removed, as were duplicate pairs or highly related individuals. A principle component

(PC) analysis was also used on each individual dataset to assess for possible population

stratification; no evidence of stratification between cases and controls within each dataset

was found. Finally, imputation was performed on the datasets in order to increase the number of overlapping SNPs between datasets. SNPs with low imputation quality were removed (Tsoi et al., 2013).

The meta-analysis revealed genome-wide significance ($P<5x10^{-8}$) for 19 of the 21 known psoriasis loci. The analysis demonstrated nominal evidence for the two remaining loci. Fifteen new risk loci for psoriasis were also identified that fulfilled genome-wide significance (Tsoi et al., 2013). Of the total 39 known and new psoriasis susceptibility loci included in this study, ten of these loci overlapped with Crohn's disease, nine with celiac disease, and five with rheumatoid arthritis.   A table has been provided below to provide a snapshot view of SNPs (known versus new) relative to disease overlap. The table also includes each SNP combined p-value and meta OR from analysis, as well as the notable genes associated with each SNP.

Table 2.1 SNP Disease Overlap

Known Loci				
SNP	Combined P-value	OR (meta)	Notable genes	Disease overlap
rs9988642	1.1×10^{-26}	1.52	*IL23R*	CrD
rs62149416	1.8×10^{-17}	1.17	*FLJ16341, REL*	RA, CrD, CD
rs27432	1.9×10^{-20}	1.20	*ERAP1*	CrD
rs1295685	3.4×10^{-10}	1.18	*IL13, IL4*	CrD
rs2233278	2.2×10^{-42}	1.59	*TNIP1*	CrD
rs12188300	3.2×10^{-53}	1.58	*IL12B*	CrD
rs582757	2.2×10^{-25}	1.23	*TNFAIP3*	CD, RA
rs1250546	$6.8x10^{-7}$	1.10	*ZMIZ1*	CD, CrD
rs34536443	9.1×10^{-31}	1.88	*TYK2*	CrD
rs4821124	3.8×10^{-8}	1.13	*UBE2L3*	CD, RA, CrD

Newly Identified Loci				
SNP	Combined P-value	OR (meta)	Notable genes	Disease overlap
rs11121129	1.7×10^{-8}	1.13	*SLC45A1, TNFRSF9*	CD
rs7536201	2.3×10^{-12}	1.13	*RUNX3*	CD
rs9504361	2.1×10^{-11}	1.12	*EXOC2, IRF4*	CD
rs2451258	3.4×10^{-8}	1.12	*TAGAP*	CD, CrD, RA
rs2700987	4.3×10^{-9}	1.11	*ELMO1*	CD, RA

(Tsoi et al., 2013)

It is important to emphasize that the authors suitably denote a very low threshold P-value supportive of genome-wide significance, indicating that the association is not due to chance alone. In a meta-analysis study where a large number of variants are being studied, the low P-value is required in order to protect against the production of large numbers of false positives (Type I error); however, such a conservative approach may therefore cause variants with small real effects to be overlooked, leading to false negatives (Type II error) (Thompson, Attia & Minelli, 2011). To overcome Type II error, sample sizes must be large enough to achieve sufficient power to identify such SNPs. Using large combined datasets significantly increases the power in GWA studies (Thompson, Attia & Minelli, 2011).

A notable limitation with GWAS studies is that they are only able to detect an association for a genomic region, and not causation of a mutation, that may be involved in the development of the disease or trait. Additionally, SNPs typically only explain a small fraction of an individual's risk for the trait (Genetics and Social Science, 2016). Tsoi et al. (2013) report that the 41 independent signals with $P < 5 \times 10^{-8}$ collectively only account for 14.3% of the total variance in psoriasis risk, or approximately 22% of its

estimated heritability. One explanation for the missing heritability is that complex diseases are caused by a large number of causal variants with small effect sizes (Stringer, Wray, Kahn and Derks, 2011). The small effect sizes are reflected in the odds ratios reported by this meta-analysis, which can be described to be modest, at best.

Odds ratios for the individual SNPs ranged from 1.09 (rs645078) to 1.88 (rs34536443), with one SNP (rs4406273) deviating from this pattern with an OR of 4.32. According to Stringer, Wray, Kahn and Derks (2011), ORs from GWA studies are typically low to modest, although they may in fact be underestimates of the true conditional odds ratios.

Despite these limitations, GWA studies should be considered foundational research in the identification of novel candidate genes, which is especially important in traits for which the biological etiology is unknown, such as the IMIDs.

Genetic Overlap Between Psoriasis and Crohn's Disease. Wolf et al. (2008) conducted a prospective case-control study in order to investigate the genetic overlap between psoriasis and Crohn's disease. Specifically, the authors analyzed the contribution of CrD genetic determinants to psoriasis susceptibility. The authors approached this study from the perspective that previous linkage studies have already repeatedly identified the psoriasis disease susceptibility locus (PSOR1), as well as loci PSORS2-10, as regions with overlapping susceptibility to other inflammatory conditions, including CrD. Therefore, 15 CrD susceptibility loci newly identified by genome-wide association analysis were assessed for significant disease associations with psoriasis (Wolf et al., 2008). This study has been rated a 2+.

Patients were recruited from within the United Kingdom via St. John's Institute of Dermatology in London (n=638), Glasgow Western Infirmary (n=211), and the Dermatology Centre, University of Manchester (n=407). A total of 1,256 patients were included in the study, 645 male and 611 female, all of northern European descent and with onset of psoriasis vulgaris occurring before 40 years of age. Less than 1% of the patients also had documented CrD. The patients were matched with 2,938 controls from the Wellcome Trust Case-Control Consortium (WTCCC).   Study approval was received from three entities, the Guy's and St. Thomas' Hospitals Ethics Committee of Kings College London, the Salford and Tafford Local Research Ethics Committee and North Glasgow University Hospitals NHS Trust Local Research Ethics Committee. Informed consent was obtained from all patients for the use of their DNA sample. Control genotypes were obtained from publicly released data available at the WTCCC (Wolf et al, 2008).

Patient DNA was typed using TaqMan assays and the frequencies of alleles for both cases and controls were compared using a X^2 test with one degree of freedom. Regression analysis was conducted with PLINK software. Significant disease association for three independent CrD markers, rs1203582 (OR=1.14; 95% CI 1.03 to 1.25), rs6908425 (OR=1.26; 95% CI 1.12 to 1.42) and rs2836754 (OR=1.17; 95% CI 1.06 to 1.30), was observed among the psoriasis cases (Wolf et al, 2008). In other words, three of the examined Crohn's disease SNPs are significantly associated with psoriasis. Interestingly, the marker that demonstrated the strongest effect, rs6908425, also maps to a gene previously associated with type 2 diabetes (Wolf et al., 2008).

Wolf et al. (2008) calculated false discovery rates (FDR), or the proportion of discoveries that are false among all discoveries (Benjamini & Hochberg, 1995), for the three significant SNP associations. The authors determined that all three significant associations surpassed the 5% FDR threshold ($P \leq 0.01$), with two SNPS (rs6908425 and rs2836754) exceeding 1% FDR ($P < 0.001$). Additionally, Wolf et al. (2008) tested for the presence of epistasis between the various disease-associated alleles using a case-only test to assess for gene-gene interaction. Pair wise comparisons of all SNPS resulted in non significant X^2 values, however, using the same approach to test for interactions between HLA-Cw*0602, the strongest determinant of disease risk from the PSOR1 locus, against the individual SNPS, suggestive evidence for an interaction with rs12035082 was generated ($p = 0.02$). Additional, larger patient cohorts would be necessary to validate, or invalidate, this epistatic effect.

The major issues concerning case-control studies design are case-control matching and presence of population stratification (Ghosh, 2007). Studies have shown that allelic distributions may vary between different ethic populations. This highlights the importance of selecting cases and controls with similar ethnic background in order to ensure that false positive associations do not result. Wolf et al. (2008) argue that their findings are unlikely to be due to population stratification, based on the fact that their cases and controls have the same ethnic and geographical origin. The data generated by WTCCC shows that the allele frequencies of SNPs rs12035082, rs6908425 and rs2836754 are homogenous across the UK, further invalidating the plausibility that associations are due to hidden population structure (Wolf et al., 2008).

The results of this study lend additional evidence to suggest that individuals with psoriasis are also predisposed to CrD. This highlights the pleiotropic effects of co-autoimmunity, in which one gene influences two or more seemingly unrelated phenotypic traits.

IL23R Association with Crohn's disease, Celiac Disease and Psoriasis. In 2006, Duer et al. first identified an association of genetic markers in the interleukin-23 receptor (IL23R) gene, as well as the intergenic region between IL23R and IL122RB2, with inflammatory bowel disease. Einarsdottir's et al. (2009) objectives were to determine if this association could be replicated with Swedish and Finnish patients with IBD. The authors expanded their study to also assess IL23R's association with two other AI diseases with chronic inflammatory features, psoriasis and celiac disease. Einarsdottir et al. (2009) utilized the Swedish and Finnish cohorts to also study the IL23R/psoriasis association; the IL23R/celiac association was studied among Finnish, Hungarian, and Italian populations. This study has been rated a 3.

Subjects for the IBD portion of the study were recruited from Karolinska University Hospital in Stockholm. A total of 803 patients were selected based on fulfillment of established clinical criteria, including endoscopic, radiological and histopathological data. Of these 803 cases, 455 were patients with ulcerative colitis and 348 were patients with Crohn's disease. Controls were randomly selected from ethnically matched, unselected individuals (Einarsdottir et al., 2009).

The celiac disease subjects were recruited from Finland, Hungary, and Italy. From Finland, 260 families with celiac disease were enrolled from the University of Tampere. From this sample, 185 families had more than one individual affected with

celiac disease (multiplex families), and 75 families had an affected father, mother and a child (trios). The rest of the 165 families had only one affected family member. Celiac disease was diagnosed mostly according to ESPGHAN criteria, however approximately 1% of the cases were diagnosed based on the presence of disease specific anti-endomysial antibodies.

The Hungarian subjects consisted of 400 families, 204 of which were multiplex families and 196 trios, plus 270 cases and 270 controls. The Italian dataset was comprised of 139 cases and 198 controls. Although Einarsdottir et al. (2009) do not describe the selection process for their Hungarian and Italian subjects in this publication, readers are referred to other studies where this process was duplicated.

The Psoriasis dataset consisted of 255 Finnish families, 64 multiplex families and 191 trios, plus 385 affected individuals. One psoriasis patient from each family was randomly selected and matched to a Finnish control. Again, the authors reference another study for a description of the selection process.

Eight SNP markers were selected based on Duerr's et al. (2006) study. All genotyping took place at the MAF core facility in Karolinksa Institute, Stockholm, Sweden. The case-control IBD dataset replicated the Duerr et al. (2006) findings with a power of approximately 89%. Of the 8 SNPs assessed, SNP rs11465804*G demonstrated the strongest association for the combined dataset including both CrD and UC (p=0.002, OR=0.42). Marker rs1004819 also indicated a strong association with Crohn's disease in the Swedish population (p=0.006, OR=1.43) (Einarsdottir et al., 2009).

Central to linkage studies is the logarithm of odds (LOD) score analysis (Nyholt, 2000). The authors used this calculation to estimate whether the observed degree of

concordance of IL23R markers between family members with celiac disease, indicates signification genetic linkage between the two (Nyholt, 2000). LOD scores greater than 3 traditionally indicate that within the marked region, there is the presence of one or more gene loci that influence the phenotypic trait; in other words, a LOD score of 3+ indicates 1000 to 1 odds that the linkage being observed did not occur by chance. This is considered to be significant linkage (Nyholt, 2000). The Finnish families demonstrated significant linkage for celiac disease (lod=3.24, p=0.00006, 135 individuals), while the Hungarian families did not (lod=0.4, p=0.08, 132 individuals) (Einarsdottir et al., 2009). Additionally, none of the celiac disease case-control datasets demonstrated significant association to any of the IL23R markers (Einarsdottir et al., 2009).

The psoriasis studies also revealed mixed results. Fifty-one of the 255 Finnish families with psoriasis were informative for linkage, yielding a LOD score of 0.83 (p=0.03). However, despite the low score, an association of IL23R with psoriasis was confirmed in the Finnish case-controls. The authors suggest that polymorphisms in both IL23R and IL12B, which encodes part of the IL23 cytokine, may collectively be more important for susceptibility to psoriasis, than is either on their own (Einarsdottir et al., 2009). As such, Einarsdottir et al. (2009) call attention to the fact that anti-IL12/IL23 antibody treatments improve psoriasis symptoms, which supports their argument that multiple components exist in the pathway of this disease.

2.5 Population Based Studies

Psoriasis and Celiac Disease. Bhatia, Millsop, Debbaneh, Koo, Linos and Liao (2014) conducted a meta-analysis of population-based studies examining the co-occurrence of psoriasis and celiac disease, investigations of celiac disease antibody

markers in psoriatic cohorts, and clinical trials examining the therapeutic benefit of a gluten free diet (GFD) in patients with psoriasis. The objective of this analysis was to examine the evidence that patients with psoriasis are at an increased risk for celiac disease and to also review studies evaluating the impact of a GFD on psoriasis improvement (Bhatia, Millsop, Debbanch, Koo, Linos & Liao, 2014). This study has been rated a 1+.

The authors searched the MEDLINE database via PubMed for articles between 1960 and 2012, and conducted a manual bibliographical search to identify additional studies that warranted inclusion; 23 articles in total met their criteria. Meta-analysis was performed in STATA using a random effects model (Bhatia et al., 2014).

Three population studies were reviewed, all of which demonstrated that patients with psoriasis are at an increased risk for celiac disease (Bhatia et al., 2014). Fourteen studies related to serological celiac disease markers in psoriasis patients were reviewed. Of these fourteen, nine studies reported a positive association between celiac disease markers, while seven did not find statistically significant evidence for an association. Bhatia et al. (2014) caution that the findings in the latter seven studies may be related to small study size and lack of control groups.

Further, Bhatia et al.'s analysis demonstrated a statistically significant relative risk of testing positive for IgA anti-gliadin antibody (AGA) in patients with psoriasis, as compared to control subjects ($OR_{total} = 2.36$; 95% C.I. 1.15-4.83) (Bhatia et al., 2014). The authors are 95% confident that the odds are between 1.15 and 4.83 greater for an individual with psoriasis to test positive for IgA AGA than for an individual without psoriasis.

Finally, the authors examined a number of studies that considered the effect of a GFD on psoriasis severity. Six studies demonstrated that patients with psoriasis, with either elevated AGA and/or tTG, showed improvement in psoriatic lesions after a GFD. One study utilized a pre- and post-GFD Psoriasis Area Severity Index (PASI) score to evaluate changes, revealing a 73% improvement. In this same study, AGA levels were lower in 82% of the psoriasis patients (Bhatia et al., 2014). The authors highlight an interesting result from this study; for the patients with both psoriasis and elevated AGA levels, and who experienced improvements after the GFD, all also had normal histological results in their pre-GFD duodenal biopsies. The authors conclude that a GFD may be beneficial in patients with psoriasis and gluten-sensitivity (marked by elevated AGA levels) even in the absence of biopsy-confirmed celiac disease (Bhatia et al., 2014).

The results of this meta-analysis demonstrate that both epidemiological and clinical studies suggest an association between psoriasis, celiac disease, and celiac disease markers. The authors conclude that health care providers should screen their patients with psoriasis for symptoms of celiac disease, including diarrhea, flatulence, fatigue and history of iron-deficiency anemia. Positive findings should flag providers to then run serological tests for celiac associated antibodies (Bhatia et al., 2014).

Association of Psoriasis with Other Autoimmune Diseases. Wu, Nguyen, Poon and Herrinton (2012) conducted a retrospective cohort study in order to examine the association between psoriasis and 21 autoimmune diseases that share common pathogenetic mechanisms, including celiac disease, Crohn's disease and RA. The authors also looked closely at patients with both psoriasis and psoriatic arthritis, hypothesizing that these individuals would be even more likely to have an additional autoimmune

disorder, compared to individuals with psoriasis alone (Wu, Nguyen, Poon & Herrinton, 2012). This study has been rated a 2+.

The study population was formed from patients who were members of the Kaiser Permanente Southern California (KPSC) health plan from January 1, 2004 to February 28, 2011. Inclusion criteria were as follows: patients of age 0 to 100 years, with at least one year of enrollment during the designated timeframe, and two or more inpatient or outpatient diagnoses codes for psoriatic disease (International Classification of Diseases, Ninth Revision (ICD-9), code 696.0-1), two codes for psoriasis only (ICD-9 code 696.1), 2 codes for psoriatic arthritis (ICD-9 code 696.0), or codes for both psoriasis and psoriatic arthritis (one code each of 696.1 and 696.0) (Wu et al., 2012). The comparison group was formed by randomly selecting individuals without psoriatic disease from KPSC at a ratio of five to one, and matching these individuals to the cohort by gender, year of birth (± one year) and length of enrollment (± one year) from the first date. 25,341 patients with psoriatic disease were ultimately matched with 126,705 control subjects (Wu et al., 2012).

Data was collected from the clinical and administrative databases of KPSC, to include patient demographics, inpatient/outpatient visits, and additional diagnoses (the outcome variables) for the 21 autoimmune diseases included in this study (Wu et al., 2012). Statistical analysis was conducted using SAS Enterprise Guide, version 4.3. The association between each autoimmune disease (the outcomes) and psoriasis (the exposure) was calculated using X^2 test. Conditional logistic regression was performed to the compare the risk of autoimmune disease between psoriatic disease and the matched control subjects (Wu et al., 2012).

Psoriasis was positively associated with 17 of the 21 studied AI diseases, with 14 of these associations being statistically significant (Wu et al., 2012). The strongest association was with RA (OR=3.6; 95% CI 3.4-3.9). Patients with psoriasis were 3.6 times more likely to have RA, as compared to persons without psoriasis. Celiac disease was the third strongest association (OR=2.3; 95% CI 1.6-3.2), and Crohn's disease was the fifth strongest association (OR=1.8; 95% CI 1.5-2.2) (Wu et al., 2012). Combining patients with both psoriasis and psoriatic arthritis demonstrated a significantly increased OR with most autoimmune diseases. And, individuals with psoriatic disease were more likely to have at least two (OR=1.6; 95% CI 1.5-1.7) or three (OR=1.9; 95% CI 1.6-2.4) immune-mediated diseases compared to persons without psoriatic disease (Wu et al., 2012). These findings suggest that patients with psoriasis are more likely than control subjects to be given the diagnosis of an additional autoimmune disease. The authors conclude their study by recommending that the evaluation of patients with psoriasis for other autoimmune diseases may be warranted as part of their health care (Wu et al., 2012).

Some of the limitations that are characteristic to cohort studies may have been present in this study. First, diagnostic information was culled from databases and prior diagnostic codes, neither of which were validatable (possible information bias). Second, due to their medical issues, the patients with psoriasis may have had more frequent contact with the health care system resulting in a greater opportunity to record associated diseases, as compared to the control group. On this point, and in defense of the study, it was conducted over a sufficient length of time that providers should have had ample opportunity to recognize additional diagnoses, even in the cohort group who may have

had fewer health care management needs. Third, a lack of data regarding possible

confounders did not allow the authors to make adjustments in relation to the outcomes.

Finally, another limitation to this study is that is was restricted to the geographic location

of southern California.

Psoriasis and Co-morbidities, Analysis of Health Insurance Data in

Germany. Augustin, Reich, Glaeske, Schaefer and Radtke (2010) conducted a

retrospective cohort study using a large sample of German health insurance information.

The authors' objective was to evaluate the prevalence of co-morbidities in patients with

psoriasis, particularly those related to metabolic syndrome. Given the existing evidence

that points to a relationship between psoriasis and other IMIDs, the authors also evaluated

the association between psoriasis and RA and Crohn's disease (Augustin, Reich, Glaeske,

Schaefer & Radtke, 2010). This study has been rated a 2+.

Patients with psoriasis were first identified from a pool of 1.3 million individuals

who were insured by a German nationwide statutory health insurance during the year

2005. Individuals were counted as cases if they had at least one visit to a healthcare

provider documented with the World Health Organization (WHO) ICD-10 codes marking

psoriasis (L40). Individuals from this dataset without a diagnosis for psoriasis were

marked as controls. In total, 33,981 individuals were identified for having psoriasis and

1,310,090 individuals without psoriasis served as the controls (Augustin et al., 2010).

The Pharmafacts Research Institute, located in Berlin, Germany, performed data

analysis. Prevalences were calculated for co-morbidities of interest and the prevalence

ratio was determined by comparing the prevalence rate of the psoriatic group to the non-

psoriatic group. Corresponding confidence intervals were computed by a general method based on constant X^2 boundaries (Augustin et al., 2010).

Individuals with psoriasis showed increased rates of co-morbidities compared to individuals without psoriasis (Augustin et al., 2010). Metabolic syndrome was more frequently diagnosed in those with psoriasis (PR=2.86; 95% CI 2.21-3.71). Moreover, the medical conditions that collectively contribute to metabolic syndrome were also significantly more common among patients with psoriasis on an individual level: diabetes mellitus (PR=2.02; 95% CI 1.96-2.08); hyperlipidemia (PR=1.75; 95% CI 1.72-1.78); arterial hypertension (PR=1.73; 95% CI1.71-1.76); and obesity (PR=1.72; 95% CI 1.68-1.76) (Augustin et al., 2010).

While not of direct interest to this IMID project, the aforementioned conditions provide additional context when considering the prevalence rates that Augustin et al. (2010) calculated for RA (PR=3.84; 95% CI 3.43-4.31) and Crohn's disease (PR=2.06; 95% CI 1.84-2.31) among patients with psoriasis. Rheumatoid arthritis and Crohn's disease ranked first and third in prevalence, respectively, among all the co-morbidities studied. This is noteworthy when one considers that approximately 34% of adults in the United States could be characterized as having metabolic syndrome (CDC, 2009), the second highest prevalent co-morbidity from this study. Whereas health care providers routinely screen for the components of metabolic syndrome (hypertension, cholesterol levels, BMI and diabetes), RA and Crohn's disease are not routinely screened for, although perhaps they should be, especially in patients with psoriasis. Augustin et al. (2010) do not directly make this recommendation, however, the authors make two significant statements: (1) the results of this study strongly support the association of

psoriasis and systemic chronic inflammatory diseases and (2) these findings should influence the healthcare management of patients with psoriasis by clinicians.

The limitations of this study are similar to those previously mentioned in the review of the Wu et al. (2012) study; possible information bias, lack of clinical data allowing for the adjustment of outcomes as related to potential confounders (smoking status or psychosocial factor), possible increased health care visits for psoriatic patients versus the controls, and geographic area.

Psoriasis and Co-morbidities, Analysis of a National Database in Taiwan.
Tsai et al. (2011) conducted a study similar to Augustin et al. (2010). A retrospective cohort study (with controls) was performed using the Taiwan National Health Insurance Research Database (NHIRD) during 2006. The authors' aim was to study the prevalence of comorbidities in patients with psoriasis. This large database, representing 99% of the total Taiwanese population, was utilized with the hopes of capturing less commonly assessed disease associations such as with the autoimmune disorders rheumatoid arthritis and Crohn's disease (Tsai et al., 2011). This study has been rated a 2+.

The NHIRD covers all benefit claims for approximately 22 million Taiwanese enrollees, and was established in 1995 by the National Health Research Institute and the National Health Insurance Bureau for the promotion of research on present and emerging medical issues in Taiwan (Tsai et al., 2011). This database was utilized to identify patients with at least one outpatient visit or admission claim with an ICD-9 diagnosis for psoriatic arthropathy (696.0) or psoriasis (696.1), resulting in a sample of 51,800 cases. 75.08% of the patients were identified at departments of dermatology, 3.42% at

departments of immunology/rheumatology, and 21.51% from "other," non-specified departments (Tsai et al., 2011).

The psoriasis cases were then further classified by severity. Individuals who had received any systemic therapy or phototherapy in 2006 were designated as moderate to severe (sPsO, n=9,063), while those who had not were designated as mild psoriasis (mPsO, n=36,252). The control group (n=207,200) was established by identifying patients without diagnoses for either psoriatic arthropathy or psoriasis, and matched at a 4:1 ratio based on age, gender and residential area (Tsai et al, 2011). Co-morbidities were defined based on at least three claims for an outpatient visit or one hospitalization with a principal/secondary diagnosis within one year of the index date, 2006 (Tsai et al., 2011).

The authors calculated prevalence associated with psoriasis and co-morbidities between cases and controls using relative risk (RRs) and 95% confidence intervals (CI) based upon a Cox proportional regression model (Tsai et al., 2011). The authors found that patients with psoriasis had a total increased risk for depression (RR=1.50; 95% CI 1.39-1.61, p-value >.0001), hypertriglyceridemia (RR=1.61; 95% CI 1.54-1.68, p-value >.0001), hypertension (RR=1.51; 95% CI 1.47-1.56, p-value >.0001), diabetes (RR=1.64; 95% CI 1.58-1.70, p-value >.0001), cardiovascular disease (RR=1.32; 95% CI 1.26-1.37, p-value >.0001) and malignancies of the digestive organs and peritoneum (RR=1.57; 95% CI 1.41-1.74, p-value >.0001).

Interestingly, in this study patients with moderate to severe psoriasis were found to have 10.25 times the risk for RA (95% CI 8.20-12.81), and patients with mild psoriasis were found to have 1.56 the risk for RA (95% CI 1.33-1.83) compared to patients without

psoriasis. The total risk for RA among all patients with psoriasis was calculated to be

3.02 times that for non-psoriatic patients (95% CI 2.68-3.41). When compared to the co-

morbidities listed in the previous paragraph, RA by far demonstrates the highest risk

among patients with psoriasis. These results echo the findings published in the Augustin

et al. (2010) study.

Finally, the percentage of psoriatic patients with Crohn's disease was actually

lower in this study as compared to patients without psoriasis, although the authors state

that this lower percentage did not show statistical significance.   Tsai et al. (2011)

postulate that the difference in association between psoriasis and Crohn's disease may

relate to ethnic differences in shared genetic susceptibility loci or, alternatively, in the

presence of disease protection loci.

The relevance of these findings is significant, particularly with regards to patients

with moderate to severe psoriatic disease. Tsai et al. (2011) conclude their study by

suggesting that clinicians should take into consideration the association of co-morbidities

when evaluating the potential burdens of psoriatic patients and designing effective health

care management plans.

A Comparison of Prevalence Ratios in Patients with Psoriatic Arthritis and

Psoriasis.   Through another retrospective cohort study, Makredes, Robinson, Bala and

Kimball (2009) investigated whether patients with psoriatic arthritis (PsA) carry a higher

AI disease burden than patients with psoriasis (PsO) alone. These authors utilized the

IMS Health Integrated Administrative Claims Database (Norwalk, CT) to compare the

prevalence of seven AI disorders among patients with PsA and PsO (Makredes,

Robinson, Bala & Kimball, 2009). The AI disorders were chosen based on a lack of

overlapping dermatologic or rheumatologic clinical manifestations to psoriasis or psoriatic arthritis (Makredes et al., 2009). Crohn's disease and inflammatory bowel disease were among the seven AI disorders examined. This study has been rated a 2+.

At the time of this study, the IMS Health Integrated Administrative Claims Database covered approximately 11 million individuals. From this dataset, patients were selected on the basis of age greater than 18, with at least one medical service visit of any kind between the dates of January 1, 2001 and December 31, 2002, and indicating at least one ICD-9 psoriasis code (696.0-1). 25,556 individuals were identified based on these criteria. These individuals were then classified into two clinical subsets, individuals with arthritic manifestations (PsA; ICD-9 696.0, n=3066) and those without arthritic manifestations (PsO; ICD-9 696.1, n=22,499). Individuals in the PsO group were not allowed to also have the presence of a PsA diagnostic code (Makredes et al., 2009).

Control groups for both subtypes were selected at a 3:1 ratio, matching for at least one medical encounter, age (within two years), sex, US census region, and length of previous medical insurance coverage. The control subjects could not have any ICD-9 psoriasis code in their records during the two year period of study (Makredes et al., 2009).

The case identification for other AI disorders required at least one medical claim for the ICD-9 diagnostic code of interest. The occurrence rates for these AI diseases were compared among control subjects, the PsO group, and the PsA group using the prevalence ratio (PR) statistic. A 95% CI was estimated with the Mantel-Haenszel test (Makredes et al., 2009). The authors found statistically significant trends between several AI disorders and both psoriasis subtypes, with the strongest relationships

belonging to PsA. Of particular interest, patients with PsO had an increased PR associated with Crohn's disease (1.6; 95% CI 1.4-2.0) and inflammatory bowel disease (1.4; 95% CI 1.2-1.6) when compared to individuals without psoriasis. Demonstrating an even stronger relationship, patients with PsA also carried an increased risk for Crohn's disease (2.1; 95% CI 1.3-3.3) and inflammatory bowel disease (1.8; 95% CI 1.3-2.5).

Based on these findings, Makredes et al. (2009) reach three conclusions. First, the data supports the premise that PsA and PsO are associated with the development of other AI diseases. Second, patients with PsA and PsO appear to be at greater risk for GI diseases. Third, these findings suggest that evaluating psoriatic patients in a prospective manner for other associated AI disorders may be important toward the patient's long-term health outcomes (Makredes et al., 2009).

Psoriasis, Psoriatic Arthritis and Increased Risk of Crohn's Disease in US Women. Li, Han, Chan and Qureshi (2013) performed a prospective cohort study in order to evaluate the association between psoriasis, psoriatic arthritis and incident UC and CrD among women in the US. The authors utilized two large, ongoing prospective studies of US women for their assessment, the Nurses' Health Study (NHS) and the NHS II (Li, Han, Chan & Qureshi, 2013). Collectively, these two datasets provide over 30 years of biennially updated data on diagnoses and lifestyle. This study has been rated a 2+.

The NHS enrolled 121,701 US female nurses aged 30-55 years in the year 1976 after a mailed questionnaire was completed detailing medical history and lifestyle factors. In 1989, NHS II was established when a similar questionnaire was completed by 116,430 US female nurses, aged 25-42 years. The information from both cohorts has been

undated every two years, with a response rate exceeding 90%. In 2005 and 2008, respectively, NHS and NHS II enrollees were questioned about physician-diagnosed psoriasis, psoriatic arthritis, and the diagnosis date. Self-reported psoriatics were confirmed by using the Psoriasis Screening Tool (PST); psoriatic arthritis was confirmed through the PsA Screening and Evaluation (PASE) questionnaire (Li et al., 2013). Participants who reported a diagnosis of UC or CrD in consecutive NHS and NHS II responses were asked to complete a supplementary questionnaire and for permission to review their medical records. Two gastroenterologists, who were blinded to exposure, reviewed these medical records; diagnosis for UC or CrD was confirmed if the original diagnosis was established through the fulfillment of standardized criteria (Li et al., 2013). A critical aspect of this study was confirmation that the psoriasis diagnosis preceded the diagnosis for either UC or CrD (Li et al., 2013).

Statistical analysis was performed using SAS and all p-values were two tailed. The following calculations were made: (1) time dependent Cox proportional hazards model stratified by age for the estimation of relative risks (RRs) and 95% CI; (2) multivariate analysis with adjustments for age, BMI, smoking, alcohol intake, physical activity, and use of postmenopausal, oral contraceptive, aspirin and NSAID drugs; (3) between-studies heterogeneity and overall association from random effects (Li et al., 2013).

Total number of participants in this study was 174,476 (78,211 from NHS and 96,265 from NHS II). 2,755 women reported a diagnosis of psoriasis at baseline (1996 for NHS and 1991 for NHS II). An additional 512 women from NHS and 1,122 women from NHS II reported psoriasis over follow-up through 2005. In NHS, there were 72

confirmed cases of CrD and 116 cases of UC from 1996 to 2008. In NHS II, there were

116 confirmed cases of CrD and 166 cases of UC from 1991 to 2007. Li et al. (2013)

report that women with psoriasis had an increased risk of developing CrD with a

multivariate adjusted RRs of 4.05 (95% CI 1.75-9.38) in NHS and 3.76 (95% CI 1.82-

7.74) in NHS II. The pooled analysis demonstrated that psoriasis was associated with a

RR of 3.86 (95% CI 2.23-6.67) for developing CrD (Li et al., 2013). The authors did not

find a statistically significant increased RR for development of UC in women with

psoriasis in either database (Li et al., 2013).

The authors also examined the risk for CrD among women with both psoriasis

and psoriatic arthritis. In addition to observing a particularly high risk of CrD among

female patients with psoriasis and psoriatic arthritis (RR_{pooled}=6.54; 95% CI 2.07-20.65),

Li et al. (2013) also observed a higher risk associated with longer duration and earlier

onset of psoriasis. Together, these findings offer additional evidence in the support of

common underlying mechanisms between psoriasis and CrD.   Because the study was

limited to US female healthcare workers, additional research should be conducted in

other populations to confirm results.

Psoriasis Associated with UC and Crohn's Disease. Cohen, Dreiher and

Birkenfeld (2009) investigated the relationship between psoriasis and the components of

inflammatory bowel disease, UC and CrD, through a case-control study that utilized the

large medical dataset of Clalit Health Services (CHS). The authors theorized that as both

UC and CrD are associated with inflammation, and that both diseases are treated with and

respond to similar medications, that these inflammatory bowel diseases may each be

independently associated with psoriasis (Cohen, Dreiher & Birkenfeld, 2009). This study has been rated a 2+.

Clalit Health Services is the largest healthcare provider organization in Israel, serving a population of approximately 3,800,000 enrollees at the time of this study.   This database receives continuous, real-time information from pharmaceutical, medical and administrative operating systems, facilitating epidemiological studies via the Clalit Research Institute. Cohen et al. (2009) identified patients from this database who had at least one documented diagnosis for psoriasis by a CHS community provider or through hospital discharge diagnosis. The authors matched the cases with controls, also from CHS, at a 2:1 ratio. Patient cases numbered 12,502; cohorts without psoriasis were matched by sex and age, equaling 24,285 patients (Cohen et al., 2009).   The authors also extracted information regarding diagnoses for UC or CrD, as well as patient use of the following three anti-TNF-α drugs, infliximab, etanercept and adalumumab.

Statistical analysis was performed using SPSS software, version 13. The authors compared the proportion of patients with IBD between patients with and without psoriasis. For categorical parameters between the groups, chi-squared tests were performed, while t-tests were used for comparison of continuous variables. Logistic regression was then used to measure the association between psoriasis and UC and CrD in a multivariate analysis of variables stratified for age, gender, socioeconomic status (SES), and smoking status (Cohen et al., 2009).

The prevalence of both UC and CrD was significantly increased in patients with psoriasis compared to those without psoriasis. The association of UC and psoriasis compared with controls was statistically significant in patients 20-39 years old (OR=5.78;

95% CI 1.81-18.5, p-value ≤ 0.001), in male patients (OR=1.78; 95% CI 1.11-2.82, p-value < 0.05), and in non-smokers (OR=1.99; 95% CI 1.34-2.95, p-value ≤ 0.001). The multivariate analysis findings indicate that ulcerative colitis was significantly associated with a co-diagnosis for psoriasis (OR=1.65; 95% CI 1.15-2.33), as well as with age, sex and SES of the patient (Cohen et al., 2009).

The association of CrD and psoriasis compared with controls demonstrated similar, but more widespread results. For example, while UC showed statistical significance with patients aged 20-39 years, CrD was associated with patients in both the 20-39 (OR=6.05; 95% CI 2.91-12.6) and 40-59 (OR=2.14; 95% CI 1.13-4.05) age brackets. A significant association was also found for patients with psoriasis and CrD for both genders, with a higher burden on females (OR=4.60; 95% CI 2.50-8.45) versus males (OR=1.66; 95% CI 1.02-2.71), as well as in smokers (OR=2.78; 95% CI 1.26-6.16) and non-smokers (OR=2.48; 95% CI 1.61-3.80), compared to controls. The multivariate analysis indicates that, likewise to UC, CrD is significantly associated with co-disease of psoriasis (OR=2.49; 95% CI 1.71-3.62), age, sex and SES (Cohen et al., 2009).

As with other epidemiological studies utilizing secondary data, the major limitation of this study was an inability to confirm patient diagnoses, either for psoriasis, CrD and UC. Misclassification of information cannot, therefore, be completely ruled out. However, the authors stand by the strength of the CHS data warehouse, which sources all data through a universal EHR system, and capitalizes upon the expertise of Israel's practitioners (Cohen et al., 2009).   In summary, the findings of this study cast additional

support for a significant association between psoriasis and the inflammatory bowel diseases.

Psoriasis and Celiac Disease. Three of the authors from the previous study Birkenfeld, Dreiher, and Cohen, collaborated with a fourth author, Weitzman (2009) to investigate the association between psoriasis and celiac disease. With the exception of the evaluated outcome (celiac disease), this study mirrored the one previously described. This case-control study also utilized the large medical dataset of Clalit Health Services (CHS) and has been rated a 2+.

This study included 12,502 patients with psoriasis who were greater than twenty years old and 24,285 patients without psoriasis who were matched on a 2:1 ratio based on age and sex (Birkenfeld, Dreiher, Weitzman & Cohen, 2009).   The prevalence of CD was greater in patients with psoriasis than in controls. The association between psoriasis and CD was further evaluated by age, 20-39 years, 40-59 years and 60-110 years. In all age groups, the association was significant, however the strength of the association decreased with increasing age. Additionally, an association was prominent among women and among those of intermediate SES (Birkenfeld et al., 2009).

There were neither significant confounding factors noted among age, sex or SES, nor effect modification by any covariate.   The multivariate logistic regression analysis revealed that psoriasis was associated with CD (OR=2.73; 95% CI 1.65-4.53, p-value < 0.001). The strength of the associated remained significant after controlling for age, sex and SES (OR=1.79; 95% CI 1.03-3.10, p-value = 0.039).

The authors conclude that healthcare providers should be aware of the possible association between psoriasis and CD. Active screening for CD may lead to a diagnosis

of latent CD in patients with other autoimmune diseases, particularly in those with psoriasis (Birkenfeld et al., 2009).

Serology of Celiac Disease in Psoriasis. Damasiewicz-Bodzek and Wielkoszynski (2008) investigated whether patients with psoriasis also had increased levels of CD-associated antibodies compared to healthy controls, implicating gluten intolerance. The authors measured titres of IgA and IgG antibodies against tissue transglutaminse from guinea pig liver (a-GP-tTG), of IgA antibodies against human recombinant tissue transglutaminase (a-h-r-tTG IgA), of anti-gliadin antibodies (AGA IgA and AGA IgG), as well as anti-endomysial antibodies for IgA (IgEmA) in patients with and without psoriasis. The aim of this study was to demonstrate whether there is an increase in the frequency of those markers of CD in patients with psoriasis (Damasiewicz-Bodzek & Wielkoszynski, 2008). This cross sectional study has been rated 3.

The cases were identified based on hospital admission for intensified psoriatic skin lesions in the Upper Silesia (Poland) region. A total of 67 patients were included; 27 females and 40 males whose mean PASI score measured 25.9 ± 14.9. Patients with psoriatic arthritis and other diseases were excluded from the study. Controls without psoriasis were matched for sex and age. Patients with a family history for either psoriasis or celiac disease were excluded from the control group. The study commenced prior to any anti-psoriasis treatment was started, and all cases and controls were on gluten-containing diets. Blood samples were collected from both groups, following an overnight fast (Damasiewicz-Bodzek & Wielkoszynski, 2008).

Approximately 6% of psoriatic patients screened positive for four serologic markers, while 28.1% had three serologic markers positive, and 17.7% had two serologic markers positive. The authors proceeded to test the data in triplicate (Kolmogorov-Smirnov, U Mann-Whitney and Wald-Wolfowitz's) revealing that patients with psoriasis have statistically significant higher mean levels of antibodies against tissue transglutaminase from guinea pig liver (a-GP-tTG) for both IgA ($p <0.001$, P=0.000000 and p=0.000006, respectively) and IgG ($p < 0.001$, p=0.000001, and p=0.01) than do patients without psoriasis. Furthermore, in 46% of the cases for IgG, and as much as 66% of the IgA cases, titres of antibodies were higher than the 90th percentile of the control values. Patients with psoriasis also had higher mean levels of IgA antibodies against the human recombinant tissue transglutaminase ($p < 0.001$, P = 0.036 and p=0.002); 54% of the cases were higher than the 90th percentile of the control values. The titres of antibodies against gliadin between psoriatics and controls were increased at statistically significant levels for IgA ($p < 0.001$, p = 0.000000 and p = 0.0005), but not for IgG ($p > 0.01$, p = 0.75, and p = 0.244). And no anti-endomysial antibodies for IgA were found in any serum, either cases or controls. (Damasiewicz-Bodzek & Wielkoszynski, 2008).

The authors also used the Spearman rank correlation to test the association between the examined antibodies and the PASI score. Concentrations of a-h-r-tTg IgA positively correlated with concentrations of a-GP-tTG IgA, a GP-tTg IgG and AGA IgA. Concentrations of a-h-r-tTG IgA, a-GP-tTG IgA and AGA IgA also positively correlated with PASI (Damasiewicz-Bodzek & Wielkoszynski, 2008). Given the widely accepted use of these serologic antibody tests to diagnose celiac disease, these results suggest that

there is an association between psoriasis and asymptomatic celiac disease/gluten

intolerance (Damasiewicz-Bodzek & Wielkoszynski, 2008).

Early Detection of Crohn's Disease in Psoriasis. Radtke et al. (2015) published

the results of a German interdisciplinary partnership whose objective was to develop

screening algorithms for dermatologists for twelve different comorbidities in patients

with psoriasis, including chronic inflammatory bowel disease. This effort stemmed from

a national survey on psoriasis care in 2005, which indicated deficits in care for those with

psoriasis in Germany. As a result, the German "National Healthcare Goals in Psoriasis

2010-2015" defined early detection of comorbidities in psoriatic patients as a nationwide

goal of dermatological care (Radtke et al., 2015). At the 2010 Healthcare Research

Conference, the establishment of a methodological basis for the implementation of this

health care goal was tasked to a working group of the conference and confirmed by the

German Society of Dermatology (DDG) and the Professional Association of German

Dermatologists (BVDD). The goal of this work was to develop descriptive and practical

screening algorithms, thereby providing dermatologists with the decision-making tools

required for early diagnosis of comorbidities (Radtke et al., 2015).   This consensus paper

would be considered expert opinion, and as such this study has been rated a 4.

The task was approached from a three-stage process. First, a national consensus

conference on psoriasis established a definition for the requirements, areas of application,

conception, and methodology of an agreed screening algorithm (Radkte et al., 2015).

Second, a literature search was conducted to investigate the most relevant comorbidities

associated with psoriasis, as well as possible screening approaches. More than 2,000

publications were included in the appraisal and evidence for the use of screening

parameters for the individual comorbidities was compiled (Radtke et al., 2015). Finally, an interdisciplinary group of the National Healthcare Conference evaluated the algorithms according to content-related, methodological, and formal characteristics, as well as practicability. The algorithms were then adopted through a Delphi consensus process (Radtke et al., 2015).

Since dermatologists in Germany are the most frequently consulted provider for patients with new onset psoriasis, it was considered imperative that these providers facilitate early detection of associated comorbidities. The twelve comorbidities chosen for screening in patients with psoriasis included arterial hypertension, dyslipidemia, obesity, diabetes mellitus, metabolic syndrome, nonalcoholic steatohepatitis, depression, nicotine abuse, alcohol abuse, psoriatic arthritis, malignant lymphoma and chronic inflammatory bowel disease (Radtke et al., 2015). The following target parameters for screening were identified for IBD.

Table 2.2 Screening Parameters for IBD

Chronic diarrhea (> 3 bowel movements per day and > 4 weeks) and ≥ 1 of the following symptoms:	Blood in stool
	Pain or bleeding during intestinal peristalsis
	Painful defecation (DD: differentiation from anal fissure, hemorrhoids)
	Abdominal pain especially in the right lower abdomen
	Pyoderma gangrenosum, erythema nodosum, oral aphthae
	Temperature > 37.8 °C (100 °F) during the past 7 days
	Weight loss
	Anal fistula, anal fissures, or perirectal abscesses or other fistulas (e.g. entero-vesical fistula)
	Ocular involvement: uveitis or iritis
	Arthritis or arthralgia

(Radtke et al., 2015)

The recommended interval for follow-up examinations for individuals with mild psoriasis is every 12 months, and every 6 months for individuals with severe psoriasis (Radtke et al., 2015). The collaborative efforts of DDG and BVDD underscore the importance of primary prevention and health promotion in at risk groups, particularly in those with psoriasis.

2.6 Synthesis of Findings

Of the fourteen articles reviewed for this evidence-based project, ten investigated the association of psoriasis with Crohn's disease, seven with celiac disease, and four with rheumatoid arthritis. Among the four genetic studies with varying research methodologies, a pattern emerges that lends support for an association between psoriasis and the three AI diseases under investigation. Tsoi et al. (2013) demonstrated that 39 psoriasis susceptibility loci are known today, ten of which overlap with Crohn's disease, nine with celiac disease, and five with rheumatoid arthritis. And, a significantly increased multiple AI disease risk was found to be associated with the CD226 Gly307Ser t allele rs763361, a gene that has been reported to be associated with psoriasis, celiac disease, and rheumatoid arthritis (Qui et al., 2013). The Wolf et al. (2008) study implies that three Crohn's disease SNPs are significantly associated with psoriasis. Finally, the results of Einarsdottir's et al. (2009) study suggest that there is an association of IL23R with Crohn's disease, psoriasis and celiac disease.

A similar pattern appears within the population based studies. Among those focusing on psoriasis and celiac disease, two studies demonstrate a positive association between psoriasis and celiac disease (Birkenfeld et al., 2009; Wu et al., 2012), while two more also demonstrate that patients with psoriasis tend to exhibit the presence of

serological markers associated with celiac disease (Bhatia et al., 2014; Damasiewicz-Bodzek & Wielkoszynski, 2008). Further, evidence suggests that a GFD, typically prescribed to patients with celiac disease, may lead to resolution or improvement of psoriatic lesions (Bhatia et al., 2014).

Six population-based studies investigated the association between psoriasis and Crohn's disease. With the exception of one study (Tsai et al., 2011), the other five studies showed statistically significant associations between the two AI diseases (Augustin et al., 2010; Cohen et al., 2009; Li et al., 2013; Makredes et al., 2009; Wu et al., 2012). It is also very compelling that dermatologists in Germany have acknowledged the relationship between psoriasis and IBD, recommending that providers screen annually for IBD in moderate cases and bi-annually in severe cases of psoriasis, in order to promote best patient outcomes (Radtke et al., 2015).

With respect to psoriasis and rheumatoid arthritis, three population-based studies highlight the relationship between these two AI diseases. Wu et al. (2012) found that among 21 different AI disorders, RA held the strongest statistically significant association with psoriasis. The Tsai et al. (2011) study found that the total risk for RA among all patients with psoriasis was calculated to be 3.02 times that for non-psoriatic patients. And, individuals with psoriasis showed increased rates of RA compared to individuals without psoriasis in the Augustin et al. (2010) study.

2.7 Summary

While it is clear that the autoimmune puzzle is by no means complete, requiring substantial and robust future research efforts, healthcare providers may be able to take into consideration and utilize the information presently available, which is as follows.

One, autoimmune disorders can take years to diagnose, primarily because symptoms may present vaguely and also due to healthcare provider knowledge deficits about AI diseases in general, and how they relate to one another. Two, earlier detection of autoimmune diseases and initiation of treatment may improve patients' long-term outcomes. Three, individuals with one autoimmune disorder are more likely than the general population to have one or more other AI diseases. Four, the most prevalent AI disease is psoriasis. Five, psoriasis belongs to a subset of AI diseases called IMIDs, which includes celiac disease, rheumatoid arthritis and Crohn's disease. There is a genetic relationship among these diseases. Six, individuals with psoriasis seem to have an increased risk of also having celiac disease, rheumatoid arthritis and Crohn's disease.

Chapter 3

Project Design

3.1 Methods

Research indicates that individuals with psoriasis may be predisposed to the three IMIDs of interest to this study, celiac disease, rheumatoid arthritis and Crohn's disease. The literature also suggests that health care providers would be prudent to evaluate psoriatic patients in a prospective manner for these AI disorders in order to improve the patient's long-term health outcomes.

The purpose of this project is to conduct a substantive review of the literature and conduct screening of primary care patients with psoriasis to determine early detection of celiac disease, rheumatoid arthritis, and Crohn's disease. The objective of this quality improvement project is to administer a patient questionnaire to adult patients aged 18 years and greater with psoriasis, screening for signs and symptoms of celiac disease, rheumatoid arthritis and Crohn's disease. This quality improvement project was guided by evidence provided by the literature search and synthesis, the methods based on the Iowa Model of Evidence-Based Practice. The Iowa Model provided a guideline to decrease barriers while instilling confidence in the new patient questionnaire. This chapter will present the methods for conducting the project. A detailed process is outlined for implementing the project, including a time frame, intervention, and data management.

3.2 Design

The project will implore a retrospective (chart review), one test design to determine if the patient with psoriasis has been screened as noted by the provider documentation. The provider will make a referral for further diagnostic testing or to a specialist based on the patient questionnaire algorithm, which will be noted in the provider's documentation.

3.3 Instrument

To date, no individual screening tools have yet been validated as having sufficient predictive ability for celiac disease, rheumatoid arthritis or Crohn's disease. Diagnosis for these AI diseases relies upon a combination of patient history, physical examination, laboratory tests, imaging studies and biopsy (Pincus, Yazici & Sokka, 2009). Current diagnostic algorithms are founded on the if/than approach: if these symptoms exist, and if positive serologies or scans/biopsy are present, than we can conclude diagnosis. The path to diagnosis still begins with a provider's strong suspicion of disease.

For groups that have been identified to be at higher risk than the general population for development of these AI diseases, including patients with psoriasis, practitioners' must have a simple tool that kindles suspicion, opens discussion, and facilitates investigation at the earliest signs of possible disease. Patient questionnaires used in clinical practice are effective toward collecting patient information, guiding management, documenting change in status, assessing outcomes, and improving the quality of care (McCollum & Pincus, 2009). Therefore, an immune-related patient questionnaire and referral algorithm have been developed based on the current understanding of signs and symptoms for these AI diseases.

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According to the guidelines developed by both the American College of Gastroenterology (Rubio-Tapia et al., 2013) and the British Society of Gastroenterology (Ludvigsson et al., 2014), any patient with signs or symptoms of CD should undergo testing. These include the following: chronic or recurrent diarrhea, weight loss, abdominal pain after eating, abdominal distention or bloating after eating, history of Irritable Bowel Syndrome (IBS), anemia, vitamin D deficiency, or elevated liver enzymes. The aforementioned guidelines, as well as those developed by the American Gastroenterological Association (AGA) Institute (Kagnoff, 2006), further indicate that symptomatic, first-degree relatives with celiac disease are at a higher risk for CD than those in the general population, with a prevalence of approximately 10%, and should be tested for CD.

According to the American College of Gastroenterology (Lichtenstein et al., 2009) and Laass, Roggenbuck and Conrad (2014) with the Institute of Immunology, patients should be suspected for Crohn's disease with the following symptomology: chronic or recurrent diarrhea, weight loss, abdominal pain after eating, painful bowel movements, blood in stool, or fever. The European Crohn's and Colitis Organization (Van Assche et al., 2009) supports testing in symptomatic patients who have previously been told they have IBS, or have a history of anemia, vitamin D deficiency, or elevated liver enzymes. All authors agree that family history is key, due to the fact that first-degree relatives of patients with Crohn's disease have a 10-15 fold risk for also having Crohn's disease. Symptomatic patients with family history should be investigated for Crohn's (Laass et al., 2014; Lichtenstein et al., 2009; Van Assche et al., 2009).

Finally, recommendations from the National Guideline Clearinghouse (2012) and

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the ACR/EULAR classification criteria (Cohen & Emery, 2010) guided the questions related to rheumatoid arthritis. Patient with the following signs and symptoms should be considered for RA, including morning stiffing for greater than 30 minutes for more than 6 weeks, joint/muscle pain on a daily basis for more than 6 weeks, tender/swollen joints on a daily basis for more than 6 weeks, tingling in hands/feet on daily basis for more than 6 weeks, plus weakness/fatigue for more than 6 weeks.

The purpose of this patient questionnaire is two-fold: (1) to improve and streamline the screening process for health care providers for celiac disease, Crohn's disease and rheumatoid arthritis among patients with psoriasis, and (2) to elicit immune-related information from the client that might otherwise be overlooked, decreasing the lag time between symptom onset and diagnosis. The purpose of the referral algorithm is to help inform provider clinical decision-making steps based on patient questionnaire responses. As such, the DNP project author developed a patient questionnaire (See Appendix D) and referral algorithms (See Appendices E, F and G) based on existing evidence and guidelines for care. Neither the patient questionnaire, nor the algorithms, has been tested for reliability or validity.

The questionnaire includes two demographic questions (age and gender), one question regarding family history for celiac disease, Crohn's disease, and rheumatoid arthritis, plus sixteen primary questions, which focus on the signs and symptoms of celiac disease, Crohn's disease, and rheumatoid arthritis. Seven of the questions pertain to both celiac disease and Crohn's disease, as symptoms can be comparable between these two AI diseases. Three questions are specific to Crohn's disease, one specific to celiac disease, and a total of five questions specific to rheumatoid arthritis.

The primary questions are dichotomous, requesting a simple "yes" or "no" answer (0 designates "no" and 1 designates "yes" for each framed question). Eight of these primary questions are conditional; if the patient provides a "yes" response, then the patient is directed to answer subsequent questions.

Three algorithms for referral have also been developed, one each for celiac disease (see Appendix E), Crohn's disease (See Appendix F), and rheumatoid arthritis (See Appendix G). The algorithms take into consideration the patient responses to the questionnaire and assist the provider's clinical decision-making regarding whether or not referral for additional specialty care and work up is merited.

3.4 Unit of analysis

The first unit of analysis is the patient questionnaire, which will be presented in descriptive statistics (frequency tables).   The second unit of analysis is the provider's documentation of the patient questionnaire and subsequent referral, if indicated based on the questionnaire.

Data will be collated using a 2 x 2 table in which the two possible outcomes include whether the patient questionnaire was administered/not administered, and whether a referral was made/not made to a specialist for additional work-up. The outcome evaluation will determine if the patient questionnaire has facilitated possible identification of co-autoimmunity (celiac disease, Crohn's disease, and/or rheumatoid arthritis) in these psoriatic patients.

Additionally, the information provided by the patient via the patient questionnaire will be entered in an Excel spreadsheet, one row per patient. The excel database will be

used to calculate the prevalence of celiac disease, rheumatoid arthritis, and Crohn's disease symptoms among the total number (N) of psoriatic patients seen in the practice.

3.5 The Setting

The administration of the patient questionnaire will take place on location at a private dermatology practice in Springfield, Virginia. The provider, referred to as "MD One," is board certified in dermatology and dermatopathology, specializing in the diagnosis and treatment of medical, surgical and cosmetic conditions of the skin, hair and nails. Practicing since 1973, MD One serves a racially diverse, urban population in the greater Northern Virginia area (48.7% Caucasian, 9.0% AA, 24.3% Asian, 25.5% Hispanic and 7.5% other). MD One accepts private insurance through Aetna, Blue Cross Blue Shield, Cigna, as well as Medicare, but not Medicaid. The lack of current protocol at this practice for screening patients with psoriasis for celiac disease, rheumatoid arthritis and Crohn's disease has created an opportunity for a quality improvement project.

3.6 Sample

Inclusion criteria will consist of patients aged 18 years or greater, who are able to speak, read and comprehend English, with a current diagnosis for psoriasis. Current diagnosis for psoriasis refers to existing patients being treated by MD One for psoriasis, as well as new referrals from primary care providers for additional psoriasis treatment. Furthermore, self-referred patients may also be included if a new psoriasis diagnosis occurs at the first visit with MD One. Approximately thirty patients are targeted for the sample project.

3.7 Description of intervention

      Staff Training. The two Patient Service Representatives (PSRs) at the

dermatology practice are the initial point-of-contact for all patients and visitors.

Responsibilities include, but are not limited to, greeting patients and visitors, assisting

patients with appointment check-ins, obtaining information from new and established

patients, accurate medical record entry, scheduling appointments, and answering

telephones. The PSRs will be critical to the implementation of the quality improvement

project, as they will be responsible for identification of potential patients with psoriasis

and with dissemination of the patient questionnaire. Therefore, the author will meet with

both PSRs on the afternoon of Friday, June 9, 2017 on-site at the practice during "down"

time, after patient appointments have finished, typically around 12:30pm.

      The project objective, an increased understanding of co-autoimmunity among the

psoriatic patients at the practice, as well as the supporting research, will be shared with

the PSRs in order to promote an understanding of the project and secure buy-in from

these participants. Additionally, the author will demonstrate respect for the PSRs, which

will encourage staff support.   PSRs will be provided with every opportunity to voice

concern or questions over the questionnaire process.   PSRs will also be asked for their

input on how to best streamline the process based on their understanding of clinic flow;

consideration will be given to their suggestions for simplifying the overall process and

this will promote ownership of project with PSRs.

      Following the project introduction, the questionnaire will be reviewed, and

instruction will be given regarding the protocol for implementation of the questionnaire.

PSRs will provide the questionnaires to adult patients aged 18 and greater that have an

ICD-9 diagnosis code of 696 (psoriasis and similar disorders) or ICD-10 diagnosis code of L40.0-L40.5 from a previous clinic visit at their check-in. This information will be determined from the practice's scheduling and billing software, MacPractice, at the beginning of the day before the first appointment has arrived and reiterated during the staff's morning "huddle." The MacPractice Management system allows the user to run reports on existing patients by diagnosis code. For newly referred patients or self-referred patients, the PSRs will review the reason for the patient's appointment, via scheduling software notes and intake form. If it is not apparent why the new patient requires dermatological expertise, the patient will simply be asked why they are being seen upon their arrival.

If the previously stated qualifications are satisfied, the PSR will retrieve a blank questionnaire from a to-be-determined storage area, and give to the patient to fill out in the lobby prior to their appointment. The PSR will collect the completed form from the patient and paper clip, content-side down, to the front of the patient's chart for MD One to review prior to their appointment.

MD One Training. MD One's buy-in is critical to the success of project implementation. As the principal provider, the project intervention could potentially fail without his ongoing support for the duration of this project. Therefore, MD One and the author project will meet Friday, June 9, 2017 in order to discuss overall project objectives, the foundations on which the project is based, and MD One's involvement.

Research findings that support the co-existence of psoriasis and celiac disease, rheumatoid arthritis, and Crohn's disease will be presented to MD One. The information will be presented in the form of a bulleted handout during a face-to-face meeting,

providing MD One with the opportunity to ask questions and address any questions or concerns. Additionally, the patient questionnaire and referral algorithms will be reviewed to ensure understanding of which symptoms will prompt additional referral needs. A project outline will also be provided defining milestones and responsibilities, project implementation, and project completion.

First and foremost, MD One's primary responsibility is to review the completed patient questionnaire, noting pertinent positives. It is important to note that this questionnaire has been designed to be simple and quick to fill-out by the patient, highlight potential co-autoimmune burdens, and facilitate conversation; however, it is not exhaustive, nor a replacement for additional medical history, physical exam, or testing. Therefore, when key indicators suggest potential symptomology for celiac disease, rheumatoid arthritis and/or Crohn's disease, MD One will also review the referral algorithms to determine if the patient is a candidate for referral to a gastroenterologist or rheumatologist. If the patient meets the criteria for referral, MD One will ask the PSR to coordinate the referral.

Although scheduling and billing for this practice are electronic, MD One uses paper charting to document patient history, systems review, assessment and treatment plans. For the purposes of this quality improvement project, MD One will also document in the paper chart that the patient has been screened via patient questionnaire and if referral was coordinated. The screening questionnaire will remain in the medical chart, becoming a part of the patient's permanent record. Post visit, MD One will place the patient chart in a discharge bin for filing by the end of the day.

Project Implementation. The implementation of the patient questionnaire will span a total of two weeks, five workdays per week, Monday through Friday. The ideal timeframe for project execution is June 12, 2017 through June 23, 2017.

Chart Review. The project author will review all charts placed in the discharge bin throughout the day on a daily basis, so as not to disrupt the office's daily rhythm and current practices. Each chart reviewed will be recorded first, on the "Coded Identifier List" form (See Appendix H) and second, on the "Chart Review Data Collection Form" (See Appendix I). The author will also transcribe data from completed screening questionnaires to the "Screening Questionnaire Data Collection Form" (See Appendix J). Table 3.1 indicates the timeframe for project implementation and the data collection process.

Table 3.1 Time Intervals for Quality Improvement Project

Activity	Timeframe
Obtain IRB approval	June 6, 2017 (See Appendix L)
MD One Training Patient Service Representatives Training	June 9, 2017
Implement Patient Questionnaire	June 12, 2017 through June 23, 2017
Data Collection and Retrieval	On a daily basis during the two weeks of project implementation

3.8 Data Management and Analysis Methods

As previously mentioned, three forms will be completed during the chart review: the coded identifier list, the chart review collection form, and the screening questionnaire collection form. This data will be input into an encrypted and also password-protected excel file, which will be stored on a password-protected laptop, known only by the author.

The objective of the coded identifier list is to create a simple log, which will provide a method for a) tracking charts reviewed, ensuring that there is no duplication of data, and b) de-identifying participants through the assignment of a subject ID number, which will then be used in the two data collection forms. The columns included in this form are patient name, chart number, visit date, and subject ID number. The subject ID numbers will begin with "1" and run consecutively in ascending order. This subject number will be transferred to the chart review collection form, and as appropriate the screening questionnaire collection form. No patient identifiers will be collected that can be traced back to the patients' charts.

The chart review collection form will record the subject ID number, and if the patient has psoriasis (yes/no). If the patient was not being seen for psoriasis management or does not have a history of psoriasis, the chart review will be completed on that patient. If the patient does fulfill the psoriasis requirements, than the following components will also be reviewed: if the questionnaire was completed (yes/no), if the provider documented the screening (yes/no), and if referral was made (yes/no).

Finally, the screening questionnaire data collection form will document the patient responses to each question for completed questionnaires. The collection form includes the subject ID number, forty columns that correspond to both the primary and conditional questions asked by the screening form, plus a final column that indicates whether this patient was referred or not.

In order to organize, sort and synthesize the answers provided by the patients, each response option has been numerically coded. The codes for each question may be reviewed in the data collection form (See Appendix J). The initial row of this form is

considered to be the master key for processing the data collected. A separate index (Appendix K) has been created for the three questions on the form (13b, 14a and 15a) uniquely pertaining to the Rheumatoid Arthritis diagram, with fifty-five designated options denoting left, right and/or bilateral anatomical body locations.

After the data has been compiled, the author, in collaboration with a statistician, will prepare the collected data for analysis. Data collected from the chart review will be categorically analyzed using either the chi square or Fisher's Exact test via SAS 9.4 statistical software. The chi square test is designed to provide marginal frequencies with information gathered from sources with two possible outcomes. Should cells frequencies have expected values of less than 5, Fisher's Exact test will be used to improve analytical accuracy.

The data will be collated using a 2 x 2 table in which the two possible outcomes include whether the patient was screened/not screened by the provider, and whether a referral was made/not made to a specialist. For this test, the alpha level of significance is 0.05 ($\alpha = 0.05$), and the degrees of freedom equals 1 (df = 1).

The data collected from the patient questionnaire will be analyzed using Excel spreadsheet tools. Descriptive statistics regarding the sample, as well as the prevalence (percentages) of symptoms relating to celiac disease, Crohn's disease, and rheumatoid arthritis for these patients with psoriasis, will be calculated.

3.9 Human Subjects

Institutional Review Board (IRB) approval will be sought from the University of South Carolina as an exempt study for quality improvement. Upon approval, this author will initiate project implementation, and be exclusively responsible for data collection

and management. Three layers of protection will safeguard all data collected in order to ensure patient confidentiality. All data collected during the creation of the coded identifier list, chart review data collection, and the screening questionnaire response collection will be migrated into three separate, encrypted and also password-protected excel files. The files will then be stored on a password-protected laptop; the master coded identifier list will be stored separately from the collection forms data, on a second password-protected laptop.

Data collection will occur throughout the lifespan of this quality improvement project, during the anticipated two-week project period, on a daily basis. The author alone will be responsible for chart reviews and data collection, which will occur in a private office on location at the clinic. The author will retrieve completed patient charts from the discharge bin, and relocate to the reserved office area for chart review and data transcription. Upon completion of chart review and data transcription, the author will return the charts to a newly designated bin, which will signal to staff that the chart is now ready for filing. At no time will charts be left alone in the private office.

Following data collection, but prior to data analysis, the identifier code list file will be destroyed via the free, downloadable *Eraser* software application (Eraser, 2016). Initiation of the Eraser program, a security tool for Windows platforms, will guarantee that the code list file has been permanently removed from the operating system. Subject number alone will ultimately catalogue and ensure non-duplication of patient data; no patient data or responses will be linkable to patient identities.

The data collected for this quality assurance project will focus solely on whether the provider screened the psoriatic patient, if the patient was referred for additional

specialty evaluation as a result, and the patients' answers from the screening

questionnaire. The descriptive statistics produced from the questionnaire will reflect the

cohort in the aggregate. Finally, this project will practice patient respect throughout;

patients have the right to refuse to participate in patient screening, no questions asked.

3.10 Framework/model of research

The Iowa model of evidence-based practice to promote quality care was very

influential throughout the development of this practice-change project (Melnyk &

Fineout-Overholt, 2011). This model provides a step-by-step framework for nurse

research utilization toward improving patient care. The model's first step was utilized to

define an opportunity for improvement regarding knowledge about psoriasis and co-

autoimmunity with celiac disease, rheumatoid arthritis and Crohn's disease. The

culmination of this step resulted in the PICO question. The second and third steps in the

Iowa model guided the evidence search and then, the critical appraisal of the literature

included in this systematic review, ensuring the integrity and quality of the data collected.

The fourth step directed the practice change design process through the identification of

proposed practice change, identifying resources, evaluation design development and plan

implementation (Melnyk & Fineout-Overholt, 2011). The final two steps, five and six,

influence the implementation of the pilot study and integration of study into standards of

practice. Step five outlines the critical steps for implementing the quality assurance

project to include an evaluation of process, outcomes, costs and the development of

conclusions and recommendations (Melnyk & Fineout-Overholt, 2011). Step six of the

model discusses how to integrate and maintain change in practice, through the process of

engaging stakeholders, incorporating the change into the practice, monitoring the process, and distribution of final outcomes (Melnyk & Fineout-Overholt, 2011).

3.11 Strategies to reduce barriers and increase supports

To reduce potential barriers, such as provider or staff resistance to the implementation of a practice change, meetings with key change champion and opinion leader, MD One, and central staff players (PSRs) will be arranged. MD One's and staff buy-in is critical to the process of project implementation. It is critical that MD One and staff appreciate the value of an increased understanding of their patient population toward promoting improved patient outcomes for patients with psoriasis. At the meetings with MD One and staff, the need for change in practice, as well as the compelling evidence that supports this need for change, will be discussed. Printed materials summarizing key points will supplement the discussion and be provided for distribution among clinic staff.

Patient resistance to participate and complete the patient questionnaire is also a possible barrier. The patient questionnaire has been designed to take no more than five minutes to complete, and will be provided to the patient with the other pre-appointment documentation. The patient will be able to complete the questionnaire while waiting in the lobby, therefore, not extending the patient's personal time burden at the visit.

Finally, the author will be onsite for the duration of the project implementation and immediately available for patient questions, as well as staff and MD One support, in order to help ease the transition of a new practice change.

3.12 Summary

Additional population studies are urgently needed in order to determine the association of psoriasis with other AI disorders, and namely with celiac disease, Crohn's

disease, and rheumatoid arthritis. This quality improvement project will demonstrate that healthcare providers may have previously not been aware of co-autoimmunity in their psoriasis patients, demonstrate the ability to determine this information with a patient questionnaire, and foster increased awareness among healthcare providers about the autoimmune state of their psoriatic patients.

Clinicians should consider psoriasis as a systemic inflammatory disorder with potential for other autoimmunity issues, rather than an isolated skin disease. Increased awareness about co-autoimmunity in the patient with psoriasis is necessary for optimal patient management and will help to facilitate best patient outcomes.

Chapter 4

Results

4.1 Introduction

The aim of this project was to assess the utility of early screening in patients with psoriasis in order to facilitate earlier diagnosis of CD, RA and CrD, which would consequently initiate earlier treatment and improve long-term patient outcomes. The outcomes measured include the responses from the patient questionnaire and if the provider documented screening for polyautoimmunity and referral indications. Chapter four provides a summary of these results from the quality improvement project and is divided into the following sections: description of the sample, analysis of the research questions, and conclusion.

The analysis is divided into four sub-sections. The first sub-section focuses on the answers to the primary questions that directly fed the algorithms. The second sub-section discusses the answers to the conditional questions, which collected additional information on symptoms. The third sub-section discusses the retrospective chart review, and the last sub-section examines more closely the patients who fulfilled the requirements for additional evaluation for celiac disease, Crohn's disease and rheumatoid arthritis based on their reported symptoms.

4.2 Description of Sample

This quality improvement project occurred during the weeks of June 12, 2017 through June 23, 2017, covering 10 business days at a Northern Virginia dermatology clinic. A total of # (n=261) were seen at the clinic for a variety of different skin disorders. Thirty-four adult patients with either a history of psoriasis or a new diagnosis of psoriasis completed the patient questionnaire during this timeframe, which assessed for the presence of evidence-based signs and symptoms for celiac disease, Crohn's disease and rheumatoid arthritis. Seventeen of these patients (50%) were female; seventeen (50%) were male. The mean age of the psoriatic patients was 55.71 years old, ranging in ages 18 to 81 years old.

4.3 Analysis of Research Questions

Two unit of analysis were identified for this quality improvement project. The first unit of analysis was the patient questionnaire. The second unit of analysis was the provider's documentation of the patient questionnaire and subsequent referral, if indicated based on the questionnaire. Six tables are presented below to review the data collected from this quality improvement project.

Patient Questionnaire: Primary Questions. Table 4.1 depicts the participants' responses to the seventeen primary questions from the patient questionnaire. Frequency data indicated that the most reported symptom was a history of vitamin D deficiency (38.24%). Thirty percent of psoriatic patients reported having a first-degree relative with celiac disease, Crohn's disease or rheumatoid arthritis. The next most frequently reported symptoms were for rheumatoid arthritis: daily joint or muscle pain > 6 weeks (29.41%), daily tender or swollen joints > 6 weeks (23.53%), and weakness or fatigue > 6 weeks

(23.53%). The most reported GI symptom was abdominal distention and/or bloating after eating (14.71%). The least reported symptoms, at 2.94% each, were abdominal pain after eating, painful bowel movements, and running a fever in the past 4 weeks (Table 4.1).

Table 4.1 Patient Questionnaire Frequency Distributions / Primary Questions

Question #	Question	Yes		No	
		N	%	N	%
11	Has a HCP ever told you that you have a Vitamin D deficiency?	13	38.24	21	61.76
1	Do you have a 1st degree relative with CD, CrD or RA?	10	29.41	24	70.59
14	Have you had joint or muscle pain on a daily basis for > 6 weeks?	10	29.41	24	70.59
15	Have you had any tender or swollen joints on a daily basis for > 6 weeks?	8	23.53	26	76.47
17	Have you had weakness or fatigue for > 6 weeks?	8	23.53	26	76.47
13	Have you had morning stiffness in any of your joints for > 60 minutes for > 6 weeks?	6	17.65	28	82.35
16	Have you had tingling sensations in your hands or feet on a daily basis for > 6 weeks?	6	17.65	28	82.35
5	Do you suffer from abdominal distention and/or bloating after	5	14.71	29	85.29

	eating?				
7	Have you ever seen blood in your stool?	5	14.71	29	85.29
12	Has a HCP ever told you that you have elevated liver enzymes?	4	11.76	30	88.24
2	Do you have chronic or recurrent diarrhea (≥ 3 loose stools per day for > 4 weeks)?	2	5.88	32	94.12
3	Have you been losing weight?	2	5.88	32	94.12
9	Has a HCP ever told you that you have IBS?	2	5.88	32	94.12
10	Has a HCP ever told you that you were anemic?	2	5.88	32	94.12
4	Do you have abdominal pain after eating?	1	2.94	33	97.06
6	Is it painful to have a bowel movement?	1	2.94	33	97.06
8	Have you had a fever in the past 4 weeks?	1	2.94	33	97.06

Patient Questionnaire: Frequency Distributions / Conditional Questions.

Tables 4.2, 4.3 and 4.4 depict the responses for the nine conditional questions

asked by the patient questionnaire. If a patient answered "yes" to any of the nine

conditional questions, they were then prompted to answer additional questions. The

additional questions were developed in order to collect supplementary information related

to the patient's initial positive response. These responses are also presented by

frequency. The primary questions are shaded in grey, by row, and the related conditional

responses are indented just below, a summary of which follows.

For the 29.41% psoriatic patients that reported having a first-degree relative with CD, CrD or RA, 46.51% of individuals reported that this relative was their mother. CD was reported in 38.46% of the cases, with CrD and RA each being reported in 30.76% of the cases of first-degree relative. One individual had a mother with both CD and RA; a second individual reported having a child with both CD and CrD, and a third individual reported having a mother with CD and a brother with CrD.

Joint and muscle pain for greater than six weeks was reported by 29.41% of psoriatic patients. Tender and swollen joints on a daily basis for greater than six weeks was reported by 23.53%. 17.65% reported morning stiffness in their joints for more than 60 minutes a day for greater than six weeks. Although responses varied per patient, collectively these individuals indicated that their pain, tenderness, swelling and stiffness was located either bilaterally, or unilaterally, at the neck, shoulders, hands, fingers, hips, knees, ankles, and feet. Sixty percent of these respondents indicated that their pain was between a 5-7 on a pain scale of 0 (no pain) to 10 (worst pain of their life). 50% reported a "constant" pain, and 40% described their pain as "aching." Fifty percent of the patients that indicated morning stiffness said that they experienced it everyday.

Weakness or fatigue for greater than 6 weeks was reported in 23.53% of psoriatic patients, and 55.56% indicated that they experienced their weakness and fatigue 1-3 days per week. Two patients (5.88%) reported weight loss over the past 6 months. One individual reported a loss of 15-pounds and the other reported a 20-pound loss. Only one patient (2.94%) reported abdominal pain after eating, in the LUQ, causing 3/10 cramping pain that lasted for one hour. Finally, one patient (2.94%) reported having a fever of 101°C in the past 4 weeks.

Table 4.2 Questionnaire Frequency Distributions / First Degree Relative

Question #	Primary Question	Conditional Question	Conditional Response	N	%
1	Do you have a 1st degree relative with CD, CrD or RA?			10 patients reported one or more 1st degree relative(s) with CD, CrD and/or RA.	29.41
		Do you have a mother/father/sister/ brother/child with …	Mother Father Sister Brother Child	6 2 1 1 3	46.15 15.38 7.69 7.69 23.07
		… CD, CrD or RA?	CD CrD RA	5 4 4	38.46 30.76 30.76

Table 4.3 Questionnaire Frequency Distributions / Conditional GI symptoms

Question #	Primary Question	Conditional Question	Conditional Response	N	%
3	Have you been losing weight?			2 patients reported losing weight.	5.88
		How much weight have you lost over the past 6 months?	15 pounds 20 pounds	1 1	50 50
4	Do you have abdominal pain after eating?			1 patient reported abdominal pain	2.94
		Where does your pain occur?	LUQ	1	100
		How would you rate your pain?	3/10	1	100
		How long does the pain last?	1 hour	1	100
		How would you describe the pain?	Cramping	1	100
8	Have you had a fever in the past 4			1 patient reported having a fever	2.94

Quest-ion #	Primary Question	Conditional Question / Response		N	%
	weeks?				
		What was your temperature?	fever=101° C	1	100

Table 4.4 Questionnaire Frequency Distributions / Conditional Arthritis Symptoms

Quest-ion #	Primary Question	Conditional Question / Response		N	%
14	Have you had joint or muscle pain on a daily basis for > 6 weeks?			10 patients reported joint or muscle pain	29.41
		Where is your pain located?			
		• bilateral knees		1	10
		• bilateral neck, bilateral shoulders, bilateral hips		1	10
		• bilateral neck, right shoulder, left knee, left ankle		1	10
		• bilateral pointer fingers, bilateral middle fingers, bilateral ring fingers, bilateral pinky fingers		1	10
		• left hand, left ankle, right foot		1	10
		• left hip, left knee		1	10
		• left shoulder, bilateral hands, bilateral hips, bilateral feet		1	10
		• left shoulder, left hand		1	10
		• left shoulder, left hip, left knee		1	10
		• right neck		1	10
		How would you rate your pain?	1/10	1	10
			3/10	1	10
			4/10	1	10
			5/10	2	20
			6/10	2	20
			7/10	2	20
			9/10	1	10
		How long does the pain last?	2-6 hrs to constant	1	10
			constant	5	50
			comes and goes	1	10
			depends on site	1	10

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			hours	1	10
			morning	1	10
		How would you describe the pain?	throbbing	1	10
			shooting	1	10
			stabbing	2	20
			cramping	1	10
			aching	4	40
			pressure	1	10
			cramping	1	10
			burning	3	30
			aching	2	20
			asleep	1	10
15	Have you had any tender or swollen joints on a daily basis for > 6 weeks?			8 patients reported tender or swollen joints	23.53
		Which joints have been tender or swollen?			
		• bilateral ankles		1	25
		• bilateral neck, bilateral shoulders		1	12.5
		• bilateral pointer fingers, bilateral middle fingers, bilateral ring fingers, bilateral pinky fingers		2	25
		• bilateral pointer fingers, bilateral middle fingers, bilateral ring fingers, bilateral pinky fingers, bilateral ankles, bilateral feet		1	12.5
		• right ankle, left foot		1	12.5
		• right knee		1	12.5
		• right pointer finger, right middle finger, right ring finger, right pinky finger		1	12.5
17	Have you had weakness or fatigue for > 6 weeks?			8 patients reported weakness/fatigue	23.53
		How often do you have weakness or fatigue?	Every day	3	33.33
			1-3 days/week	5	55.56
			4-6 days/week	1	11.11
13	Have you			6 patients reported	17.65

				joint stiffness	
had morning stiffness in any of your joints for > 60 minutes for > 6 weeks?					
		How often do you have morning stiffness > 60 minutes?	Every day	3	50
			1-2 days/wk	2	33.33
			4-6 days/wk	1	16.67
		Which joints are stiff?			
		• bilateral hands, left knee		1	16.66
		• bilateral neck, bilateral shoulders, bilateral hips		1	16.66
		• bilateral neck, bilateral shoulders, right wrist, bilateral pointer finger, bilateral middle fingers, bilateral ring fingers, bilateral pinky fingers, right hip, bilateral feet		1	16.66
		• bilateral pointer finger, bilateral middle finger, bilateral ring finger, bilateral pinky finger		1	16.66
		• left hand, left ankle, right foot		1	16.66
		• left pointer finger, left middle finger, left ring finger, left pinky finger		1	16.66

Chart Review. Table 4.5 depicts the data collected during the chart review. A total of 261 patient charts were reviewed. For 227 of the charts, the review was completed and closed when the DNP project investigator determined that the patient did not have a history of, or a new diagnosis for, psoriasis. The remaining 34 patient charts demonstrated either a history of, or a new diagnosis for, psoriasis. Provider documentation for all 34 patients demonstrated 100% compliance for noting that the patient a) had been screened, and b) if referral was or was not indicated.

During the project-planning phase that was summarized in chapter 3, the author

initially had intended on categorically analyzing the chart review data with a chi square

test or Fisher's Exact test. The purpose of this analysis was to provide marginal

frequencies with information gathered from sources with two possible outcomes.   Since

100% compliance occurred, neither the chi square nor Fisher's Exact test could be

utilized. On the recommendation of the collaborating statistician, no alternative tests

were appropriate for further analyzing this data.

Table 4.5 Chart Review

Total Sample	Pts with psoriasis	Patients Screened		Documentation of screening		Documentation of referral (y/n)	
(n)	N	N	%	N	%	N	%
261	34	34	100	34	100	34	100

     Referred Patient Symptoms. Table 4.6 depicts the signs and symptoms for the

eleven patients who were referred for additional evaluation based on their patient

questionnaire responses. Prior to discussing these results, a brief recap is provided first

of the evidence-based algorithms for referral care. CD should be considered in any

patient with a first-degree relative with CD and who also demonstrates any of the targeted

GI symptoms. Without a first-degree relative, CD should be considered if the patient has

three or more of the GI symptoms (See Appendix E). CrD evaluation is indicated for

patients who have a first-degree relative with CrD and who demonstrate any of the GI

symptoms acknowledged to occur with CrD. If the patient does not have a first-degree

relative, they may be considered if they have had chronic diarrhea for more than 4 weeks

and have at least one of the identified GI symptoms (See Appendix F). Finally, patients

should be considered for RA if they have synovitis in at least one joint or three or more

arthralgia symptoms (See Appendix G).

As per the chart review, the responses provided by 11 of the 34 psoriatic patients indicated that they should receive additional evaluation by either a gastroenterologist or a rheumatologist. Upon development of Table 4.6, however, the author realized that two of the patients (subjects 8 and 23) did not actually satisfy the algorithm requirements. This indicates that an element of user-error compromised the process when evaluating the completed questionnaires.

The remaining nine patients (26.47%) did, in fact, satisfy the algorithms. Based on the patient questionnaire responses, five individuals fulfilled the requirements for additional celiac disease evaluation and six individuals fulfilled the requirements for additional rheumatoid arthritis evaluation. Two of the nine patients merited additional evaluation for both celiac disease and rheumatoid arthritis. No patients were referred for possible Crohn's disease. In the table below, for each of the subjects a red "X" depicts the patient's reported GI symptoms, while a blue "X" depicts reported arthritis symptoms.

Table 4.6 Patient Symptoms Warranting Additional Evaluation

ID#	Gender	Age	Relative	Diarrhea	Weight Loss	Abd Pain	Abd distention	Painful BM	Blood in stool	Fever	Hx IBS	Hx Anemia	Hx Vit D Def.	Hx LFTs	Stiffness	Pain Joint	Swelling	Tingling	Weakness	Eval
8	F	40													X	X				X
11	M	49	X						X							X				X
12	M	57	X	X	X				X	X						X		X	X	X X
23	M	50												X				X			X
46	M	64	X						X												X
68	M	4											X		X	X	X	X		X	X

93

		1															
13 3	F	4 8				X			X		X						X	X
13 9	F	5 9											X	X	X	X	X	X
19 4	M	5 7											X	X	X	X		X
22 1	M	4 3									X			X	X	X	X
23 0	F	7 5				X	X	X	X	X	X		X	X	X		X	X X

GI Symptoms = X; arthritis symptoms =X

4.4 Conclusion

This quality improvement project highlights several important facts. First, with proper planning, time commitment and a champion for change, real process modifications in health care management are possible. By utilizing and implementing the steps provided by the Iowa Model for Evidence Based Practice, the foundation for change was established for successful screening of adult patients with psoriasis for celiac disease, Crohn's disease, and rheumatoid arthritis. Of the 34 patients identified with a diagnosis for psoriasis, all were appropriately screened for polyautoimmunity. Provider documentation demonstrated buy-in and compliance with this project.

Although two patients were inappropriately flagged for additional evaluation, this provides an opportunity to re-evaluate the patient questionnaire review step. This DNP Project investigator theorizes that the responses to the conditional questions, whose answers are not applied against the algorithms, but were meant for collecting additional symptom history, may have complicated the questionnaire review. With this in mind, three possible methods for improving this step have been identified.

The simplest option would be to have a PSR pre-screen the questionnaire and indicate via highlighter marker only the positive answers to primary questions before

provider review. Further, an algorithm check-box could be developed and completed for each questionnaire. This would provide an alternative and more concise view of responses as they relate to the algorithms. Unfortunately, with both of these alternatives, an opportunity for human-error still exists. The most sophisticated option includes the development of a computer-based questionnaire that would have built in rules for analyzing the data and automatically determining whether a referral is indicated. Obviously, this would require additional cost for software development and hardware (tablets or laptops for patient use), but would effectively eliminate user-error.

The second significant take-away from this quality improvement project is that a real need exists for evaluating adult patients with psoriasis for polyautoimmunity and familial autoimmunity. The fact that nine of the 34 patients, or 26.47% of psoriatic patients indicated for further evaluation based on their reported gastrointestinal and/or arthritic symptoms underscores that need for provider screening and is consistent with the literature. Additionally, 29.41% of the psoriatic patients reported having a first-degree relative with CD, CrD and/or RA (8.82% of whom merited additional evaluation) supports the literature that states providers should be asking about their family history of autoimmune disorders.

Despite having flagged nine patients with psoriasis for referrals, it is important to note that an indication for referral does not automatically indicate a diagnosis for co-autoimmunity. Additional evaluation is necessary in order to rule-out the many other possible differential diagnoses that could be associated with these symptoms. The best-case scenario as it relates to this quality improvement project is that these individuals with psoriasis may be identified as having celiac disease, Crohn's disease or rheumatoid

arthritis earlier in the course of their disease, improving long-term patient outcomes. Worst-case scenario is that these patients are evaluated for these symptoms that need additional evaluation anyway.

Despite this limitation, this quality improvement project demonstrates the merging of two relatively distinct evidence-based practices and research: 1) the current practice for evaluating patients for celiac disease, Crohn's disease and rheumatoid arthritis and 2) the literature that suggests that these practices should be proactively applied to patients with psoriasis.

Chapter 5

Discussion

5.1 Introduction

The purpose of this project was to conduct a substantive review of the literature to determine if screening primary care patients with psoriasis will improve early detection of celiac disease, rheumatoid arthritis, and Crohn's disease. The aim of this project was to assess the utility of early screening in patients with psoriasis in order to facilitate earlier diagnosis of CD, RA and CrD, which would consequently initiate earlier treatment and improve long-term patient outcomes. The evidence-based practice question is: In adult patients aged 18 years and greater with psoriasis, does screening for celiac disease, rheumatoid arthritis, and crohn's disease improve early detection for these autoimmune disorders?   A retrospective chart audit of 261 adult patients with psoriasis was conducted for polyautoimmunity screening. Chapter five presents recommendations and implications for practice, education, research and policy development.

5.2 Recommendations for Practice

According to the quality improvement project and consistent with the literature, there is evidence supporting prospective evaluation of adult patients with psoriasis for polyautoimmunity, specifically celiac disease, Crohn's disease and rheumatoid arthritis. Findings from the project underscore the need for provider utilization of a patient

questionnaire that promotes identification of family history of autoimmune disorders, as well as significant symptoms for each of these three autoimmune disorders in the patient with psoriasis.   Further, the adoption of a screening process for polyautoimmunity in psoriatic patients in outpatient settings would help to narrow the provider's focus on polyautoimmunity. This is as opposed to managing symptoms without respect for the relationship among autoimmune diseases, missing the potential connection, and allowing AI disease to progress unchecked.

5.3 Recommendations for Education

Improved clinical awareness among health care providers about the coexistence of AI diseases within individuals may also play a critical role in providing the best patient care and in achieving the best patient outcomes. Health care practitioners must acknowledge that the presence of one AI disease may be indicative for the potential of other AI diseases. Dermatologists and primary care providers in particular, as the usual gatekeepers for diagnosis and management of psoriasis, should been keenly aware of the possibility of other, latent AI disease in the adult patient with psoriasis.

Ideally, this improved awareness should start in the classroom. The educational institution's commitment to producing the best future health care providers should include foundational instruction regarding autoimmune disorders as a disease continuum worthy of its own category, and not simply as part of the current and traditional disease classification by organ system.

Educating providers about prospective evaluation of polyautoimmunity in patients with psoriasis must include discussions on the background and significance of the most current genetic and population-based studies that tie psoriasis, celiac disease, Crohn's

disease and rheumatoid arthritis to each other.   Research publications continue to be the best method for reaching the most providers in the field.

5.4 Recommendations for Research

Additional research and improved awareness of autoimmune disorders, among both the public and healthcare providers, remains the cornerstone of future efforts to better understand autoimmune disorders, to better understand their co-existence, and toward a better plan for diagnosis and management of AI disorders. Despite research advances made in the past two decades, substantial deficits remain in the understanding of psoriasis, the most commonly diagnosed AI disorder in the United States. Specifically, a greater understanding of the pathogenesis of psoriasis, comorbidities, and patient treatment demands further research in these areas. However, psoriasis research should not be conducted within a vacuum. While it is critical to understand how psoriasis stands alone as an autoimmune disorder, it is also imperative to develop research toward understanding how and why psoriasis co-exists with other autoimmune disorders. For example, why is there a 2.3-fold greater risk of celiac disease co-occurring with psoriasis (Wu et al., 2013)? And compared to individuals without psoriasis, why do subjects with psoriasis have a 3.02-fold increased risk of rheumatoid arthritis (Tsai et al., 2011)? Aside from seeking answers to these questions about psoriasis and its co-existence with other AI disorders, there also exist other compelling reasons for targeting psoriasis in autoimmune research.

First, psoriasis is known to be the most prevalent AI disorder in the United States, affecting as many as 7.5 million Americans, and 125 million worldwide (National Psoriasis Foundation, 2014). Second, the concept of pan autoimmunity, or diathesis of

autoimmunity (Ali & Warren, 2013; Pender et al., 2002), proposes that individuals with one autoimmune disease are predisposed genetically to other autoimmune diseases. Extrapolating the pan autoimmunity theorem to apply to patients with psoriasis, we can therefore expect that these individuals would also be genetically predisposed to other autoimmune diseases. However, this supposition is not just a leap of blind faith; epidemiological data already supports this hypothesis. The literature reviewed for this project strongly suggests a link between psoriasis and celiac disease, rheumatoid arthritis and Crohn's disease (Augustin et al., 2010; Bhatia et al., 2014; Birkenfeld et al., 2009; Cohen et al., 2009; Damasiewicz-Bodzek & Wielkoszynski, 2008; Einarsdottir et al., 2009; Li et al., 2013; Makredes et al., 2009; Qui et al., 2013; Radtke et al., 2015; Tsai et al., 2011; Tsoi et al., 2013; Wolf et al., 2008; Wu et al., 2012).

Therefore, given the sheer number of individuals available for basing research inquiries, plus the existing data suggesting AI co-existence patterns, individuals with psoriasis would seem to be a highly relevant patient population by which to start building on our current understanding of polyautoimmunity. The research community must, therefore, pay greater attention to the underlying genetic relationships between psoriasis and other autoimmune disease, and to how this genetic relationship influences the individual and familial clustering of many inflammatory and metabolic disease processes.

Another challenge to the field of immunology that demands attention is the development of reproducible, cost-efficient, and sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals (NIH, 2005). Fortunately, many research initiatives are currently underway and increased NIH research funding for autoimmune diseases has trended upward from $587 million in 2007 to $821

100

million in 2013 (AARDA, 2011). And in 2009, the Centers for Disease Control and

Prevention (CDC) led an effort to develop the first-ever public health agenda for psoriasis

and psoriatic arthritis, which will guide future public health efforts and research into

these diseases. Congress approved $1.5 million to the CDC to begin the first federal

effort to collect data on people with psoriatic diseases (CDC, 2010).

Among the many initiatives currently in place are the Multiple Autoimmune

Diseases Genetics Consortium (MADGC), Environment/Infection/Gene Interactions in

Autoimmune Diseases, Autoimmunity Centers of Excellence, Autoimmune Biomarkers

Collaborative Network, Cooperative Study Group for Autoimmune Diseases Prevention

(Prevention Centers), Autoimmunity Centers of Excellence, and Clinical Trials and

Clinical Markers in Immunologic Diseases (AARDA, 2011). Each of these initiatives'

overall objective, while unique, is to facilitate autoimmunity research collaboration, to

identify and characterize the genes that are common to these diseases, to develop biologic

markers for measuring disease activity, risk, and therapeutic effect, and to advance our

understanding of treatment interventions (AARDA, 2011).

5.5 Recommendations for Policy

The challenges, and solutions, to the autoimmune problem are wide-ranging and

complex. As the work continues in solving the autoimmunity puzzle, the immediate need

is for increased awareness among patients and healthcare providers about the immensity

of this public health concern and for Congress to recognize autoimmunity's overall

financial burden to the nation. The challenges of autoimmunity need to be recognized as

a high priority agenda item today.

5.6 Limitations

This quality improvement project capitalizes on the most current research and evidence-based literature, however, there are many limitations to this project that must be acknowledged. A prominent limitation of this project is that the patient questionnaire and algorithms' ability to adequately assist with the identification of celiac disease, Crohn's disease and rheumatoid arthritis have not been investigated; neither the questionnaire, nor the algorithms have been tested for reliability or validity. Fortunately, it was never intended for this questionnaire to be a replacement for additional medical history, physical exam, or testing. The objective was to assist the provider in identifying potential signs and symptoms for other AI disease in an at risk patient population, adult patients with psoriasis.

Other limitations include location, sample size, and length of study. While a dermatology clinic lends itself perfectly to this quality improvement project in terms of patient population, a limitation is that the patient must then be referred out for additional evaluation, if suspicion is high for other disease. The dermatologist in this case, and most likely in other dermatology clinics, will not be willing to conduct further studies prior to the specialty referral. While this is considered to be a disadvantage in the dermatology clinic, it would actually be an advantage in the primary care practice setting. Additional testing could be conducted in the primary care setting before deciding if specialty referral was merited.

Finally, the sample size for this quality improvement project was relatively small (n = 34) and all patient participants were from an urban part of the state of Virginia. The length of time for the project was a significant limitation to this study, allotting for only

two weeks to implement the patient questionnaire. Due to the short lifespan of the

project, the author does not know the result of any of the patient referrals.

5.7 Conclusion

While many of the AI diseases have low prevalence as a single occurring health

disease, collectively autoimmune diseases are the third most common category of disease

in the United States after cancer and heart disease (NIH, 2005) affecting approximately 5-

8% of the population or approximately 23.5 million Americans.   Psoriasis is known to be

the most prevalent AI disease in humans (Raychaudhuri, 2014), affecting approximately

2-5% of the world population and as many as 7.5 million Americans (NIH, 2005). The

concept of pan autoimmunity, or diathesis of autoimmunity (Ali & Warren, 2013; Pender

et al., 2002), proposes that individuals with one autoimmune disease are predisposed

genetically to other autoimmune diseases. Finally, the literature suggests that there is a

genetic link between psoriasis, celiac disease, Crohn's disease and rheumatoid arthritis

(Augustin et al., 2010; Bhatia et al., 2014; Birkenfeld et al., 2009; Cohen et al., 2009;

Damasiewicz-Bodzek & Wielkoszynski, 2008; Einarsdottir et al., 2009; Li et al., 2013;

Makredes et al., 2009; Qui et al., 2013; Radtke et al., 2015; Tsai et al., 2011; Tsoi et al.,

2013; Wolf et al., 2008; Wu et al., 2012).

In light of these statistics, as providers, researchers, educators and policy makers,

we must recognize the two following realities: 1) the significance of familial

autoimmunity and polyautoimmunity to the adult patient with psoriasis, and 2) the

possibility of encountering many undiagnosed and subclinical cases of "other"

autoimmune disease in the psoriatic patient population. By acknowledging these

autoimmune principles, the provider is able to then act proactively for the patient and

routinely consider the possibility that a patient with psoriasis may develop celiac disease, Crohn's disease or rheumatoid arthritis over the course of their lifetime. Providers are able to have a lasting impact on the well-being of psoriatic patients through the prospective evaluation of signs and symptoms of these autoimmune diseases.

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Scottish Intercollegiate Guidelines Network (SIGN) Grading System 1999 – 2012: Levels of Evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

(SIGN, 2013)

Appendix B

Evidence Table

	Brief Reference	Type of study/ Quality rating	Methods	Threats to validity/ reliability	Findings	Conclusions
1 Psoriasis Crohn's Celiac	Tsoi, L.C., Spain, S.L, Knight, J., Ellinghaus, E., Stuart, P.E., Capon, F.,…Trembath, R.C. (2013). Identification of fifteen new psoriasis susceptibility loci highlights the role of innate immunity. *Nature Genetics, 44*(12), 1341-1348.	Meta-Analysis Level of evidence: 1+	A meta-analysis of three GWAs and two independent datasets genotyped on the "Immuno-chip," to include a total of 10,588 cases (patients with psoriasis) and 22,806 controls.	GWAS studies are only able to detect an association for a genomic region, and not causation of a mutation, that may be involved in the development of the disease or trait.	A genome-wide significance ($P<5\times10^{-8}$) for 19 of the 21 known psoriasis loci. Nominal evidence was demonstrated for the two remaining loci. Fifteen new risk loci for psoriasis were also identified that fulfilled genome-wide significance Of the total 39 known and new psoriasis susceptibility loci included in this study, ten of these loci overlapped with Crohn's disease, nine with celiac disease, and five with rheumatoid arthritis.	Additional genomic studies are required to further identify the underlying causal variants with psoriasis susceptibility loci, leading to increased understanding of pathogenic mechanisms and new therapeutic targets.

| 2 Psoriasis RA Celiac | Qiu, Z.X., Zhang, K., Qiu, X.S., Zhou, M. & Li, W.M. (2013). CD226 Gly307Ser association with multiple autoimmune diseases: A meta-analysis. *Human Immunology, 74*, 249-255. | Meta-Analysis Level of evidence: 1+ | A meta-analysis to evaluate the relationship between the non-synonymous single nucleotide polymorphism (SNP) Gly307Ser (rs763361) in the CD226 gene that has been reported to be associated with several AI diseases, including psoriasis, celiac disease, and rheumatoid arthritis. The authors conducted a comprehensive search of the U.S. National Library of Medicine's PubMed and Embase databases. Seven published studies met the | This study lacked the original information for the individuals in the included studies; as such, data could not be stratified by other variables, such as gender, and mean age at onset (Qui et al, 2013). The lack of original data also means that the authors would not have been able to validate each case for the meta-analysis. Therefore, the possibility of diagnoses misclassification in the original studies cannot be completely excluded. Second, races other than South American, Asian, European and Estonian were not represented in this meta-analysis. Third, the authors note that while their publication bias showed no significance, it | The evaluation of the association of CD226 Gly307Ser (rs763361) polymorphism with multiple AI diseases demonstrated an overall OR 1.19 (95% CI: 1.12-1.27, $P_{heterogeneity}$=0.136), The authors also conducted a subgroup analysis by ethnicity, where increased risks were found for South Americans (OR=1.31, 95% CI=1.17-1.48, Pheterogeneity = 0.644), Asians (OR=1.23, 95% CI=1.11-1.38, Pheterogeneity = 0.690), and Europeans (OR=1.13, 95% CI=1.04-1.24, Pheterogeneity = 0.085) (Qui et al, 2013). Heterogeneity existed among both the overall | A significantly increased multiple AI disease risk was found to be associated with the t allele rs763361. |

			inclusion criteria, covering 7,876 cases and 8,558 controls. The sample sizes varied from 90 to 2,838 and included two European, two Asian, one South American and three Estonian studies.	cannot be completely ruled out due to exclusion of relevant publications that were not indexed by their selected databases, PubMed and Embase (Qui et al, 2013).	comparison and in sub-group analysis, but none were notable.	
3 Psoriasis Celiac	Bhatia, B.K., Millsop, J.W., Debbanch, M. Koo, J., Linos, E. & Liao, W. (2014). Diet and psoriasis, part II: Celiac disease and role of a gluten-free diet. *Journal of the American Academy of Dermatology, 71*(2), 350-358.	Meta-Analysis Level of evidence: 1+	Meta-analysis of population-based studies examining the co-occurrence of psoriasis and celiac disease, investigations of celiac disease antibody markers in psoriatic cohorts, and clinical trials examining the therapeutic benefit of a gluten free diet (GFD) in patients with psoriasis		Three population studies were reviewed, all of which demonstrated that patients with psoriasis are at an increased risk for celiac disease. Fourteen studies related to serological celiac disease markers in psoriasis patients were reviewed. Of these fourteen, nine studies reported a positive association between celiac disease markers, while seven did not find statistically significant evidence	health care providers should screen their patients with psoriasis for symptoms of celiac disease, including diarrhea, flatulence, fatigue and history of iron-deficiency anemia. Positive findings should flag providers to then run serological tests for celiac associated antibodies

					for an association. A statistically significant relative risk of testing positive for IgA anti-gliadin antibody (AGA) in patients with psoriasis, as compared to control subjects (OR_{total} = 2.36; 95% C.I. 1.15-4.83) Six studies demonstrated that patients with psoriasis, with either elevated AGA and/or tTG, showed improvement in psoriatic lesions after a GFD.	
4 Psoriasis RA Celiac Crohn's	Wu, J.J., Nguyen, T.U., Poon, K.Y.T., & Herrinton, L.J. (2012). The association of psoriasis with autoimmune diseases. *Journal of the American Academy of Dermatology, 67*(5), 924-930. doi:10.1016/j.jaad.2012.04.039	Retrospective Cohort study (with control group) Level of evidence: 2+	A retrospective cohort study in order to examine the association between psoriasis and 21 common autoimmune diseases that share common pathogenetic mechanisms, including celiac disease, Crohn's	First, diagnostic information was culled from databases and prior diagnostic codes, neither of which were validatable (information bias). And due to their medical issues, the patients with psoriasis may have had more frequent contact with the	Psoriasis was positively associated with 17 of the 21 studied AI diseases, with 14 of these associations being statistically significant. The strongest association was with RA (OR=3.6; 95% CI 3.4-3.9). Celiac disease was the third strongest association	These findings suggest that patients with psoriasis are more likely than control subjects to be given the diagnosis of an additional autoimmune disease. The authors conclude their study by recommending

			disease and RA. 25,341 patients with psoriatic disease were ultimately matched with 126,705 control subjects from KPSC.	health care system resulting in a greater opportunity to record associated diseases, as compared to the control group (selection bias). Another limitation to this study is that is was limited to the geographic location of southern California.	(OR=2.3; 95% CI 1.6-3.2), and Crohn's disease was the fifth strongest association (OR=1.8; 95% CI 1.5-2.2). Individuals with psoriatic disease were more like likely to have at least two (OR=1.6; 95% CI 1.5-1.7) or three (OR=1.9; 95% CI 1.6-2.4) immune-mediated diseases compared to persons without psoriatic disease.	that the evaluation of patients with psoriasis for other autoimmune diseases may be warranted as part of their medical care.
5 Psoriasis RA NOT Crohn's	Tsai, T.F., Wang, T., Hung, S., Tsai, P.I., Schenkel, B., Zhang, M. & Tang, C. (2011). Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *Journal of Dermatological Science*, *63*, 40-46. doi:10.1016/j.jdermsci.2011.03.002	Retrospective Cohort study (with control group) Level of evidence: 2+	A retrospective cohort study (with controls) was performed using the Taiwan National Health Insurance Research Database (NHIRD) during 2006. The authors' aim was to study the prevalence of comorbidities in patients with psoriasis.	Possible information bias, lack of clinical data allowing for the adjustment of outcomes as related to potential confounders (smoking status or psychosocial factor), possible increased health care visits for psoriatic patients versus the controls, and geographic area.	Patients with psoriasis had a total increased risk for depression (RR=1.50; 95% CI 1.39-1.61, p-value >.0001), hypertriglyceridemia (RR=1.61; 95% CI 1.54-1.68, p-value >.0001), hypertension (RR=1.51; 95% CI 1.47-1.56, p-value >.0001), diabetes (RR=1.64; 95% CI 1.58-1.70, p-value >.0001),	Clinicians should take into consideration the association of co-morbidities when evaluating the potential burdens of psoriatic patients and designing effective health care management plans.

| | | | Patients were identified with at least one outpatient visit or admission claim with an ICD-9 diagnosis for psoriatic arthropathy (696.0) or psoriasis (696.1), resulting in a sample of 51,800 cases.

The psoriasis cases were then further classified by severity. Moderate to severe (sPsO, n=9,063), mild psoriasis (mPsO, n=36,252). Control group (n=207,200) was matched at a 4:1 ratio based on age, gender and residential area.

Co-morbidities were defined based on at least | | cardiovascular disease (RR=1.32; 95% CI 1.26-1.37, p-value >.0001) and malignancies of the digestive organs and peritoneum (RR=1.57; 95% CI 1.41-1.74, p-value >.0001).

Patients with moderate to severe psoriasis were found to have 10.25 times the risk for RA (95% CI 8.20-12.81, p value > .0001), and patients with mild psoriasis were found to have 1.56 the risk for RA (95% CI 1.33-1.83, p value > .0001) compared to patients without psoriasis. The total risk for RA among all patients with psoriasis was calculated to be 3.02 times that for non-psoriatic patients (95% CI 2.68-3.41, p value > .0001).

Patients with Crohn's disease was | |

				three claims for an outpatient visit or one hospitalization with a principal/secon-dary diagnosis within one year of the index date, 2006 (Tsai et al., 2011). The authors calculated prevalence associated with psoriasis and co-morbidities between cases and controls using relative risk (RRs) and 95% confidence intervals (CI) based upon a Cox proportional regression model.		actually lower in this study as compared to patients without psoriasis, although the authors state that this lower percentage did not show statistical significance.	
6 Psoriasis RA Crohn's	Augustin, M., Reich, K., Glaeske, G., Schaeffer, I. & Radtke, M. (2010). Co-morbidity and age-related prevalence of Psoriasis: Analysis of health insurance data in Germany. *Acta Dermato-Venereologica, 90*, 147-151. doi:	Retrospective cohort study (with control group) Level of evidence: 2+		Evaluation of the prevalence of co-morbidities in patients with psoriasis, particularly	Possible information bias, lack of clinical data allowing for the adjustment of outcomes as related to potential	Individuals with psoriasis showed increased rates of co-morbidities compared to individuals without psoriasis.	The results of this study strongly support the association of psoriasis and systemic chronic inflammatory

	10.2340/00015555-0770		those related to metabolic syndrome and RA and Crohn's disease. 33,981 individuals were identified for having psoriasis and 1,310,090 individuals without psoriasis served as the controls from a German nationwide statutory health insurance database. Prevalences were calculated for co-morbidities of interest and the prevalence ratio was determined by comparing the prevalence rate of the psoriatic group to the non-psoriatic group. Corresponding confidence intervals were	confounders (smoking status or psychosocial factor), possible increased health care visits for psoriatic patients versus the controls, and geographic area.	RA (PR=3.84; 95% CI 3.43-4.31) Metabolic syndrome (PR=2.86; 95% CI 2.21-3.71). Crohn's disease (PR=2.06; 95% CI 1.84-2.31) Diabetes mellitus (PR=2.02; 95% CI 1.96-2.08); hyperlipidemia (PR=1.75; 95% CI 1.72-1.78); arterial hypertension (PR=1.73; 95% CI1.71-1.76); and obesity (PR=1.72; 95% CI 1.68-1.76)	diseases. These findings should influence the healthcare management of patients with psoriasis by clinicians.

			computed by a general method based on constant X^2 boundaries.			
7 Psoriasis Crohn's	Makredes, M., Robinson, D., Bala, M., & Kimball, A.B. (2009). The burden of autoimmune disease: A comparison of prevalence ratios in patients with psoriatic arthritis and psoriasis. *Journal of the American Academy of Dermatology, 61*(3), 405-410. doi:10.1016/j.jaad.2009.02.015	Retrospective Cohort study (with control group) Level of evidence: 2+	A retrospective cohort study. The authors investigated whether patients with psoriatic arthritis (PsA) carry a higher AI disease burden than patients with psoriasis (PsO) alone. These authors utilized the IMS Health Integrated Administrative Claims Database (Norwalk, CT) to compare the prevalence of seven AI disorders among patients with PsA and PsO, including Crohn's disease and IBD.	Possible information bias, lack of clinical data allowing for the adjustment of outcomes as related to potential confounders (smoking status or psychosocial factor), possible increased health care visits for psoriatic patients versus the controls, and geographic area.	Patients with PsO had an increased PR associated with Crohn's disease (1.6; 95% CI 1.4-2.0) and inflammatory bowel disease (1.4; 95% CI 1.2-1.6) when compared to individuals without psoriasis. Demonstrating an even stronger relationship, patients with PsA also carried an increased risk for Crohn's disease (2.1; 95% CI 1.3-3.3) and inflammatory bowel disease (1.8; 95% CI 1.3-2.5).	First, the data supports the premise that PsA and PsO are associated with the development of other AI diseases. Second, patients with PsA and PsO appear to be at greater risk for GI diseases. Third, these findings suggest that evaluating psoriatic patients in a prospective manner for other associated AI disorders may be important toward the patient's long-term health outcomes.
8 Psoriasis Celiac	Birkenfeld, S., Dreiher, J., Weitzman, D, & Cohen, A.D. (2009). Coelic disease associated with psoriasis. *British Journal of*	Case-Control study Level of	A case-control study investigating the association	Inability to confirm patient diagnoses, either for psoriasis, CrD and UC.	The prevalence of CD was greater in patients with psoriasis than in	Healthcare providers should be aware of the possible

	Dermatology, 161, 1331-1334. Doi:10.1111/j.1365-2133.2009.09398.x	evidence: 2+	between psoriasis and celiac disease, via the large medical dataset of Clalit Health Services (CHS). Patient cases n=12,502; cohorts without psoriasis were matched by sex and age, n= 24,285	Misclassification of information cannot, therefore, be completely ruled out.	controls. The association between psoriasis and CD was further evaluated by age, 20-39 years, 40-59 years and 60-110 years. In all age groups, the association was significant, however the strength of the association decreased with increasing age. Additionally, an association was prominent among women and among those of intermediate SES (Birkenfeld et al., 2009). There were neither significant confounding factors noted among age, sex or SES, nor effect modification by any covariate. The multivariate logistic regression analysis revealed that psoriasis was associated with CD (OR=2.73; 95% CI 1.65-4.53, p-value <	association between psoriasis and CD. Active screening for CD may lead to a diagnosis of latent CD in patients with other autoimmune diseases, particularly in those with psoriasis.

					0.001). The strength of the associated remained significant after controlling for age, sex and SES (OR=1.79; 95% CI 1.03-3.10, p-value = 0.039).	
9 Psoriasis Crohn's	Li, W-Q., Han, J-L., Chan, A.T. & Qureshi, A.A. (2013). Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Annals of the Rheumatic Diseases, 72*, 1200-1205.	Prospective Cohort study Level of evidence: 2+	A prospective cohort study evaluated the association between psoriasis, psoriatic arthritis and incident UC and CrD among women in the US, using two large, ongoing prospective studies of US women, the Nurses' Health Study (NHS) and the NHS II. Statistical analysis included (1) time dependent Cox proportional hazards model stratified by age	Because the study was limited to US female healthcare workers, additional research should be conducted in other populations to confirm results.	Women with psoriasis had an increased risk of developing CrD with a multivariate adjusted RRs of 4.05 (95% CI 1.75-9.38) in NHS and 3.76 (95% CI 1.82-7.74) in NHS II. The pooled analysis demonstrated that psoriasis was associated with a RR of 3.86 (95% CI 2.23-6.67) for developing CrD (Li et al., 2013). The authors did not find a statistically significant increased RR for development of UC in women with psoriasis in either database.	These findings offer additional evidence in the support of common underlying mechanisms between psoriasis and CrD.

			for the estimation of relative risks (RRs) and 95% CI; (2) multi-variate analysis with adjust-ments for age, BMI, smoking, alcohol intake, physical activity, and use of postmeno-pausal, oral contraceptive, aspirin and NSAID drugs; (3) between-studies heterogeneity and overall association from random effects.			
10 Psoriasis Crohn's	Cohen, A.D., Dreiher, J. & Birkenfeld, S. (2009). Psoriasis associated with ulcerative colitis and Crohn's disease. *Journal of the European Academy of Dermatology and Venereology, 23*, 561-565. doi:10.111/j.1468-3083.2008.03031.x	Case-Control study Level of evidence: 2+	Case-control study investigating the relationship between psoriasis and the components of inflammatory bowel disease, UC and CrD, Utilization of a large, Israeli medical dataset via Clalit Health	Inability to confirm patient diagnoses, either for psoriasis, CrD and UC. Misclassification of information cannot, therefore, be completely ruled out.	The prevalence of both UC and CrD was significantly increased in patients with psoriasis compared to those without psoriasis. The association of UC and psoriasis compared with controls was statistically significant in patients 20-39 years	The findings of this study cast additional support for a significant association between psoriasis and the inflammatory bowel diseases.

| | | | Services (CHS). | | old (OR=5.78; 95% CI 1.81-18.5, p-value ≤ 0.001), in male patients (OR=1.78; 95% CI 1.11-2.82, p-value < 0.05), and in non-smokers (OR=1.99; 95% CI 1.34-2.95, p-value ≤ 0.001). The multivariate analysis findings indicate that ulcerative colitis was significantly associated with a co-diagnosis for psoriasis (OR=1.65; 95% CI 1.15-2.33), as well as with age, sex and SES of the patient (Cohen et al., 2009). | |
| | | | Patient cases n=12,502; cohorts without psoriasis were matched by sex and age, n= 24,285 | | The association of CrD and psoriasis compared with controls demonstrated similar, but more widespread results. For example, while UC showed statistical significance with patients aged 20-39 years, CrD was | |

					associated with patients in both the 20-39 (OR=6.05; 95% CI 2.91-12.6, p-value ≤ 0.001) and 40-59 (OR=2.14; 95% CI 1.13-4.05, p-value < 0.05) age brackets. A significant association was also found for patients with psoriasis and CrD for both genders, with a higher burden on females (OR=4.60; 95% CI 2.50-8.45, p-value ≤ 0.001) versus males (OR=1.66; 95% CI 1.02-2.71, p-value < 0.05), as well as in smokers (OR=2.78; 95% CI 1.26-6.16, p-value < 0.05) and non-smokers (OR=2.48; 95% CI 1.61-3.80, p-value < 0.05), compared to controls. The multivariate analysis indicates that, likewise to UC, CrD is significantly associated with co-disease of psoriasis	

					(OR=2.49; 95% CI 1.71-3.62, p-value < 0.001), age, sex and SES (Cohen et al., 2009).	
11 Psoriasis Crohn's	Wolf, N., Quaranta, M., Prescott, J.J., Allen, M., Smith, R., Burden, A.D., …Trembath, R.C. (2008). Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. *Journal of Medical Genetics, 45,* 114-116. doi:10.1136/jmg.2007.053595	Case-Control study Level of evidence: 2+	15 CrD susceptibility loci newly identified by genome-wide association analysis were assessed for significant disease associations with psoriasis. A total of 1,256 patients were included in the study, 645 male and 611 female, all of northern European descent and with onset of psoriasis vulgaris occurring before 40 years of age. Less than 1% of the patients also had documented CrD. The patients were		Significant disease association for three independent CrD markers, rs1203582 (p=0.009; OR=1.14; 95% CI 1.03 to 1.25), rs6908425 (p=0.00015; OR=1.26; 95% CI 1.12 to 1.42) and rs2836754 (p=0.0003; OR=1.17; 95% CI 1.06 to 1.30), was observed among the psoriasis cases (Wolf et al, 2008).	Three of the examined Crohn's disease SNPs are significantly associated with psoriasis. The results of this study lend additional evidence to suggest that individuals with psoriasis are also predisposed to CrD. This highlights the pleiotropic effects of co-autoimmunity, in which one gene influences two or more seemingly unrelated phenotypic traits.

			matched with 2,938 controls from the Wellcome Trust Case-Control Consortium (WTCCC). Patient DNA was typed using TaqMan assays and the frequencies of alleles for both cases and controls were compared using a X^2 test with one degree of freedom. Regression analysis was conducted with PLINK software.			
12 Psoriasis Celiac	Damasiewicz-Bodzek, A. & Wielkoszynski, T. (2008). Serologic markers of celiac disease in psoriatic patients. *Journal of the European Academy of Dermatology and Venereology, 22*, 1055-1061. doi:10.1111/j.1468-3083.2008.02713.x	Case-control study Level of evidence: 2+	Investigated whether patients with psoriasis also had increased levels of CD-associated antibodies compared to healthy controls, implicating gluten		5.7% of psoriatic patients screened positive for four serologic markers, while 28.1% had three serologic markers positive, and 17.7% had two serologic markers positive. By Kolmogorov-	Given the widely accepted use of these antibody tests to diagnose celiac disease, these results suggest that there is an association between psoriasis and asymptomatic

			intolerance. The authors measured titres of IgA and IgG antibodies against tissue transglutaminse from guinea pig liver (a-GP-tTG), of IgA antibodies against human recombinant tissue transglutaminase (a-h-r-tTG IgA), of anti-gliadin antibodies (AGA IgA and AGA IgG), as well as anti-endomysial antibodies for IgA (IgEmA) in patients with and without psoriasis.		Smirnov, U Mann-Whitney and Wald-Wolfowitz's tests, patients with psoriasis have statistically significant higher mean levels of antibodies against tissue transglutaminase from guinea pig liver (a-GP-tTG) for both IgA (p <0.001, P=0.000000 and p=0.000006, respectively) and IgG (p < 0.001, p=0.000001, and p=0.01) than do patients without psoriasis. Furthermore, in 46% of the cases for IgG, and as much as 66% of the IgA cases, titres of antibodies were higher than the 90th percentile of the control values. Patients with psoriasis also had higher mean levels of IgA antibodies against the human recombinant tissue transglutaminase (p	celiac disease/gluten intolerance.

					< 0.001, P = 0.036 and p=0.002); 54% of the cases were higher than the 90th percentile of the control values. The titres of antibodies against gliadin between psoriatics and controls were increased at statistically significant levels for IgA (p < 0.001, p = 0.000000 and p = 0.0005), but not for IgG (p > 0.01, p = 0.75, and p = 0.244). And no anti-endomysial antibodies for IgA were found in any serum, either cases or controls. Concentrations of a-h-r-tTg IgA positively correlated with concentrations of a-GP-tTG IgA, a GP-tTg IgG and AGA IgA. Concentrations of a-h-r-tTG IgA, a-GP-tTG IgA and AGA IgA also positively correlated with PASI .	

| 13 Psoriasis Crohn's Celiac | Einarsdottir, E., Koskinen, L.L.E., Dukes, E., Kainu, K., Suomela, S., Lappalainen, M., …Saavalainen, P. (2009). IL23R in the Swedish, Finnish, Hungarian and Italian populations: association with IBD and psoriasis, and linkage to celiac disease. *BMC Medical Genetics, 10*, 1-10. doi: 10.1186/1471-2350-10-8 | Cross sectional study

Level of evidence: 3 | Investigated the association of genetic markers in the interleukin-23 receptor (IL23R) gene, as well as the intergenic region between IL23R and IL122RB2, with inflammatory bowel disease and psoriasis in with Swedish and Finnish patients with IBD. Also, investigated IL23R's association with celiac disease among Finnish, Hungarian, and Italian populations. | Underrepresentation of non-Swedish, Finnish, Italian, Hungarian races | SNP rs11465804*G demonstrated the strongest association for the combined dataset including both CD and UC (p=0.002, OR=0.42). Marker rs1004819 also indicated a strong association with Crohn's disease in the Swedish population (p=0.006, OR=1.43) (Einarsdottir et al., 2009).

The Finnish families demonstrated significant linkage for celiac disease (lod=3.24, p=0.00006, 135 individuals), while the Hungarian families did not (lod=0.4, p=0.08, 132 individuals) (Einarsdottir et al., 2009). Additionally, none of the celiac disease case-control datasets demonstrated significant association to any of | 1st study to report association of IL23R with Crohn's disease and UC in Swedish pts with IBD. Also 1st to demonstrate linkage and association of the IL23R region wih psoriasis in the Finnish population. Also reports the novel finding of linkage with IL23R to celiac disease. |

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					the IL23R markers Fifty-one of the 255 Finnish families with psoriasis were informative for linkage, yielding a lod score of 0.83 (p=0.03). However, despite the low score, an association of IL23R with psoriasis was confirmed in the Finnish case-controls.	
14 Psoriasis Crohn's	Radtke, M.A., Mrowietz, J.U., Feuerhahn, M.H., Von Kiedrowski, R., Nast, K.R.A., Stromer, J.K. & Wohlrab, M.A. (2015). Early detection of comorbidity in psoriasis: recommendations of the National Conference on Healthcare in Psoriasis. *Journal of the German Society of Dermatology, 13*(7), 674-90. doi: 10.1111/ddg.12643	Expert opinion Level of evidence: 4	A German interdisciplinary partnership whose objective was to develop screening algorithms for dermatologists for twelve different comorbidities in patients with psoriasis, including chronic inflammatory bowel disease. First, a national consensus conference on		The twelve comorbidities chosen for screening in patients with psoriasis included arterial hypertension, dyslipidemia, obesity, diabetes mellitus, metabolic syndrome, nonalcoholic steatohepatitis, depression, nicotine abuse, alcohol abuse, psoriatic arthritis, malignant lymphoma and chronic inflammatory bowel	The following target parameters for screening were identified for IBD. Chronic diarrhea (> 3 bowel movements per day and > 4 weeks) and ≥ 1 of the following symptoms: − Blood in stool − Pain or bleeding during intestinal peristalsis − Painful defecation (DD:

| | | | | psoriasis established a definition for the requirements, areas of application, conception, and methodology of an agreed screening algorithm. Second, a literature search was conducted to investigate the most relevant comorbidities associated with psoriasis, as well as possible screening approaches. More than 2,000 publications were included in the appraisal and evidence for the use of screening parameters for the individual comorbidities was compiled Finally, an interdisciplinary group of the National | | disease. | differentiation from anal fissure, hemorrhoids) − Abdominal pain especially in the right lower abdomen − Pyoderma gangrenosum, erythema nodosum, oral aphthae − Temperature > 37.8 °C during the past 7 days − Weight loss − Anal fistula, anal fissures, or perirectal abscesses or other fistulas (e.g. enterovesical fistula) − Ocular involvement: uveitis or iritis − Arthritis or arthralgia |

			Healthcare Conference evaluated the algorithms according to content-related, methodological, and formal characteristics, as well as practicability. The algorithms were then adopted through a Delphi consensus process.			

Appendix C

Scottish Intercollegiate Guidelines Network (SIGN) Grading System 1999 – 2012: Grades of Recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Appendix D

Patient Questionnaire

Age: _____
Gender:

    ☐ Male
    ☐ Female

1) Do you have a first-degree relative with celiac disease, Crohn's disease or rheumatoid arthritis?

    ☐ No
    ☐ Yes

    If you answered yes to the question above, please complete the following:
    My mother / father / sister / brother / child has:
    ☐ Celiac disease
    ☐ Crohn's disease
    ☐ Rheumatoid arthritis

2) Do you have chronic or recurrent diarrhea? ($\geq$ 3 loose stools per day for > 4 weeks) (CD/CrD)
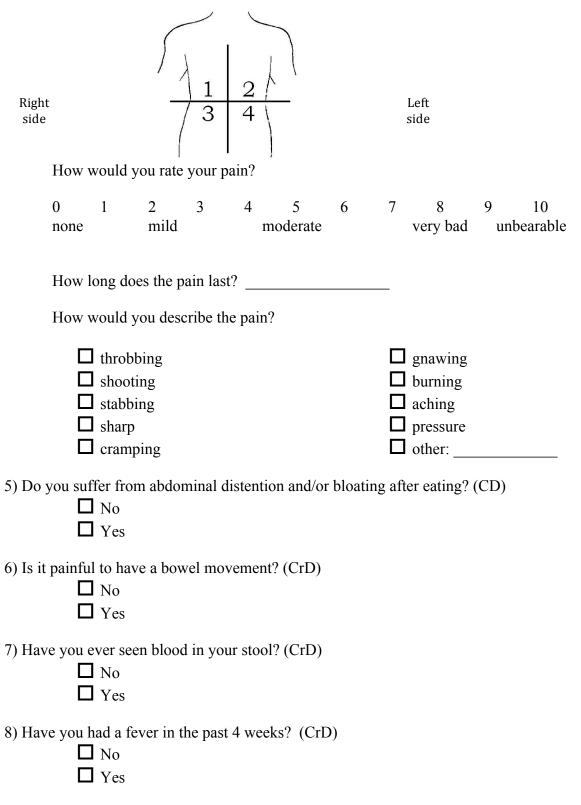
    ☐ No
    ☐ Yes

3) Have you been losing weight? (CD/CrD)

    ☐ No
    ☐ Yes

    If yes, how much weight have you lost over the past 6 months? _____

4) Do you have abdominal pain after eating? (CD/CrD)

    ☐ No
    ☐ Yes

If yes, indicate on the diagram below where your pain occurs:

1	2
3	4

Right side

Left side

How would you rate your pain?

0	1	2	3	4	5	6	7	8	9	10
none		mild			moderate			very bad		unbearable

How long does the pain last? _____

How would you describe the pain?

☐ throbbing   ☐ gnawing
☐ shooting   ☐ burning
☐ stabbing   ☐ aching
☐ sharp   ☐ pressure
☐ cramping   ☐ other: _____

5) Do you suffer from abdominal distention and/or bloating after eating? (CD)
     ☐ No
     ☐ Yes

6) Is it painful to have a bowel movement? (CrD)
     ☐ No
     ☐ Yes

7) Have you ever seen blood in your stool? (CrD)
     ☐ No
     ☐ Yes

8) Have you had a fever in the past 4 weeks? (CrD)
     ☐ No
     ☐ Yes

If yes, what was your temperature? _____

9) Has a health care provider ever told you that you have irritable bowel syndrome? (CD/CrD)

☐ No
☐ Yes

10) Has a health care provider ever told you that you were anemic? (CD/CrD)

☐ No
☐ Yes

11) Has a health care provider ever told you that have a vitamin D deficiency? (CD/CrD)

☐ No
☐ Yes

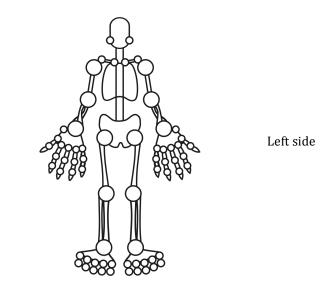12) Has a health care provider ever told you that you have elevated liver enzymes? (CD/CrD)

☐ No
☐ Yes

13) Have you had morning stiffness in any of your joints for > 30 minutes for > 6 weeks? (RA)

☐ No
☐ Yes

If yes, how often do you have morning stiffness > 30 minutes?

☐ every day
☐ 1-3 days a week
☐ 4-6 days a week
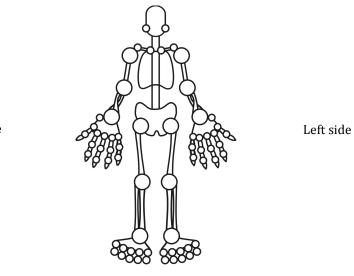
Indicate on the diagram below which joints are stiff:

14) Have you had joint or muscle pain on a daily basis for > 6 weeks? (RA)
   ☐ No
   ☐ Yes

If yes, indicate on the diagram below where your pain is located:

How would you rate your pain?

0	1	2	3	4	5	6	7	8	9	10
none		mild			moderate			very bad		unbearable

How long does the pain last? _____

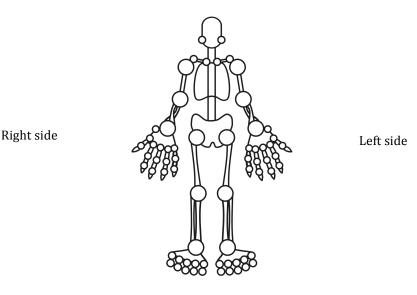How would you describe the pain?
- ☐ throbbing   ☐ gnawing
- ☐ shooting   ☐ burning
- ☐ stabbing   ☐ aching
- ☐ sharp   ☐ pressure
- ☐ cramping   ☐ other: _____

15) Have you had any tender or swollen joints on a daily basis for > 6 weeks? (RA)
- ☐ No
- ☐ Yes

If yes, indicate on the diagram below which joints are tender or swollen:

Right side   Left side

16) Have you had tingling sensations in your hands or feet on a daily basis for > 6 weeks? (CD/RA)
- ☐ No
- ☐ Yes

17) Have you had weakness or fatigue for > 6 weeks? (RA)
- ☐ No
- ☐ Yes

If yes, how often do you have weakness or fatigue?
- ☐ every day
- ☐ 1-3 days a week
- ☐ 4-6 days a week

Appendix E

Referral Algorithm for Celiac Disease

Patient has a 1st degree relative with Celiac disease?	
Yes	No
Refer if patient presents with any of the following: - $\geq$ 3 loose stools per day for > 4 weeks - Abdominal pain after eating - Abdominal distention/bloating after eating - Weight loss - Has ever been told they have IBS - Hx of malabsorption problems (anemia, vitamin D deficiency) - Hx of elevated liver enzymes	Refer if patient presents with $\geq$ 3 of the following: - $\geq$ 3 loose stools per day for > 4 weeks - Abdominal pain after eating - Abdominal distention/bloating after eating - Weight loss - Has ever been told they have IBS - Hx of malabsorption problems (anemia, vitamin D deficiency) - Hx of elevated liver enzymes

Appendix F

Referral Algorithm for Crohn's Disease

Patient has a 1st degree relative with Crohn's disease?	
Yes	No
Refer if patient presents with any of the following: - ≥3 loose stools per day for > 4 weeks - Abdominal pain after eating - Weight loss - Painful defecation - Blood in stool - Has ever been told they have IBS - Hx of malabsorption problems (anemia, vitamin D deficiency) - Hx of elevated liver enzymes	Refer if patient presents with ≥ 3 loose stools per day for > 4 weeks AND ≥ 1 of the following symptoms: - Abdominal pain after eating - Weight loss - Painful defecation - Blood in stool - Fever in the last 4 weeks - Has ever been told they have IBS - Hx of malabsorption problems (anemia, vitamin D deficiency) - Hx of elevated liver enzymes

Appendix G

Referral Algorithm for Rheumatoid Arthritis

Refer if patient presents with at least 1 joint with clinical synovitis (swelling) for > 6 weeks.

-or-

Refer if patients presents with ≥ 3 of the following:
- Morning joint stiffness for > 60 minutes for > 6 weeks
- Joint/muscle pain for > 6 weeks
- Tender joints for > 6 weeks
- Tingling sensations in the hands/feet for > 6 weeks
- Weakness/fatigue for > 6 weeks

Appendix H

Coded Identifier List

Patient Name	Chart Number	Visit Date	Subject Number

Appendix I

Chart Review – Data Collection Form

Subject #	Psoriasis	Questionnaire completed	Screening documented	Referral documented
1,2,3…	No=0 Yes=1	No=0 Yes=1	No=0 Yes=1	No referral=0 Yes referral=1

Appendix J

Screening Questionnaire – Data Collection Form
(Excel columns shown below in vertical format)

Subject #	Visit Date	Visit Time	Age (years)	Gender	1
1,2,3…	mm/dd/yyyy	0:00	#	male=0 female=1	No=0 Yes=1
if yes - 1a	if yes - 1b	2	3	if yes - 3a (lbs)	4
mother=0 father=1 sister=2 brother=3 child=4	CD=0 CrD=1 RA=2	No=0 Yes=1	No=0 Yes=1	#	No=0 Yes=1
if yes - 4a	if yes - 4b	if yes - 4c (hrs)	if yes - 4d	if "other" - 4e	5
RUQ=0 LUQ=1 RLQ=2 LLQ=3	0=0 1=1 2=2 3=3 4=4 5=5 6=6 7=7 8=8 9=9 10=10	#	throbbing=0 shooting=1 stabbing=2 sharp=3 cramping=4 gnawing=5 burning=6 aching=7 pressure=8 other=9		No=0 Yes=1
6	7	8	if yes - 8a (°F)	9	10
No=0 Yes=1	No=0 Yes=1	No=0 Yes=1	#	No=0 Yes=1	No=0 Yes=1
11	12	13	if yes - 13a	if yes - 13b	14
No=0 Yes=1	No=0 Yes=1	No=0 Yes=1	every day=0 1-2 days/wk=1 4-6 days/wk=2	See Appendix K	No=0 Yes=1
if yes - 14a	if yes - 14b	if yes - 14c (hrs)	if yes - 14d	if "other" - 14e	15

See Appendix K	0=0 1=1 2=2 3=3 4=4 5=5 6=6 7=7 8=8 9=9 10=10	#	throbbing=0 shooting=1 stabbing=2 sharp=3 cramping=4 gnawing=5 burning=6 aching=7 pressure=8 other=9		No=0 Yes=1
if yes - 15a	16	17	If yes - 17a	if yes - 15a	Referred?
See Appendix K	No=0 Yes=1	No=0 Yes=1	every day=0 1-2 days/wk=1 4-6 days/wk=2	See Appendix K	No=0 Yes=1

Appendix K

Key For Questions 13b, 14a and 15a

jaw (right)=0
jaw (left)=1
jaw (bilateral)=2
neck (right)=3
neck (left)=4
neck (bilateral)=5
shoulder (right)=6
shoulder (left)=7
shoulder (bilateral)=8
elbow (right)=9
elbow (left)=10
elbow (bilateral)=11
wrist (right)=12
wrist (left)=13
wrist (bilateral)=14
hand (right)=15
hand (left)=16
hand (bilateral)=17
thumb (right)=18
pointer finger (right)=19
middle finger (right)=20
ring finger (right)=21
pinky finger (right)=22
thumb (left)=23
pointer (left)=24
middle finger (left)=25
ring finger (left)=26
pinky finger (left)=27
thumb (bilateral)=28

pointer (bilateral)=29
middle finger (bilateral)=30
ring finger (bilateral)=31
pinky finger (bilateral)=32
hip (right)=33
hip (left)=33
hip (bilateral)=34
knee (right)=35
knee (left)=36
knee (bilateral)=37
ankle (right)=38
ankle (left)=39
ankle (bilateral)=40
great toe (right)=41
second toe(right)=42
third toe (right)=43
fourth toe (right)=44
fifth toe (right)=45
great toe (left)=46
second toe (left)=47
third toe (left)=48
fourth toe (left)=49
fifth toe (left)=50
great toe (bilateral)=51
second toe (bilateral)=52
third toe (bilateral)=53
fourth toe (bilateral)=54
fifth toe (bilateral)=55

Appendix L

IRB Approval

NOT HUMAN SUBJECT RESEARCH

ID: Pro00066977
Title: Not Human Subjects Research
PI: Susan Ashbaugh
Study Title: Best Practice for Screening Adult Patients with Psoriasis for
                Polyautoimmunity: Celiac Disease, Rheumatoid Arthritis and Crohn's
                Disease
Description: A study application has been confirmed to be not human subject
                research. To navigate to the project workspace, click on the above ID.