Another Brick in the Wall: Building Epidemiologic Evidence of Infectious Risks by Psoriasis Therapy Types

by

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A DISSERTATION

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CERTIFICATE OF APPROVAL

This is to certify that the PhD dissertation of

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DEDICATION

For my family.

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ABSTRACT OF THE DISSERTATION

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by

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Background: Psoriasis is a chronic, inflammatory disease that affects about 10 million individuals in the United States. New psoriasis treatments target the dysregulated immune system functions responsible for disease pathogenesis. However, many of these immune pathways are also responsible for protecting the body from fungal and bacterial infections. Due to the increasing number of biologic therapies recently approved to treat psoriasis, understanding the comparative infectious risk associated with different biologic therapies is of upmost importance.

Methods: This dissertation work represented an overall effort to investigate the infectious risks of various therapies for psoriasis. In Aim 1, I used data from two national registries linked to Medicare to develop and validate a severity score to account for psoriasis disease activity. In Aim 2, I examined the association between biologic therapy type, interleukin (IL)-12/23, IL-17, and tumor necrosis factor alpha (TNF-α) inhibitors, and risk of hospitalized infections in a national claims database. In Aim 3, I investigated the association between therapy type, (IL-12/23, TNF-α inhibitors, and methotrexate) and risk of infection-specific

mortality utilizing Medicare linked to the National Death Index.

Results: I developed and validated a severity score based on 12 claims-based variables with a moderate classification rate, and a good positive predictive value. Analysis of the Medicare cohort found that IL-12/23 inhibitors exhibited a protective effect on developing a hospitalized infection, as compared to TNF-α inhibitors. Risk of infection-related mortality was not significantly different between biologic therapies and non-biologic systemic therapies.

Impact: Biologic therapies, specifically IL-12/23 inhibitors, appear to exhibit decreased risk in developing a hospitalized infection in the Medicare population. There was a significant increase in risk of mortality for IL-12/23 inhibitors, as compared to TNF-α inhibitors. However, this increase could be due to channeling bias based on medical history prior to Medicare data. The role of psoriasis disease severity must be further explored in the context of administrative databases. These findings will be used to direct treatment choice, as decisions on medication must be tethered to evidence-based observations for patient safety.

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LIST OF ABBREVIATIONS

aHR	Adjusted Hazard Ratio
ANOVA	Analysis of Variance
BADBIR	British Association of Dermatologists Biologic Interventions Register
BIOBADADERM	Spanish Registry of Adverse Events from Biological Therapy
BMI	Body Mass Index
BSA	Body Surface Area
CDC	Centers for Disease Control and Prevention
CEPPA	Center for Psoriasis and Psoriatic Arthritis
CI	Confidence Interval
CIRAS	Claims-Based Index for Rheumatoid Arthritis Severity
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cadriovascular Disease
DMARD	Disease Modifying Anti-Rheumatic Drugs
EMR	Electronic Medical Records
EOP	Early-Onset Psoriasis
FDA	Food and Drug Administration
HCPCS	Hea;thcare Common Procedure Coding System
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
IL	Interleukin
IPTW	Inverse Probability of Treatment Weighting
IWHS	Iowa Women's Health Study
LASSO	Least Absolute Shrinkage and Selection Operator
LOP	Late-Onset Psoriasis
MACE	Major Adverse Cardiovascular Events
MOA	Mechanisms of Action
nbUVB	narrowband Ultraviolet B
NDC	National Drug Codes
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NPF	National Psoriasis Foundation
OHSU	Oregon Health & Science University
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PSOLAR	Psoriasis Longitudinal Assessment and Registry
RA	Rheumatoid Arthritis
RCT	Randomized Control Trial
ROC	Receiver-Operator Curve
SSN	Social Security Number

Th	T helper
THIN	The Health Improvement Network
TNF-α	Tumor Necrosis Factor alpha

PREFACE

Over a decade ago, the National Psoriasis Foundation (NPF) approached the Centers for Disease Control and Prevention (CDC) to investigate how a public health lens integrated alongside more mainstream research could be focused on clinical and biomedical aspects of disease. Since psoriasis was originally believed to be mainly a nonfatal, cosmetic disease, there had been minimal well-designed research studies to better understand disease comorbidities. By 2010, however, the United States Congress supported an effort on psoriasis by directing funding to the CDC that was earmarked to "…support the collection of epidemiologic and longitudinal data on individuals with psoriasis and psoriatic arthritis … [to] gain insight into the long-term impact and treatment of these two conditions." The results were to develop the first-ever government data collection effort on psoriasis and psoriatic arthritis. Continuing this momentum, in 2013 the World Health Organization (WHO) identified psoriasis as a major global health problem, making psoriasis one of the few non-communicable diseases the WHO has highlighted.

Up to a few years ago, I was not aware of the burden of disease for patients with psoriasis, nor the world focus on this chronic disease. Psoriasis is the most prevalence autoimmune disease in the United States; however, to-date there is a dearth of evidence regarding the risk of serious infections by psoriasis therapy class. The goal of this dissertation was to help add another brick in the wall of evidence regaring the infectious risks of biologic psoriasis therapies.

Chapter 1: Introduction and Research Aims

1.1 Introduction

Psoriasis is an immune-mediated, chronic, inflammatory disease that affects roughly 10 million Americans.[1-4] Psoriasis is an incurable disease that manifests with erythematous, scaly, thick plaques on the skin. High levels of morbidity, including cardiovascular disease,[5-18] renal disease,[19] metabolic syndrome,[20-22] diabetes,[23-25] and obesity,[26] are all associated with psoriasis. Individuals with psoriasis are also more likely to experience poor quality of life,[27,28] suffer from depression,[29] and more frequently smoke and drink alcohol.[30-35] In addition to reduced quality of life and increased frequencies of multiple co-morbidities, studies have found that individuals with severe psoriasis are more likely to have reduced lifespans compared to individuals without psoriasis.[36] The National Institutes of Health (NIH) has recognized the high health impact that psoriasis has on individuals and populations.[37]

Disease severity plays a large role in the health outcomes of those with psoriasis. Moderate-to-severe psoriasis, which accounts for approximately 20% of all cases,[38] increases the risk of cardiovascular disease,[39] diabetes,[23,40] and hypertension,[41] in comparison to individuals with mild psoriasis. Recent research has found a dose-response with disease severity and other comorbidities[42] as well as increased risks in mortality.[10,36] Most studies to date have utilized indirect measures of disease severity, such as treatment utilization patterns (e.g., initiation of medications)[43,44] and number of hospital visits or procedures.[45] Each of these

methods are indirect and allow for potential residual confounding due to misclassification. Disease severity classification by treatment initiation, such as biologic therapy, creates methodologic concerns when trying to understand risks associated with specific therapies for psoriasis.

Psoriasis treatment has evolved since the late 20th century. Traditionally, older therapies for psoriasis include topical medications, phototherapy, and non-biologic oral systemic drugs. Systemic oral drugs are still commonly used for long-term management of moderate-to-severe psoriasis, predominantly due to their low cost. One such example, methotrexate, is one of the most commonly prescribed systemic treatment for psoriasis,[46,47] and works as an anti-inflammatory drug that reduces both the onset and growth of psoriasis plaques, although it is only effective in approximately one-third of patients.[48] Methotrexate is also poorly tolerated (e.g., nausea, fatigue) and has shown an increased risk of adverse side effects, such as liver fibrosis or cirrhosis.[49,50]

In response to the development of treatment for other autoimmune diseases, such as rheumatoid arthritis, there has been a large increase in the number of biologic therapies available to treat psoriasis since the early 2000s. These drugs selectively block function of key cytokines involved in psoriasis pathogenesis, including, tumor necrosis factor (TNF)-α, interleukin (IL)-12/IL-23, IL-17A, and IL-23.[51]

Few population-based studies have been conducted within the setting of psoriasis to determine the safety of biologic therapies.[43] New guidelines from the American

Academy of Dermatology and the National Psoriasis Foundation focusing on biologic treatment were recently published,[52] which include information on several classes of biologic therapy. The rate of new biologic therapies being developed and approved for psoriasis, however, continues to move forward and there is a lack of real-world data on whether the use of various types of biologic therapy affects risk of hospitalization due to infection for individuals with psoriasis, although retrospective studies analyzing large administrative datasets have been designed to help answer this question.

Historically, psoriasis was not considered a disease associated with increased risk of mortality. In recent years, there have been several studies that have evaluated the link between psoriasis and risk of mortality.[36,53] The underlying mechanism for psoriasis is inflammation, and many early studies focused on cardiovascular-specific mortality as an outcome of interest.[8,10,15,16,54] Non-cardiovascular cause-specific mortality for individuals with psoriasis has not yet been thoroughly investigated.

The association between mortality and treatment type in the population of individuals with psoriasis has not yet been studied, and thus it is unknown whether specific psoriasis therapies affect risk for mortality. It is possible that biologic therapies may confer risks that would increase mortality and, perhaps just as likely, that these medications would decrease risk of mortality by decreasing overall inflammation within the body. The research described here will examine rates of adverse events and risk of excess mortality, which no study to date has been able to adequately evaluate.

1.2 Research Aims

The goal of this dissertation research was to develop and validate a psoriasis disease severity score using administrative claims data linked to registry data that contain direct measures of psoriasis severity. This disease severity score would then be used to control for confounding in a large real-world dataset of individuals with psoriasis, to better understand both the risk of infection and the risk of mortality by therapy type.

I propose a study evaluating the association between treatment type and psoriasis-related morbidity and mortality among Medicare beneficiaries, taking into account disease severity via index. Medicare beneficiaries will be linked to the Corrona and the Center for Psoriasis and Psoriatic Arthritis (CEPPA) registries. Corrona is a national database for individuals with autoimmune diseases, with a separate registry for psoriasis that is jointly supported by Corrona and the National Psoriasis Foundation.[55,56] CEPPA is an Oregon Health & Science University-based registry of individuals with psoriasis with or without psoriatic arthritis.[57] The National Death Index is a centralized database that provides data on causes of death. I will combine clinical data and population health data to fill critical knowledge gaps related to adverse outcomes and mortality in the psoriasis population.

Research Aim 1 (Chapter 3): develop a psoriasis disease severity index for clinical measures in a claims database. I will develop and validate an index using a gold standard to predict severe psoriasis in Medicare claims-based data, using both the Corrona and CEPPA clinical registries.

Research Aim 2 (Chapter 4): determine the risk of hospitalized infections with treatment type in the Medicare psoriasis population. Using Medicare data, and taking into account disease severity via a claims-based index, I will compare rates of adverse events, including hospitalizations due to infection, by treatment type.

Research Aim 3 (Chapter 5): determine the risk of all-cause and infection-specific mortality by treatment in a Medicare cohort. Using Medicare data linked to the National Death Index, I will determine the risk of all-cause and infection-specific mortality, by treatment type.

Chapter 2: Literature Review

2.1 Epidemiology of psoriasis

Psoriasis is a chronic disease that manifests with thick, scaly plaques on the skin. It wasn't until the early 1800's that psoriasis was identified as a disease separate from the more commonly diagnosed leprosy.[58] Originally, psoriasis was thought to be a disorder of the epidermal keratinocytes, affecting individuals only cosmetically and causing lesions to develop on the skin.[59] Psoriasis is now understood to be an immune-mediated disease, systemically affecting both an individual's skin and overall health.

A recent systemic review of psoriasis incidence and prevalence studies found that prevalence appears to be higher in locations further from the equator. Countries located closer to the equator saw psoriasis prevalence for the overall population ranging from 0.19% to 0.50%.[60-64] By contrast, reported psoriasis prevalence in more northern countries is typically greater than a value of 1%, with values reaching 2.9% for some countries.[65-68] It is unknown why latitude is associated with increasing prevalence of psoriasis, though factors such as genetics[69] and exposure to sunlight may contribute.[70]

Psoriasis onset has been known to occur at any age, though epidemiologic studies have shown a bimodal distribution for age of onset. For both males and females, there is early-onset psoriasis (EOP) with peak onset between 16-22 years of age, and late-onset psoriasis (LOP) that peaks between 57-60 years of age.[71] Individuals with EOP are more likely to experience frequent skin flares, high levels

of BSA, nail involvement, and a family history of psoriasis as compared to those with LOP.[72] EOP is more likely than LOP, though onset of psoriasis can occur at any age.

The incidence of psoriasis for adults has been reported in few studies. A study from the US found that incidence of psoriasis was slightly higher in males than females (85.5/100,000 person-years vs. 73.2/100,000 person-years).[73] An Italian study of adults with newly diagnosed psoriasis, that did not stratify by sex, reported a higher incidence rate of 230/100,000 person-years.[74] The authors utilized data from over 900 primary care providers across Italy, and may reflect an artificially high incidence rate of psoriasis as this information is not necessarily population-based. Incidence rates for all ages combined vary more across different locations and database types. These incidence rates range from a US epidemiologic database 59.9/100,00 person-years,[75] to 120-130/100,000 person-years for primary care database in the Netherlands,[76] and 140/100,000 person-years for another primary care database in the United Kingdom.[77] To date, there has been only one population-based study of the incidence of psoriasis in children, which stratified the rates of incidence to find a slightly increased rate in females than males (43.9/100,000 person-years vs. 37.9/100,000 person-years).[78]

Historically, psoriasis was thought to be a disease limited to the skin and, in some scenarios, a patient's joints. However, there is an increasing body of evidence that the underlying inflammatory processes that cause psoriatic lesions have far-reaching systemic effects.[79-81] There is ample evidence to suggest that psoriasis is causally associated with increased risk of several different comorbidities,

including, but not limited to, cardiovascular disease, metabolic syndrome, diabetes, chronic kidney disease, gastrointestinal disorders, infections, cancer, and depression or anxiety.[82] Infections are discussed in detail in Section 2.4 below. It is thought that the underlying inflammatory processes leading to psoriasis also lead to endothelial dysfunction, which in turn eventually causes cardiovascular disease.[83] This concept, known as the "psoriatic march," has been used to describe the process by which psoriatic inflammation drive cardiovascular disease (CVD) through insulin resistance, endothelial dysfunction, and atherosclerosis.[84] The development of atherosclerosis ultimately leads to cardiovascular events such as stroke or myocardial infarction.

Systematic reviews and meta-analyses have found significant associations between psoriasis and cardiovascular disease.[85] A systemic literature review found that individuals with psoriasis alone, or with psoriatic arthritis, were at an increased risk of cardiovascular events, as compared to the general population.[15] The authors postulate that the underlying inflammatory process associated with psoriasis is the root cause of inflammation leading to cardiovascular events. Similarly, a meta-analysis analyzing the association between psoriasis and stroke and/or myocardial infarction in cohort studies found an increased relative risk of 1.21 (95% CI: 1.04, 1.40) and 1.22 (95% CI: 1.05, 1.42) for stroke and myocardial infarction, respectively.[86]

A population-based study of inhabitants of a suburb of Rotterdam, Germany found no association between psoriasis and the development of cardiovascular disease (HR = 0.73; 95% CI: 0.50, 1.06), which was defined as myocardial infarction (either

fatal or non-fatal), or fatal coronary heart disease.[87] The authors performed a sensitivity analysis using subclinical measures of atherosclerosis, including carotid plaque percentage, ankle-brachial index, peripheral artery disease, and pulse-wave velocity, to reduce the likelihood that those in the study did not have underlying CVD. However, it is likely that individuals with psoriasis have underlying inflammatory responses that are further upstream of development of atherosclerosis. For example, levels of certain biomarkers, such as C-reactive protein, may be a better predictor of subclinical cardiovascular disease for this analysis. There are some methodological concerns with this study, in particular the authors used initiation of certain therapies as a marker for "probable" psoriasis potentially biasing the hazard ratio (HR) towards the null since these therapies have multiple indications for use.

Additional evidence supporting the association between psoriasis and cardiovascular disease is the observation of a dose-response between the severity of psoriasis and the risk of cardiovascular events. A recent systematic review found that individuals with severe psoriasis had increased risk of stroke (HR = 1.38; 95% CI: 1.20, 1.60), myocardial infarction (HR = 1.70; 95% CI: 1.18, 2.43), as well as cardiovascular death (HR = 1.37; 95% CI: 1.13, 1.67).[88] It should be noted that the majority of the studies included in the systematic review defined severe psoriasis as taking a systemic therapy along with a diagnosis of psoriasis, leading to the potential for misclassification bias. The use of systemic therapy as a proxy for moderate-to-severe or severe psoriasis has become problematic with the advent of newly approved biologic therapies. As therapy has fewer side-events,

dermatologists are more likely to prescribe these therapies for individuals with psoriasis in sensitive areas, such as the genitals, hands, or scalp.[89] Patients with these affected areas may technically fall into the category of mild psoriasis, with <3% of their boy surface area is affected. The inclusion of these individuals who have localized psoriasis will bias any associations towards the null, if their underlying inflammation is not as extensive as those with widespread skin involvement.

To further understand the between psoriasis and cardiovascular disease, there have been several studies that have investigated the dose-response relationship between psoriasis severity, measured as percent body surface area (BSA) affected, and cardiovascular events. Two meta-analyses further support this association.[13,17]

Diabetes is another comorbidity associated with psoriasis, which is also thought to be caused by the underlying inflammation due to psoriasis. There have been heterogeneous results for this association in the literature. A cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) found no association between self-reported psoriasis and diabetes. However, this study found associations between psoriasis and hypertension, obesity, and waist circumference, all of which are considered risk factors for diabetes.[90] Cross-sectional studies lack the ability to establish temporality, and it is possible that individuals with psoriasis have yet to develop diabetes. Conversely, results from the Nurses' Health Study II found a significant risk of new onset diabetes among those with psoriasis, compared to those without psoriasis (HR = 1.67; 95% CI:

1.25, 2.12), after multivariate adjustment.[25] All the nurses with psoriasis who reported incident diabetes developed only type II diabetes during the course of this study. A strength to the Nurses' Health Study II is that as a prospective cohort study, the presence of psoriasis has been established prior to the development of diabetes, providing a clear causal relationship.

Similar to the risk of cardiovascular disease, the risk of developing diabetes has been studied in terms of psoriasis severity. A study looking at a population-based cohort in the United Kingdom found an increasing risk across patients with mild (HR = 1.14; 95% CI: 1.10, 1.18), moderate (HR = 1.11; 95% CI: 1.07, 1.15), and severe psoriasis (HR = 1.46; 95% CI: 1.30, 1.65).[23] As with cardiovascular disease, the risk of developing diabetes increasing with those who have more severe psoriasis.

Recent studies have found that in addition to an increased burden of comorbidities associated with psoriasis, there is an increased burden of mortality associated with psoriasis.[36,53] In a population study of the U.K., the authors found that individuals with severe psoriasis had an increased risk for mortality, compared to those with no medical diagnosis of psoriasis, which was not seen in those with mild psoriasis (HR = 1.5; 95% CI: 1.3, 1.7 vs. HR = 1.0; 95% CI: 0.97, 1.02).[53] This corresponds to a 50% increase in mortality for those with severe psoriasis, which was defined as a diagnosis of psoriasis in addition to some form of systemic therapy. The use of an indirect measure of psoriasis severity may lead to an under-estimation of the actual risk of mortality, as it is likely that individuals with lesser severe psoriasis affecting certain areas such as their genitals or hands, would be using a form of

systemic therapy. This study also found that there was a significant difference between males and females with psoriasis, with males dying 3.5 (95% CI: 1.2, 5.8) years and females dying 4.4 (95% CI: 1.3, 1.8) years younger than their counterparts without psoriasis.[53] These results are supported by several studies looking at the risk of mortality in those individuals with psoriasis who have been hospitalized, compared to the general population,[91,92] or compared those with mild (e.g., non-hospitalized psoriasis).[93]

There are several population-based studies that have investigated cause-specific mortality for individuals with psoriasis. There are several different causes of mortality associated with those with who have psoriasis: cardiovascular disease, chronic lower respiratory disease, diabetes, dementia, endocrine disease, infection, kidney disease, malignancies, metabolic disease, or parasites.[36,94,95] Individuals with both psoriasis and cardiovascular disease have the greatest risk of mortality. One study found that the absolute risk of mortality was 61.9 deaths per 1,000 person-years and the excess risk of mortality was 3.5 deaths per 1,000 person-years for patients with severe psoriasis.[36] As the underlying mechanism for psoriasis development and maintenance relies on inflammation, increases in cardiovascular-specific mortality are to be expected.

A recent study utilizing a prospective cohort subset of The Health Improvement Network (THIN), a population-based cohort in the U.K., found that patients with severe psoriasis had 1.79 (1.23, 2.59) times increased risk of death, when compared to age- and sex-matched adults without psoriasis and controlling for other risk factors.[96] After excluding individuals who received any type of oral

systemic or biologic therapy, the risk of mortality for those with severe psoriasis was 1.87 (1.26, 2.75) times those without psoriasis. This study furnished evidence that psoriasis disease severity is an independent risk factor for mortality. A limitation of this study is that inability to understand the relative risk of mortality based on type of oral systemic or biologic therapy.

2.2 Mechanisms of psoriasis

Individuals with psoriasis experience a dysregulated immune system,[97,98] with both environment and genetic susceptibility[99] playing roles in the initial development of psoriasis and the maintenance of psoriatic lesions. Over the past decade, there have been considerable advances in understanding the underlying biologic mechanisms of psoriasis.[100-102] Individuals with psoriasis have been found to have abnormal accumulation and activation of T helper (Th)17 T cells within the skin and blood, which subsequently lead to keratinocyte activation/proliferation, increased vascularity, and marked infiltration of numerous other inflammatory cells. Clinically, this process creates erythematous, thick, scaly plaques within the skin. Additional cytokines are released by the changes in the epidermis and dermis, furthering the cyclic dysregulation of the immune system (**Figure 2.1**).[97]

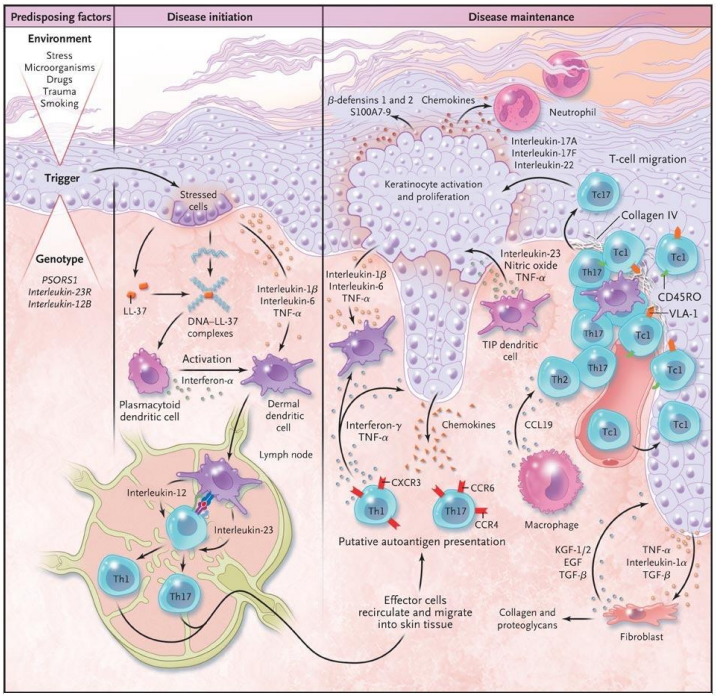

Figure 2.1. Evolution of a Psoriatic Lesion from Initiation to Maintenance of Disease. Nestle *et al*[97]

The IL-23/Th17 immune system pathway is involved in the initiation, progression, and maintenance phases of psoriasis (**Figure 2.2**).[103-105] The key regulatory cytokine in this pathway is IL-23, which consists of two protein subunits, p19 and p40.[102] IL-23 stimulates differentiation, activation, proliferation, and survival of Th17 cells; these cells make IL-17A as their signature cytokine, which is now considered the key effector cytokine in psoriasis pathogenesis. The IL-23/Th17 pathway normally functions to maintain mucocutaneous immunity against pathogens, and is not involved in systemic immunity. Importantly, increased understanding of the IL-23/Th17 pathway has led to the development of new highly effective targeted therapies for psoriasis in recent years.

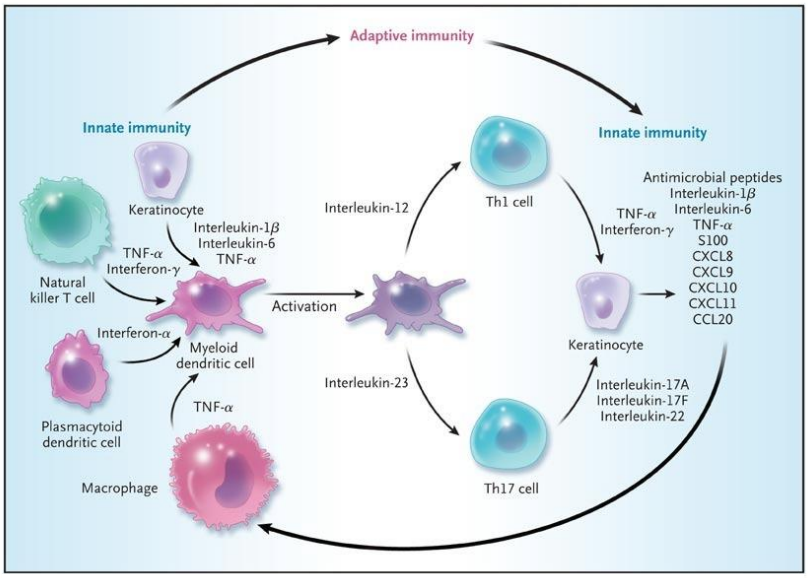

Figure 2.2. Key Cells and Mediators in the IL-23/T_H17 Pathway. Nestle *et al*[97]

2.3 Therapy Options for Psoriasis

Psoriasis has been shown to greatly impair patients' physical, emotional, and social well-being. Respondents to an NPF survey described psoriasis as affecting their ability to perform tasks using their hands as well as problems interacting with others due to social stigmatization.[106] In addition to detrimental effects on quality of life, psoriasis also increases risk of a number of internal diseases, notably psoriatic arthritis and cardiovascular disease (e.g., myocardial infarction and stroke). Thus, therapies for psoriasis need to address both psychologic and physical aspects of the disease.

Treatment of psoriasis ranges from topical therapies, to phototherapy, to systemic therapy, both non-biologic and biologic. Historically, patients with limited disease are treated with topical therapies, and sometimes phototherapy. As the

understanding of the underlying nature of psoriasis has increased, the use of systemic therapies has become more prevalent. These treatments are typically reserved for patients with more widespread disease. Methotrexate was one of the first systemic therapies approved for use in psoriasis and helped to manage underlying inflammation. Systemic non-biologic therapies like methotrexate, however, have a host of adverse effects for the user, and long-term use is challenging. For several decades, there were no new breakthrough therapies for psoriasis until researchers developed a better understanding of the cytokines and associated immunologic pathways involved in the development and maintenance of psoriasis. With this knowledge, research has focused on disrupting these specific immunologic pathways by developing more targeted disease-specific drugs. These medications are known as biologics, and include tumor necrosis factor (TNF) antagonists, an interleukin (IL) 12/23 antagonist, IL-17A antagonists, and IL-23 blockers.[51,52]

TNF blockers used in the psoriasis population were first developed for use in the rheumatoid arthritis population. As such, there is a large body of evidence investigating the risk of infection and other serious adverse events by therapy type in these patients. Unlike the rheumatoid arthritis population, few population-based studies have been conducted within the setting of psoriasis to determine the long-term safety of biologics in real-world settings.

2.3.1 Non-biologic systemic therapy

Systemic oral drugs and therapies are still commonly used for long-term management of moderate-to-severe psoriasis, predominantly due to their low cost, availability, and well-established safety profile.

2.3.1.1 Methotrexate

One such example, methotrexate, the most commonly prescribed oral systemic treatment for psoriasis,[46] works as an anti-inflammatory drug that reduces both the onset and growth of psoriasis plaques, although it is only effective in approximately one-third of patients.[48] Methotrexate is a folate antagonist and has a complex pharmacologic profile with several different mechanisms of action (MOA) suggested. Methotrexate acts against cells with rapid turnover, such as malignant, fetal, and buccal and intestinal mucosa cells.[107] It is thought that the MOA of methotrexate in psoriasis is to interfere with keratinocyte proliferation and/or with specific T-cells infiltrating skin that are involved in development of psoriatic lesions.[108]

While effective against psoriasis, methotrexate is also poorly tolerated (e.g., nausea, fatigue) and has shown an increased risk of adverse side effects such as liver fibrosis or cirrhosis.[49,50] Furthermore, severe psoriasis is associated with certain behaviors and diseases, such as alcohol use, obesity, hepatitis, and diabetes mellitus, which all increase the risk of hepatotoxicity.[50] Methotrexate is therefore less than ideal as a long-term treatment for psoriasis.

2.3.1.2 Phototherapy

An example of a non-oral, systemic therapy used for treating psoriasis is phototherapy, which has a long history of being used to treat other skin conditions.[109] It was in the early 20th century when phototherapy was harnessed to treat psoriasis, mainly in combination with topical therapies such as coal tar,[110] or coal tar in conjunction with anthralin paste,[111] which is kept on the body underneath a stocking sleeve. These procedures are repeated until active lesions are no longer present on the body. More recently, phototherapy has been paired with the drug psoralen, to sensitize the skin to light.

Phototherapy acts through several different mechanisms of action, including the alteration of the cytokine profile, induction of apoptosis, and promotion of immunosuppression. Phototherapy is thought to reverse the cytokine profile which is normally seen in psoriasis, by up-regulatory the immune response via the Th2 axis, and down-regulating the Th1/Th17 inflammatory axis.[112] Interestingly, narrowband ultraviolet B (nbUVB) radiation has been shown to induce apoptosis of T lymphocytes from the epidermis and dermis of psoriatic lesions. These results were observed in both *in vivo* and *in vitro*.[113]

There are several different modalities of phototherapy for the treatment of psoriasis. The selection of phototherapy modality is important to prevent unnecessary exposure leading to erythema, skin burning, and photoaging.[114] A benefit of phototherapy is the lack of severe adverse events; however, phototherapy is mainly for the treatment of mild-to-moderate psoriasis and not the treatment of severe psoriasis.

2.3.2 Biologic systemic therapy

Methotrexate and other traditional oral systemic therapies focus on inhibition of systemic cell replication, which has widespread implications for an individual's overall health. More targeted therapies have been developed in the form of biologics, and are desired to reduce adverse events, while still providing high levels of efficacy. Biologic therapy focuses on interrupting cell signaling processes that are critical for psoriatic inflammation. Numerous randomized control trials (RCTs) with biologic therapies targeting key cytokines have demonstrated excellent clinical efficacy, with many capable of high degrees of complete skin clearance, in combination with fewer adverse events than traditional systemic therapies.[115-121]

2.3.2.1 Tumor Necrosis Factor Inhibitors

Etanercept, adalimumab, infliximab, and certolizumab all target TNF-α, which is a cytokine involved in systemic inflammation.[122] TNF-α is present in abundance within affected tissues in several inflammatory diseases, including psoriasis. Within psoriasis lesions, TNF-α is involved in signaling between keratinocytes and activated dendritic cells, signaling between activated dendritic cells and fibroblasts, as well as in activation of the IL-23/Th17 pathway.[123]

The use of TNF-α blocker has been associated malignancy, heart failure, infusion and injection site and reactions, as well as induction of autoimmunity in both clinical trials and post-marketing surveillance.[124] However, these side effects typically

occur less frequently in the psoriasis population, as compared to the rheumatoid arthritis population. Blocking TNF-α has more wide-ranging effects within the body when compared to blocking cytokines that are more specific to psoriatic inflammation, and as such, the variety of adverse events is expected to be greater for TNF-α blockers.

The long-term efficacy of TNF-α blockers is variable, with Psoriasis Area and Severity Index (PASI) scores of less than 5, indicating good response, occurring in at least 50% of individuals using adalimumab[125] and 45% of individuals using etanercept.[126] PASI scores combine assessment of the severity of skin lesions including erythema, induration, and desquamation, as well as the location and the percent of involved areas. PASI scores range from 0 to 72, with a lower value indicating less severe psoriasis disease.[127,128] Individuals discontinuing TNF-α blockers do so for a few reasons, including adverse events, lack of effectiveness, and inconvenience with receiving infusions.[126] These patients typically move on to more targeted, more effective, and safer biologics for psoriasis, e.g., IL-12/23, IL-17, or IL-23 blockers.

2.3.2.2 Interleukin-12/23 blockers

Ustekinumab is an IL-12/IL-23 blocker that binds to the p40 subunit shared by both IL-12 and IL-23.[102] IL-23 stimulates differentiation, activation, proliferation, and survival of Th17 cells; these cells make IL-17A as their signature cytokine, which is considered a key effector cytokine in psoriasis pathogenesis. A systematic review and meta-analysis recently found that using weight-based dosages of ustekinumab provided the best overall skin clearance in 12-16 weeks,[129] as well

as high levels of efficacy over 3 years.[130] Similarly, the higher dose of ustekinumab (90 mg) appears to perform better in terms of reduced adverse events, as compared to the lower dose of ustekinumab (45 mg).[131]

A relatively new adverse event reported with ustekinumab in the psoriasis population is the development of noninfectious pneumonia, including hypersensitivity pneumonitis.[132] This study had a few limitations, mainly small number of cases and the retrospective nature of the study design, but the association between noninfectious pneumonia and ustekinumab is supported by temporal reporting.

Major adverse cardiovascular events (MACE) are of interest in the psoriasis population, as there have been several studies linking an increased risk of cardiovascular disease with psoriasis.[5-9,13,16,39,54] There are few trials looking at MACE in ustekinumab leading to a potentially under-powered question, and the trial lengths were relatively short (12 to 20 weeks).[133] It has been hypothesized that any increase in MACE risks for users of ustekinumab could be due to the temporary increase of inflammatory mediators, typically increasing dramatically around week 12 before decreasing to roughly baseline levels by week 32.[134] Interestingly, however, a recent meta-analysis of RCTs investigated the risk of MACE in patients with psoriasis taking biologic therapies found that there was no statistically significant difference in the risk of MACE for patients with plaque psoriasis, as compared to placebo.[135] A limitation of this analysis is that the RCTs included had the primary aim to examine the efficacy of the biologic therapy, and only a subset of the trials included an explicit definition of MACE.

2.3.2.3 Interleukin-17A blockers

Secukinumab, ixekizumab, and brodalumab are IL-17A blockers, with the first two drugs blocking the cytokine IL-17A and the latter drug blocking the IL-17A receptor. Treatments that targets the IL-17A pathway are thought to be more specific to psoriatic inflammation, and therefore will be more efficacious than TNF-α inhibitors. Further, IL-17A blockers are thought to have reduced side effects.

All IL-17A blockers exhibit high proportions of patients achieving high levels of efficacy. For example, PASI 75 indicates the number of patients who experienced a 75% or more reduction in their PASI score from baseline. A recent systematic review of randomized controlled trials for IL-17A blockers found that these therapies performed very well in terms of PASI 75. Specifically, secukinumab, ixekizumab, and brodalumab had PASI 75 values of 83.8%, 89.5%, and 88.6%, respectively.[136] A 2015 study compared ixekizumab to both etanercept and placebo for individuals with moderate-to-severe psoriasis in two separate clinical trials. For both clinical trials, 90% of subjects randomized to ixekizumab every 2 weeks achieved PASI 75 by week 12, compared to only 2% of subjects randomized to placebo. Similarly, at week 12, only 42% of subjects randomized to etanercept achieved PASI 75.[137]

Non-invasive mucocutaneous fungal infections have emerged as an important signal in anti-IL-17 therapy trials; infections with *Candida albicans* were more common with IL-17A blockers as compared to placebo.[115,138-141] The proportion of psoriasis patients with *Candida* infections on ixekizumab were 1.8% and 0.8%, for every 2 week and every 4 weeks, respectively, as compared to 0.5% for placebo,

all of which were mild-to-moderate in severity.[140] For brodalumab, *Candida* infections were also more common in the active arm than the placebo arm (2.3%, 0.5%, and 1.4% for 210 mg brodalumab, 140 mg brodalumab, and placebo, respectively), though none of these infections were serious.[141] For individuals with inflammatory bowel disease (IBD), the use of IL-17A blockers has also been associated with severe exacerbations of IBD.[142,143] Both of these adverse events are considered rare in the untreated psoriasis population.[144]

2.3.2.4 Interleukin-23 blockers

Guselkumab, tildrakizumab, and risankizumab are IL-23 blockers, which are the newest type of biologic therapy to be approved by the FDA to treat psoriasis. These drugs specifically target the p19 subunit of IL-23.[145],[146] These therapies have proven to be very safe thus far in both clinical trial and clinical practice settings.

Clinical trials have shown that IL-23 blockers are effective in skin clearance.[147-149] A recent systematic review of randomized controlled trials for IL-23 blockers found that these therapies performed very well in terms of efficacy, similarly to the IL-17A blockers. Guselkumab, risankizumab, and tildrakizumab had PASI 75 values of 86.5%, 89.0%, and 63.8%, respectively.[150] Interestingly, the efficacy results for tildrakizumab are different than the other IL-23 blockers, perhaps because it does not bind its target, IL-23 p19, as efficiently as the other two IL-23 blockers.

In comparison to IL-12/23 blockers, IL-23 is thought to be the key regulator for psoriasis, with mouse models showing the p19 knock-out mice are protected

against developing psoriasis.[151] There is also evidence that IL-12 may act as an anti-inflammatory cytokine,[152] and the use of IL-12 blockers may decrease anti-inflammatory actions making IL-23 blockers more effective in treating psoriasis.

A recent phase III clinical trial for guselkumab found that the distribution of adverse effects was comparable between guselkumab and the placebo group, with the most frequent reported events being nasopharyngitis and upper respiratory infection.[153] Similar results were found in other clinical trials for guselkumab.[154,155] Risankizumab has a similar safety profile with no meaningful difference between the rates of adverse events, serious adverse events, and adverse events leading to discontinuation between risankizumab and placebo.[156] Tildrakizumab also features a positive safety profile with treatment-emergent adverse events being lower in the two tildrakizumab groups (100 mg and 200 mg), as compared to placebo and etanercept, 35.20 (95% CI: 32.55, 37.84), 37.18 (95% CI: 34.49, 39.88), 148.6 (95% CI: 131.6, 165.6), and 148.6 (95% CI: 128.9, 168.3) events/100 person-years, respectively. The common adverse event in all treatment arms was nasopharyngitis.[157]

2.4 Risk of infection in the psoriasis population

2.4.1 Infection and psoriasis

Psoriatic disease, like other autoimmune diseases, seems to predispose individuals to infection independent of immunosuppressive treatment. A 2011 Dutch study found that individuals with psoriasis have twice the risk of serious infections leading to hospitalization (aHR: 1.58 [95% CI: 1.48, 1.68]), compared to

individuals without psoriasis. The risk of infection was similar for individuals with psoriasis being treated with topical therapy only (aHR: 1.54 [95% CI: 1.44, 1.65)], but increased for patients who were prescribed phototherapy, systemic drugs, or inpatient treatment (aHR: 1.851 [95% CI: 1.57, 2.08]).[43]

A more recent Taiwanese study from 2014 found a similarly increased incidence of pneumonia for those with psoriasis compared to those without psoriasis (HR: 1.50 [95% CI: 1.21, 1.86]). Kao *et al*. utilized the Taiwan Longitudinal Health Insurance Database 2000 to review the medical records of individuals with psoriasis and then match them to non-psoriasis individuals who utilized ambulatory care within the same time period. These individuals were followed for 3 years and tracked for admission due to pneumonia. Both patients with mild and moderate-to-severe psoriasis had increased risks of hospitalization due to pneumonia (aHR: 1.36 [95% CI: 1.09, 1.70] and HR: 1.68 [95% CI: 1.12, 2.52], respectively) compared to individuals without psoriasis.[158]

The University of Toronto Psoriasis Cohort was used to prospectively identify and observe individuals diagnosed with psoriasis and psoriatic arthritis. Of the 695 patients with psoriatic arthritis, 264 (40.0%) patients developed an infection, compared to 62 (12.2%) of those with cutaneous disease alone.[159] Correspondingly, when looking at the numbers of patients who experienced multiple infections in this cohort, those with psoriatic arthritis experienced a higher burden of infection than those with psoriasis. This study found that 27.7% of those with psoriatic arthritis had 3 or more infections compared to 3.2% of those with psoriasis alone had two or more infections during the course of follow-up within the

study.[159] Infections were self-reported and included all infections individuals experienced after the baseline visit including both serious and non-serious infections.

Similarly, a cross-sectional study of the Nationwide Inpatient Sample data from 2002 to 2012 was reviewed to determine rates of infection in the psoriasis population.[160] This study tracked admitted patients with a diagnosis of psoriasis over time and found that the rates of serious infections increased when compared to a similar group of patients lacking psoriasis, specifically methicillin-resistant *Staphylococcus aureus* (OR: 1.76 [95% CI: 1.52, 2.03]), cellulitis (OR: 3.21 [95% CI: 3.12, 3.30]), herpes simplex virus infection (OR: 2.21 [95% CI: 1.70, 2.89]), infectious arthritis (OR: 1.82, [95% CI: 1.58 2.09]), osteomyelitis (OR: 1.31 [95% CI: 1.18, 1.46]), meningitis (OR: 1.31, [95% CI: 1.16, 1.47]), encephalitis (OR: 1.22 [95% CI: 1.02, 1.47]), and tuberculosis (OR: 1.34 [95% CI: 1.20, 1.49]). [160] The authors were unable to evaluate the impact of disease-modifying therapies in this analysis, and some of the reported risk differences could have been attributable to such therapies.

In a 2018 study, Takeshita *et al*. utilized The Health Improvement Network (THIN), which is an electronic medical records database that includes a large cohort of the general United Kingdom population, to ascertain the risk of infection in a large cohort of individuals with psoriasis.[161] In this cohort, the risk of serious infection for all individuals with psoriasis was significant (aHR: 1.21 [95% CI: 1.18, 1.23]), as compared to those without psoriasis, and the risk was even higher for those with moderate-to-severe psoriasis (aHR: 1.63 [95% CI: 1.52, 1.75]). A similar,

albeit weaker, signal was seen for risk of herpes zoster infection in the mild and moderate-to-severe psoriasis groups (aHR: 1.07 [95% CI: 1.05, 1.10] and aHR: 1.17 [95% CI: 1.06, 1.30], respectively), compared to the healthy population. Interestingly, the increased risk of opportunistic infection was only seen in the moderate-to-severe psoriasis group (aHR: 1.57 [95% CI: 1.06, 2.34]) as compared to those without psoriasis. It should be noted that in the overall cohort the moderate-to-severe psoriasis group was not defined by BSA, but instead by receiving either phototherapy or systemic therapy.[161] This classification of disease severity prevented separation of disease effect from treatment effect. The authors addressed this limitation by utilizing a nested cohort within the THIN network, which included clinical data such as BSA. The results of this sub-analysis found an elevated risk of serious infection for those with any psoriasis (aHR: 1.21 [95% CI: 11.09, 1.35]) and those with moderate-to-severe psoriasis (aHR: 1.27 [1.10, 1.47]), compared to a set of randomly selected patients who were matched on age category, were still alive, were registered at the same practice, and who did not have psoriasis.[161] Importantly, this analysis suggests that increased disease severity is a predictor for an increased risk of serious infection.

2.4.2 Infection and psoriatic arthritis

Individuals with psoriasis may also experience inflammatory arthritis, also known as psoriatic arthritis. Literature indicates that psoriatic arthritis affects 1.3% to 34.7% of the population of patients diagnosed with psoriasis.[162,163] Psoriatic arthritis is an immune-mediated inflammatory disease, which involves the inflammation of the peripheral joints, enthesitis, arthritis in the fingers, or

dactylitis. Patients with psoriatic arthritis often have several comorbidities hypothesized to be associated with risk of infection, including age, history of infection, and diabetes. Due to the chronic inflammatory nature of psoriatic arthritis, patients often require long-term treatment, and will be potentially exposed to multiple types of therapies.[164]

2.4.3 Disease severity control

The evaluation of infection risk associated with biologic or other psoriasis therapies is confounded by the influence of disease severity. Administrative databases frequently used in "real-world" analyses do not contain disease severity measures, and it is difficult to control for the effect of disease severity upon infection risk. Some variables proxy for more advanced disease, which can be used in modeling of infectious risk, include treatment utilization patterns (e.g., initiation of medication)[42-44] and the number of hospital visits or procedures over a certain time period.[45] These methods, however, are indirect and still allow for potential residual confounding and channeling bias.

Some studies using registry data have overcome this, as registries allow for access to direct disease severity measures. One of the few studies that actually has direct disease severity access found an elevated risk of serious infection for those with psoriasis (all types) and those with moderate-to-severe psoriasis, as measured by BSA, compared to a set of randomly selected patients who were matched by age category, were still alive, were registered at the same practice, and who did not have psoriasis.[161] Importantly, this analysis suggests that increased disease severity is a predictor for increased risk of serious infection.

2.4.4 Influence of psoriasis therapy on infection risk

In the context of infection, genetic polymorphisms in p40 cause dysfunction of normal IL-12 or IL-23 signaling, which leads to increased susceptibility to mycobacterial infections (**Figure 2.3**).[123,165-168] However, ustekinumab, a biologic for psoriasis that targets p40, has only rarely been associated with mycobacterial infections. Similarly, genetic defects in IL-17A lead to widespread chronic mucocutaneous candidiasis, whereas biologics for psoriasis that target IL-17A cause candidiasis in approximately 5% of those treated, with most cases being mild, localized to the oral mucosa, and easily treated.[169] So while infectious consequences of genetic defects are important to understand normal immune function, targeting similar immune function pathways with psoriasis biologic therapy usually leads to less impact on susceptibility to infection (when compared to genetic knockouts). In addition to relatively minor *Candida* infection, IL-17A blockade also has the potential to disrupt epithelial cell integrity in the intestine, exacerbating or causing inflammatory bowel disease.[143,170,171]

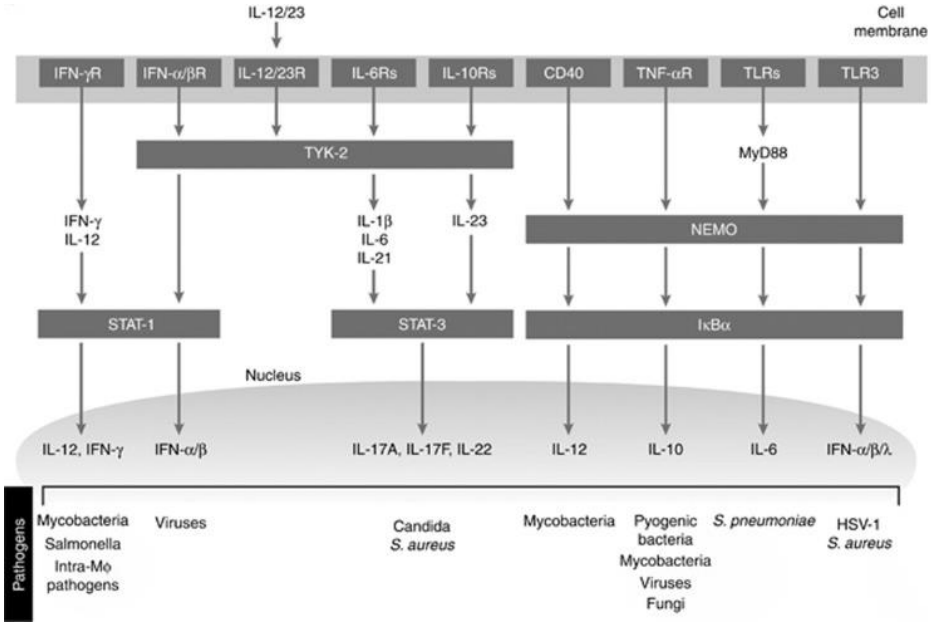

Figure 2.3. Pathways of Cytokines and Their Associated Pathogens. Blauvelt *et al*[116]

Most drug safety studies are RCTs,[36,117,119-121,172] with strict eligibility criteria, generally healthy populations, and placebo controls. RCTs may exclude older individuals or those with certain types of comorbidities, preventing the results of RCTs to be easily generalized outside of the study population. Observational cohorts provide the necessary size and patient complexity to better understand "real-world" outcomes. To date, there have been few non-interventional studies focused on the risk of infection associated with treatments for psoriasis.

2.4.4.1 Registry Studies

One of the most well-known longitudinal, disease-based, dermatology registry is the Psoriasis Longitudinal Assessment and Registry (PSOLAR).[173] An analysis of PSOLAR data published by Kalb *et al*. found a higher risk of serious infections in the psoriasis population for those individuals treated with adalimumab and infliximab, when compared to non-methotrexate, non-biologic therapies (HR: 2.13

[95% CI: 1.33, 3.41] and HR: 2.51 [95% CI: 1.45, 4.33], respectively).[172] These data are in line with other studies suggesting an increased rate of infection for biologics that target TNF-α, including infliximab, adalimumab, etanercept, and certolizumab.[159,169,174,175] One of the concerns with this analysis is that the authors included both prevalent and incident therapy users in their analysis, and observed a similar association when restricting to only incident therapy users of adalimumab (HR: 2.52 [95% CI: 1.47, 4.34]) compared to non-methotrexate, non-biologic users. When the analysis was further restricted to bionaïve therapy users, a slight elevated risk between therapy and serious infection (HR: 2.10 [95% CI: 0.93, 4.75]) when compared to non-biologic therapy users was observed, however, it was not statistically significant. These data are potentially confounded by indication, since a signal was observed when prevalent and incident biologic users were included together in the analysis, but that signal further diminished in the incident and previously bionaïve biologic user analyses.

Papp *et al*. performed additional analyses utilizing the PSOLAR database and found similar results as Kalb *et al*. In the population of individuals with psoriasis, those who were on anti-TNF-α biologics (infliximab, adalimumab, or etanercept) had a significant increased risk of serious infections as compared to those who were on non-biologic therapy (aHR: 1.96 [95% CI: 1.57, 2.44]). For those individuals who were on ustekinumab, there was no association between risk of serious infection and starting therapy, as compared to those on non-biologic therapies (1.06 [95% CI: 0.77, 1.46]).[174]

Three additional studies in recent years have found significant associations between serious infection and biologic use in the psoriasis population. The 2016 Haddad *et al*. study found that when biologic therapy use was considered a time-dependent covariate, the psoriatic arthritis group taking biologic therapy had nearly twice as many serious infections as those taking non-biologic therapy (HR: 1.56 [95% CI: 1.22, 2.0]). The study, however, did not identify a statistically significant association in the population of patients with psoriasis who lacked psoriatic arthritis (HR: 1.50 [95% CI: 0.64, 3.54]).[159] Patients self-reported the occurrence of infection, which included serious infections as defined by infections that required hospitalization or intravenous antibiotics, potentially introducing bias into the results, but this was likely to be non-differential in nature. In 2017, Dávila-Seijo *et al*. also found an increased risk of infection associated with biologic therapy in a Spanish dermatology registry. In this group of individuals with psoriasis, infection risk was increased for individuals treated with infliximab or etanercept compared to those treated with methotrexate (aRR: 1.71 [95% CI: 1.1, 2.65] and aRR: 1.34 [95% CI: 1.02-1.76], respectively).[169] Curiously, a similar risk for infection was seen when biologic therapy was prescribed with systemic therapy, such as methotrexate, as compared to biologic use alone. There was elevated risk for individuals taking adalimumab with methotrexate, or ustekinumab with methotrexate, compared to methotrexate as a monotherapy (aRR: 2.13 [95% CI: 1.2, 3.7] and aRR: 1.56 [95% CI: 1.08, 2.25]).[169] This speaks to the potential for an additive immunosuppressive effect of both the biologic therapy and

methotrexate, which has been previously discussed in the rheumatoid arthritis population.[176]

Data from PSOLAR has shown a similar interactive effect between methotrexate and biologic therapies in the population of patients with psoriasis. A 2015 study found that the risk of herpes zoster in the PSOLAR registry was not associated with monotherapies, including either methotrexate, biologics, phototherapy or non-methotrexate non-biologic therapies.[177] However, when methotrexate and biologic therapies were administered in combination, the risk of incidence herpes zoster became significant (RR:1.66 [95% CI: 1.08, 2.57]). The authors did not test methotrexate with each individual biologic therapy, but instead binned them together into one category.[177] There is a potential for misclassification, as some biologic therapies and their respective mechanism of actions may affect the risk in combination with methotrexate differently, as compared to others.

Some patient registry data have failed to find associations between biologic therapy and serious infection. The BIOBADADERM database, the Spanish Registry of Adverse Events from Biological Therapy in psoriasis, prospectively enrolls patients with psoriasis who are starting new therapy. Medina *et al*. compared the risk of infection for initiating biologic therapy as compared to non-biologic therapy found no significant association for adverse events and serious adverse events, both including infection (HR: 0.7 [95% CI: 0.6, 0.7] and HR: 1.4 [95% CI: 0.9, 2.3], respectively).[178] One limitation of this observational study was that the authors only controlled for age, which may explain the lack of observed association due to potential confounding. The British Association of

Dermatologists Biologic Interventions Register (BADBIR) also found no significant increase in risk of infection for etanercept (aHR: 1.10 [95% CI: 0.75, 1.60]), adalimumab (aHR: 0.93 [95% CI: 0.69, 1.26]), or ustekinumab (aHR: 0.92 [95% CI: 0.60, 1.41]), compared to non-biologics.[179] Similar risks were found when comparing biologic therapy use to methotrexate use alone (aHR: 1.47 [95% CI: 0.95, 2.28], aHR: 1.26 [95% CI: 0.86, 1.84], aHR: 1.22 [0.75, 1.99] for etanercept, adalimumab, and ustekinumab, respectively). This particular analysis adjusted for a wide range of variables, including demographics, disease severity, comorbidities, and immunodeficiency syndromes.[179]

Data from the BIOBADADERM and BADBIR registries were pooled with those from the PsoCare database, an Italian registry of psoriasis patients who newly prescribed either systemic or biologic therapy. The results of this prospective meta-analysis found that there was no significant association between biologic therapy (infliximab, adalimumab, and etanercept) use and serious infection, compared to non-biologic (acitretin, methotrexate, or cyclosporine) therapies (aHR: 0.98 [95% CI: 0.80, 1.19] pooled from all 3 registries).[180] Analysis by Garcia-Doval *et al*. found that the variation across countries, including prescribing trends, did not contribute to the lack of association.[181]

2.4.4.2 Health plan or administrative database studies

Most recently in 2017 among a large cohort of individuals with psoriasis, an association between serious infection and biologic therapy was identified in a large real world population-based health plan.[175] Dobry *et al*. utilized the Kaiser Permanente system of Northern California and found that after controlling for age,

sex, race and ethnicity, as well as comorbidities, those individuals with psoriasis who were prescribed biologic therapy were more likely to develop serious infections, as compared to individuals with psoriasis treated with non-biologic therapy (aHR: 1.31 [95% CI: 1.02, 1.68]). Both skin and soft tissue infection, as well as meningitis, had strong significant associations (aHR: 1.75 [95% CI: 1.19, 2.56] and aHR: 9.22 [95% CI: 1.77, 48.10], respectively).[175] While this signal was strong, this study was unable to determine associations for specific therapies most likely due to small numbers for each therapy, and instead grouped all biologic therapies together in comparison to non-biologic therapies. Conversely, a 2011 study by Grijalva *et al*. found that among patients on anti-TNF therapy for psoriasis, psoriatic arthritis, or ankylosing spondylitis, the rate of serious infections was not significantly higher than those taking non-biologic DMARDs (HR: 1.05 [95% CI: 0.76, 1.45]).[44] This study also noted a dose-dependent increase in the risk of serious infection and corticosteroid use (HR: 2.01 [95% CI: 1.08, 3.73] and HR: 2.77 [95% CI: 1.44, 5.32] for 5-10 mg/day and >10 mg/day use of corticosteroid use, respectively), which has previously been reported in the rheumatoid arthritis population.[182] One limitation to this study was that psoriasis, psoriatic arthritis, and ankylosing spondylitis patients were lumped together, all of which are related conditions; the risk of infection could potentially differ between these different disease populations.

A 2017 study by Desai *et al*. used administrative healthcare databases (Medicaid and Optum Clinformatics) to investigate an association between risk of serious infections and therapy in a cohort of pregnant women with inflammatory disease,

including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease.[183] The analysis found that there was no increased risk for serious infection in this population for the following pairwise comparisons: non-biologic systemic therapy vs. corticosteroid monotherapy (HR: 0.81 [95% CI: 0.48, 1.37]), TNF inhibitors vs. corticosteroid monotherapy (HR: 0.91 [95% CI: 0.36, 2.26]), and TNF inhibitors vs. non-biologic systemic therapy (HR: 1.36 [95% CI: 0.47, 3.93]).[183] The authors controlled for a wide variety of confounders including demographics, comorbidities, presence of infections prior to the start of the observation period, both prescription and illicit drug use, as well as hospital admissions and outpatient visits. This study did not address disease severity, potentially confounding the results, as well as lumped together several inflammatory diseases making a measurement of the effect of therapy type on psoriatic arthritis unclear.[183] Even though there was no risk of serious infection based on therapy type, the authors reported a dose-response trend with increase corticosteroid use. Similar to other studies[36,184], an increased risk of serious infections in the population of pregnant women with inflammatory disease was associated with higher corticosteroid dose (p=0.02).[183]

Winthrop *et al*. analyzed Medicare data and failed to find a statistically significant risk of serious infection and initiation of any single biologic therapy, as compared to UV therapy in the population of individuals with psoriasis (aHR: 1.13 [95% CI: 0.96, 1.33], aHR: 1.13 [95% CI: 0.97, 1.32], aHR: 1.15 [95% CI: 0.96, 1.39], aHR: 0.89 [95% CI: 0.64, 1.24] for adalimumab, etanercept, infliximab, and ustekinumab, respectively).[185] The lack of association was potentially due to the lack of power

associated with a small sample size with regard to some of the drug-exposure groups. To further support this hypothesis, when all TNF blockers were pooled together, there was an increased risk of serious infection (HR: 1.18 [95% CI: 1.04, 1.34]).[185] The authors hypothesized that this signal was observed in the pooled therapies group as an artifact of being unable to account directly for psoriatic disease severity.

Patients with psoriasis are at increased risk for infection from both their disease and at least some of their therapies. Available data regarding risk of infection as associated with treatment type is heterogeneous (**Figure 2.4**), with the majority of studies evaluating risks of anti-TNF-α therapy revealing elevated risk estimates. By contrast, biologic therapies inhibiting IL-17A or IL-23 have shown reduced risks of serious infection in individuals with psoriasis.[186] Although fewer real world data exist for IL-12/23 blockers and more recently approved biologics like those

inhibiting IL-17A or IL-23, the emerging picture is that their ability to cause infections is diminished as compared to anti-TNF therapies.

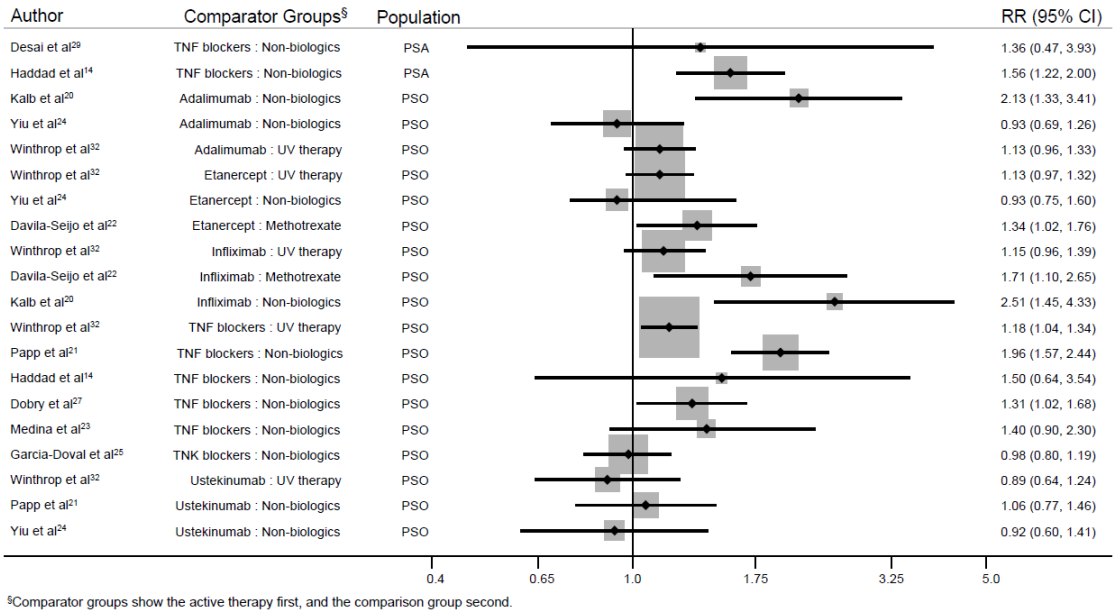

Figure 2.4. Recent Studies of Risk of Serious Infection and Biologic Therapy. Siegel *et al*[186]

When comparing the absolute risk of serious infection between registries, health plans, or administrative data, we observe a marked increase in incidence rates for Medicare data. Winthrop *et al*. noted crude incidence rates of serious infection range from 9.7 (95% CI: 7.5, 12.7) per 100 person-years for ustekinumab, to 11.9 (95% CI: 10.8, 13.2) per 100 person-years for infliximab.[185] These rates are higher than the rates documented in the registry or health plan databases, but similar to other analyses utilizing claims data. Grijalva *et al*. observed incidence rates for serious infection of 5.41 per 100 person-years for individuals with psoriasis or spondyloarthropathies initiating TNF-α inhibotrs.[44] This is to be expected, as individuals in Medicare are typically older, as compared to registry participants. Rates of serious infection in the registries studies, where patients are typically

much younger and at lower baseline risk, were much lower. PSOLAR found incidence rates for serious infection range from 0.83 (95% CI: 0.61, 1.09) for ustekinumab to 2.49 (95% CI: 1.88, 3.23) for infliximab.[172] Similar incidence rates were reported for the BIOBADADERM Registry, 0.559 (95% CI: 0.12, 2.87) for ustekinumab, 0.92 (95% CI: 0.46, 1.84) for adalimumab, and 1.27 (95% CI: 0.49, 3.31) for infliximab.[169] Incidence rates for serious infections by exposure were similar to both PSOLAR and BIOBADADERM in the BADBIR Registry and the Psonet registries.[179,180]

2.5 Risk of mortality in the psoriasis population

Historically, psoriasis had not been considered a disease associated with increased risk of mortality. More recently, however, there have been a handful of studies that have looked at both all-cause mortality within the psoriasis population. All of these studies have found an association with psoriasis and all-cause mortality.[10,53,94,95,187-191] These studies have been conducted in a wide variety of locations, including the United Kingdom, Denmark, Sweden, and Taiwan, leading to the assumption that these results are potentially generalizable. These results are further supported by a systematic review and meta-analysis published within this year, which found an increased risk for all-cause mortality for individuals with psoriasis. The results of this meta-analysis also supported a dose-response with psoriasis severity and increased risk of mortality.[192]

Cause-specific mortality for individuals with psoriasis has not been thoroughly investigated. To date, research has focused on cardiovascular disease in particular[8,16,54,190] as well as more exploratory studies looking at multiple causes of

mortality.[36,94,187,189,191] All of these studies found some type of significant association between psoriasis and infection-specific mortality. Of interest, a population-based study of the Swedish Register did not find an association between infection-specific mortality and severe psoriasis; however, they found a significant association for infection-specific mortality and mild psoriasis.[187] This seemingly contradictory result could be due to the method in which the authors controlled for disease severity, which was to classify severe disease as either hospitalization with psoriasis as a primary diagnosis, or having one episode of treatment with systemic therapy. Misclassification bias is a potential threat to validity, as the authors classified patients who were prescribed non-biologic or biologic therapies from a rheumatologist or gastroenterologist as having mild psoriasis. The authors performed a sensitivity analysis to understand the effect of this bias on the results for those with severe psoriasis, excluding individuals with at least one primary diagnosis of a relevant rheumatic or gastrointestinal disease and were treated with a systemic therapy. The point estimate of the all-cause mortality increased for those with severe psoriasis, but the authors did not report the effect on the point estimate for those with mild psoriasis.[187]

The method by which researchers control for psoriasis severity affects the results of these studies. Several studies made no mention of severity and did not control for this factor. Two studies defined severe psoriasis as at least one episode of systemic treatment,[95,189] one study included both one episode of systemic treatment or hospitalization with psoriasis as a primary diagnosis classified as severe psoriasis,[187] and three studies defined severe psoriasis as patients who

had a history of systemic treatment.[53,54,190] The use of an indirect measure for psoriasis severity, as well as the heterogeneous definition of severity in these studies, indicates a potential for confounding by indication.

A recent study utilizing The Health Improvement Network database in the United Kingdom was able to utilize physician-reported BSA as a direct covariate in an analysis on mortality in a population of individuals with psoriasis.[96] The results showed a significant increase in risk of death for those individuals classified as having 10% BSA or greater affected by psoriasis, compared to individuals without psoriasis. These results are consistent with previously published studies discussed above and underscore the importance of being able to directly assess the effect of psoriasis severity on outcomes associated with therapy type.

2.6 Limitations of the existing data

New guidelines for psoriasis treatment with biologic therapy includes several of the newer biologic treatments.[52] These new cytokine blockers, e.g., IL-17A and IL-23 blockers, are being developed and tested to simultaneously achieve improved skin clearance and reduction of adverse events. The approvals for these newer psoriasis therapies continue to progress rapidly. There are few studies, however, that have been able to compare rates of hospitalization between different therapy types, and many are not able to take disease severity into account due to lack of clinical information in claims databases.[43,44] Thus, there is a critical gap in fully understanding potential adverse effects of current biologic therapies for psoriasis.

To-date, current data available regarding the risk of infection by treatment type in the psoriasis population are unclear. The bulk of scientific publications finding no increased risk of infection associated with treatment type for individuals with psoriasis are derived from RCTs.[117,119-121] Although essential for determining efficacy, RCTs suffer from limited generalizability of results as patients with psoriasis who participate in RCTs are more likely to be healthier and have fewer co-morbidities than patients in real-world practice settings. The use of placebo for the comparison group in RCTs also limits comparisons between therapies to determine the best treatment for specific individuals. There are few observational studies that have compared rate of infection by treatment type. No association was found in a large administrative database,[44] but an association of increased risk of infection was observed in a study utilizing a registry.[172]

Clinical assessments such as the percentage of BSA involved with psoriasis provide a standard for disease severity, which is not available in claims data. Moderate-to-severe psoriasis, as defined as BSA ≥3%, accounts for approximately 20% of all psoriasis patients.[38] It is currently not understood how disease severity affects risk of serious infection, though disease severity is associated with greater likelihood of biologic therapy usage.[193,194] To address this potential confounder, it is vital to account for disease severity when comparing outcomes associated with treatment type.

There are currently few available methods to determine disease severity, including treatment utilization patterns, initiation of medication,[43,44] and number of hospital visits or procedures,[45] all of which are indirect proxies. Few registries

exist that are capable of linking clinical information like disease severity with more broadly available data such as treatment type and outcomes. The Psoriasis Longitudinal Assessment and Registry is one such registry.[173] PSOLAR is a national institution-based registry where patients voluntarily enrolled. Registries like PSOLAR suffer from selection bias, as individuals must volunteer to take part in the program, and volunteers are much more likely to be healthier with fewer co-morbidities when compared to non-volunteers. Thus, results from registries like PSOLAR may not be applicable to the general population.

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Chapter 3: Development of a Psoriasis Severity Score for Clinical Measures in a Claims Database

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3.1 Abstract

3.1.1 Purpose: To develop a severity score for psoriasis in a claims database, allowing for control of disease severity in additional analyses of psoriasis drug safety in large healthcare claims databases.

3.1.2 Methods: We linked patients in two registries with Medicare to create a retrospective cohort of adults in the United States diagnosed with PsO between 2006-2017. The outcome was body surface area as measured by a dermatologist in the registry data, and was dichotomized at 3% BSA based on the National Psoriasis Foundation's classification system. Predictors were selected *a priori* and tested for significance with the dichotomized outcome of BSA. We used Least Absolute Shrinkage and Selection Operator (LASSO) with k-fold cross-validation (k=5) for variable selection and cross-validation.

3.1.3 Results: A total of 64 CEPPA patients and 172 Corrona patients were included. We developed a model for moderate-to-severe psoriasis that included 17 claims-based variables. The classification error for our model was 32.2%, and had 5 false negatives and 14 false positives. Our model's predictive value for positive and negative values were 58.8% and 80.0%, respectively.

3.1.4 Conclusions: We have developed a psoriasis severity score utilizing claims data with 17 claims-based variables. Our score may be used to adjust for psoriasis disease severity in pharmacoepidemiologic studies utilizing claims data.

3.2 Introduction

Psoriasis is an immune-mediated, chronic, inflammatory disease that affects ~3% of Americans.[1,2] Psoriasis disease severity is an important factor for determining risk of common comorbidities such as cardiovascular disease,[3,4] diabetes,[5,6] and obesity.[7] Recent research has also found that higher disease severity increases risk of other comorbidities and clinical outcomes,[8] including infections[9] and mortality.[10,11] Certain therapies for the treatment of psoriasis are known to be associated with increased risk of infection,[12] providing two pathways for individuals with moderate-to-severe psoriasis to experience risk of infection. It is estimated that moderate-to-severe psoriasis accounts for approximately 20% of all psoriasis patients,[13] indicating a substantial proportion of psoriasis patients are at increased risk for adverse health consequences because of their skin disease. Comparative evaluation of psoriasis therapies with regard to their safety and efficacy should account for psoriasis disease severity.

While the use of healthcare claims databases has been useful in understanding the safety of psoriasis therapies, their lack of clinical information limits the ability to control for disease severity, especially when assessing various outcomes such as the risk of infections. Thus, indirect methods of accounting for psoriasis severity are needed when using these databases to evaluate clinical questions, such as risk of infection. There are a few different methods currently being used to determine disease severity within databases, including treatment utilization patterns (e.g., initiation of medication)[14,15] and the number of hospital visits or procedures over a certain time-period.[16] These methods, however, are indirect

and do not account for the possibility of channeling bias in treatment decisions by clinicians. Disease severity classification by treatment initiation, such as biologic therapy, create methodologic concerns when trying to understand associations of certain outcomes with specific therapies. Indeed, without the ability to control for underlying severity, the evaluation of biologics and other therapies in healthcare claims data is limited.

Psoriasis severity has traditionally been measured through clinical measurements, including body surface area (BSA), Physician's Global Assessment (PGA), and the Psoriasis Area and Severity Index (PASI). BSA has been found to be a reliable measure for disease severity, is simple for patients to self-report,[17] and is considered to be fairly robust against misclassification errors by providers.[8,18] Ideally, direct measures of disease severity, like the BSA, would be available to control for confounding. This has been utilized for cohort studies, but not for large healthcare claims databases such as Medicare. Here, we developed a psoriasis severity score for Medicare, which should prove useful in controlling for disease severity for further evaluations of psoriasis drug safety in large healthcare claims databases.

3.3 Methods

3.3.1 Patient population

We used data from two previously established registries of adult patients with psoriasis: the Center for Excellence in Psoriasis and Psoriatic Arthritis (CEPPA), which is housed at Oregon Health & Science University (OHSU) and the Corrona

Psoriasis Registry, which is a national registry.[19] Briefly, patients aged ≥18 years evaluated in CEPPA at OHSU for psoriasis from November 1st, 2006 onward were prospectively enrolled. The Corrona Psoriasis Registry was started in April 2015 and treating dermatologists prospectively enroll patients aged ≥18 years. Patients with a psoriasis diagnosis by their dermatologist and initiated eligible therapy,[1] either at their enrollment or within the past 12 months prior to enrollment.[20] For our study, we collected all variables at the enrollment visit for both registries. The Corrona registry collected clinical information typically unavailable in a claims database, such as patient scores for skin pain, itch, fatigue, and work productivity.[21] The CEPPA registry collected self-administered questionnaires, including demographic information, and information regarding the extent of their psoriasis, presence and severity of musculoskeletal symptoms, and quality of life (QoL).[22] The OHSU IRB approved this research and patients consented to participate in their respective registries.

We utilized the complete Medicare dataset including Part A, B, and D from January 1st, 2006, through December 31st, 2017, to link to the two registries described above. Patients who enrolled in either registry by December 31st, 2017 were included in the model building cohort. Patients within the Medicare dataset needed to have the following: 1) at least ≥ 1 dermatologist-assigned diagnosis code for psoriasis (ICD-9 code 696.1 or ICD-10 code L40); 2) at least 12 months (365 days) of continuous enrollment in Medicare part A and B plans; and 3) had

[1] Eligible therapies include adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab

not been enrolled in a Medicare Advantage (Part C) plan prior to their registry enrollment date. Medicare part D was not included in the eligibility criteria due to concerns with further reducing the sample size. For the Corrona registry, we had access to historic and current medications of patients at the time of their enrollment. For the CEPPA registry, we had access to the patient's electronic medical records (EMR) to verify medications. Due to limitations of accessing older Medicare data outside of the range of data available to us, patients in the CEPPA cohort had their enrollment date pushed forward 12 months to ensure that there were ensure patients with 12 months of Medicare data for covariate analysis. BSA was collected at 12 months (+/- 3 month window). The use of older Medicare data outside the range of data available was not an issue for the Corrona cohort. Medicare is public health insurance that provides coverage for >90% of U.S. residents age ≥ 65 years and those who are younger than 65 years and disabled.[23,24]

3.3.2 Data linkage

We linked two registries, CEPPA at OHSU and Corrona's national psoriasis registry, with Medicare data for 2006-2017. Both direct linkage using social security number (SSN) and linkage using probabilistic linkage using birth date, sex, dermatology provider name, and most recent dermatology encounter date were used. Prior studies using similar linkage methodologies, including those using the rheumatoid arthritis Corrona database, with linkage success of more than 90% of individuals matched.[25-27]

3.4 Measures

3.4.1 Outcome measure

Our outcome was BSA, defined using a modified version of the National Psoriasis Foundation's classification system as mild (limited disease with ≤2% BSA affected), moderate (scattered disease with 3%-10% BSA affected), or severe (extensive disease with >10% BSA affected). We placed patients into just two categories based on the National Psoriasis Foundation's classification system: mild-to-moderate disease (<10% BSA affected) or severe disease (≥10% BSA affected). BSA was determined by a dermatologist at the date of enrollment into either the CEPPA or Corrona registry, and recorded in the registry data. Historic BSA values were not used in the development of the psoriasis severity score.

3.4.2 Covariate measures

The index dates for our model building cohort were either the date of enrollment in the Corrona registry or the, 12 months (+/- 3 months window) post-enrollment date in the CEPPA registry. We evaluated a number of *a priori* defined variables from the Medicare data set prior to the index date. Claims data include certain demographic characteristics and clinic-based claims, including inpatient, outpatient, and pharmacy dispensation. We used the *International Classification of Diseases – 9th and 10th Revisions* (ICD-9 and ICD-10, respectively) to classify procedural and diagnostic codes. Demographics characteristics were assessed at the time of an individual's enrollment in either registry and included age, gender, race, and Medicare plan information.

3.5 Data analysis

3.5.1 Descriptive analysis

Within our model building cohort, we performed descriptive analyses of sociodemographic and clinical characteristics of interest. Univariate comparisons to the outcome of dichotomized BSA were done using Fisher's exact or chi-square tests for binary predictors, T-test for continuous predictors, or ANOVA for categorical predictors, as appropriate.

3.5.2 Model building

We developed a list of *a priori* predictors (**Tables A2.1, A2.2, and A2.3**), including specific diagnoses, therapy treatment patterns, number and type of patient visits, and select demographic characteristics. Within our model building cohort we explored the relationship between these variables and the dichotomized outcome of BSA. Only variables with a prevalence of >3% were included. All *a priori* covariates that met our univariate analysis cut-off of $p < 0.20$ were included for further extensive testing. No variables were forced into the model. Predictors were tested for collinearity and variables with a significant Pearson Correlation coefficient ≥0.5 were excluded. If two variables were found to be correlated, then the variable with the more significant p-value was kept.

Penalized logistic regression using Least Absolute Shrinkage and Selection Operator (LASSO) was used for variable selection and cross-validation. We performed all phases of model-fitting using LASSO on a training subset, which was 75% of the model building cohort data. Within the training subset, k-fold cross-validation (k=5) was used to reduce statistical bias, simulate validation by

an external dataset, and protect against overfitting of the model.[28] LASSO coefficients are provided in **Table A2.4**.

We used the remaining 25% of the observations as a test data set to test the fit of our model. The final set of variables were used to develop our score variable within the test dataset. We created a dichotomized variable as the predicted score, based on the actual score with a cut-off of 0.29 based on ROC values and cutpoint analyses, and classified individuals with a score of >0.29 predicted to have severe psoriasis, and individuals ≤0.29 predicted to have mild-to-moderate psoriasis. The fit of our model was assessed using classification error based on the dichotomized variable and the actual score. We calculated classification error based on the percentage of discordant pairs within the entire test dataset. Receiver-operator curve (ROC) was tested to understand the discrimination of the score in the test dataset. Statistical analyses were performed using SAS version 9.4 and R version 3.5.2.

3.6 Results

3.6.1 Baseline Characteristics

We identified a total of 195 patients in the CEPPA registry and 430 patients in the Corrona registry linked to the Medicare database. After restricting to those who enrolled prior to December 31st, 2017 and requiring at least 12 months of Medicare Parts A and B prior to the index date, 64 CEPPA patients and 172 Corrona patients included for further analyses. At time of enrollment in each respective registry, the mean age of 65.9 years and 54.7% were female. The majority of patients were Caucasian, had a body mass index (BMI) of <25, and

never had smoked (**Table 3.1**). Psoriasis disease severity was relatively evenly distributed amongst the three categories (27.1% with mild disease, 31.8% with moderate disease, and 41.1% with severe disease), based on the National Psoriasis Foundation's classification system.

Within the registries, the CEPPA population had a mean age 67.1 years and 53.1% were female, and the Corrona population had a mean age 65.5 years and 55.2% were female (**Table 3.1**). Corrona patients had a higher BMI and were more likely to be non-Caucasian. Comorbidities occurred at similar prevalences among both cohorts, with the exceptions of anxiety, diabetes, joint surgery, and long-term drug use, all of which were more likely among the Corrona cohort. For the CEPPA cohort, 12 (18.8%) patients had mild disease, 20 (31.3%) had moderate disease, and 32 (50.0%) had severe disease. In the Corrona cohort, 52 (30.2%) patients had mild disease, 55 (32.0%) had moderate disease, and 65 (37.8%) had severe disease. The distribution of moderate-to-severe psoriasis was similarly high between the two registries, with 81.3% and 69.8% in the CEPPA and Corrona registries, respectively. Patients had median BSAs of 9.5% (IQR: 3-18%) and 5% (IQR: 2-12%) for the CEPPA and Corrona registries, respectively.

Table 3.1. Demographic and Clinical Characteristics of CEPPA and Corrona Cohorts

Charactersitic	Both Cohorts (n=236)	CEPPA (n=64)	Corrona (n=172)
Body Surface Area (%)			
Mean (SD)	11.8 (16.2)	14.0 (16.6)	11.0 (16.1)
Median (IQR)	6 (13.0)	9.5 (14)	5 (10)
Mild (<3%)	64 (27.1%)	12 (18.8%)	52 (30.2%)
Moderate (≥3%, <10%)	75 (31.8%)	20 (31.3%)	55 (32%)
Severe (≥10%)	97 (41.1%)	32 (50%)	65 (37.8%)
Moderate-to-Severe (≥3%)	172 (72.9%)	52 (81.3%)	120 (69.8%)
Age (years)			
Mean (SD)	65.9 (10.0)	67.1 (7.2)	65.5 (10.9)
Median (IQR)	67 (11.0)	68 (11.5)	66 (11.0)
Female sex, n (%)	129 (54.7%)	34 (53.1%)	95 (55.2%)
Race			
White	186 (78.8%)	52 (81.3%)	134 (77.9%)
Black	<11	<11	<11
Asian	13 (5.5%)	<11	13 (7.6%)
Hispanic	<11	<11	<11
North American Native	<11	<11	<11
Other	<11	<11	<11
Unknown	<11	<11	<11
Body mass index (kg/m^2)			
Underweight/normal, <25 BMI	174 (73.7%)	59 (92.2%)	115 (66.9%)
Overweight, 25-29 BMI	<11	<11	<11
Obesity, >30 BMI	53 (22.5%)	<11	48 (27.9%)
Smoking history			
None	186 (78.8%)	59 (92.2%)	127 (73.8%)
Ever	50 (21.2%)	<11	45 (26.2%)
Anxiety	41 (17.4%)	<11	39 (22.7%)
Chronic obstructive pulmonary disease	37 (15.7%)	<11	29 (16.9%)
Coronary heart disease	<11	<11	<11
Depression	49 (8.1%)	<11	40 (23.3%)
Diabetes (types 1 and 2)	76 (32.2%)	14 (21.9%)	62 (36.0%)
Dyslipidemia	110 (46.6%)	27 (42.4%)	83 (48.3%)
Fatty liver	<11	<11	<11
Heart failure	<11	<11	<11
Hypertension	168 (71.2%)	40 (62.5%)	128 (74.4%)
Infection (treated outpatient)	129 (54.7%)	30 (46.9%)	99 (57.6%)
Inflammatory bowel disease	<11	<11	<11
Joint Surgery	55 (23.3%)	<11	45 (26.2%)
Longterm drug use	95 (40.3%)	16 (25.0%)	79 (45.9%)
Metabolic	<11	<11	<11
Osteoarthritis	16 (6.8%)	<11	13 (7.6%)
Prior myocardial infarction	14 (5.9%)	<11	<11
Psoriatic arthritis	82 (34.7%)	19 (29.7%)	63 (36.6%)
Rheumatoid arthritis	28 (11.9%)	<11	23 (13.4%)
Sleep apnea	23 (9.7%)	<11	17 (9.9%)
Stroke	11 (4.7%)	<11	<11
Systemic lupus erythematosus	<11	<11	<11

3.6.2 Psoriasis disease severity prediction model

Our analysis developed a model for moderate-to-severe psoriasis that included 17 claims-based variables. Nine (53%) of the factors were provider-given diagnoses, including depression, fibromyaligia, lower back pain, stroke associated with myocardial infarction, or diagnosis of an infection either in the outpatient or inpatient setting, all within 12 months of the index date, and any diagnosis of dyslipidemia, osteroarthritis, and prior myocardial infarction. Three (18%) of the factors were related to therapy: prescription of adalimumab within 6 months of the index date, prescription for narcotic or anti-hyperlipidemia drugs within 12 to 6 months of the index date. One (6%) of the predictors was a combination variable of any diagnosis of influenza immunization (alone or with pneumococcal) or procedural code for influenza immunization, within 12 months of the index date. One (5%) of the predictors was solely procedural, any procedures administered at a skilled nursing facility within 12 months of the index date. One (5%) of the predictors was an indicator variable for those patients who did not have visits for diagnoses of myocardial infarction, congestive heart disease, peripheral vascular disorder, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, or acquired immunodeficiency syndrome. The final predictor (5%) was female sex.

The classification error on our test subset of data for our model was 32.2%. The misclassification error had 5 false negatives and 14 false positives. Our predictive value for positive and negative values were 58.8% and 80.0%, respectively. The ROC results of the score in the test dataset were 0.694, indicating that our score performed better than the flip of a coin.

3.7 Discussion

This work represents the first formal evaluation to develop and internally validate a psoriasis disease severity prediction score using data available in the Medicare healthcare claims database. There were 17 variables used as part of our severity score broken into 6 domains; diagnoses were fibromyalgia, depression, lower back pain, stroke associated with myocardial infarction, and diagnosis of an infection either in the outpatient or inpatient setting all within 12 months of the index date, or any diagnoses of dyslipidemia, osteoarthritis, or prior myocardial infarction; prescription of adalimumab within 6 months of the index date and prescription for narcotic or anti-hyperlipidemia drugs within 12 to 6 months of the index date; any diagnosis of influenza immunization (alone or with pneumococcal) or procedural code for influenza immunization, within 12 months of the index date; those with no visits for diagnoses of myocardial infarction, congestive heart disease, peripheral vascular disorder, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, or acquired immunodeficiency syndrome

within 12 months of the index date; any procedures administered at a skilled nursing facility within 12 months of the index date; and female sex. Our results found that the use of our Medicare algorithm within our model building cohort correctly classified patients with severe psoriasis 67.8% of the time. The results of the ROC indicate that the model has borderline acceptable ability to discriminate between those with severe and mild-to-moderate psoriasis.

Efforts to build a similar model to predict disease activity for rheumatoid arthritis (RA) solely using healthcare claims data have also shown a lower level of predictive ability. Sauer *et al.* used LASSO with 5-fold cross-validation to predict RA disease activity as measured by the Disease Activity Score (DAS28). Their research yielded models able to correctly classify the DAS28 categories 39.9% to 40.5% of the time.[29] Ting *et al*. developed a model for predicting RA disease activity in healthcare claims, the claims-based index for RA severity (CIRAS).[30] While the authors showed moderate correlation ($R^2 = 0.31$) for their model, a recent study tested the validation of CIRAS in an external population.[31] Desai *et al.* found that the CIRAS correlated poorly with clinically validated markers of RA severity. The authors hypothesized that the poor performance of the CIRAS was due to only validating the model internally.[31] Our model was also validated with k-fold cross-validation, which improves the out-of-sample accuracy of our model on the test subset of data. This may be reflected in our higher classification ability (67.8%) as compared to the RA studies.

Our misclassification error may be explained by the relatively high-level of heterogeneity within our dataset. At enrollment, 49% of the CEPPA patients had

never received any systemic therapy,[22] while all Corrona patients must have initiated therapy either with a biologic or a non-biologic systemic drug for psoriasis within 12 months of enrollment.[21] Patients who are prescribed systemic therapies are more likely to experience a higher burden of comorbidities and have higher BSA. This difference between therapy utilization in each population could account for some of the differences observed in the demographic and clinical data between our two cohorts. Indeed, this heterogeneity inclusion and exclusion criteria could contribute to our model's misclassification error, but the variety of our two registries can also be viewed as a strength of our model. Healthcare claims data includes a diverse population and our two distinct registries may allow for better representation of this diversity.

A potential threat to validity for our analysis is selection bias. The CEPPA registry recruits volunteers from a large, academic medical institution, biasing the type of individuals that can either afford to, or travel to, see a clinician at OHSU. Participants in Corrona are recruited out of different sites across the U.S. and Canada, though clinicians must opt-in to participating in Corrona. Furthermore, individuals that choose to participate in research are typically healthier than those who do not participate.[32] While our results showed an increased percentage of participants may have had fewer comorbidities than similar patients who chose not to participate in a registry. The overall effect is to reduce the generalizability of our severity score in the general Medicare population.

A primary strength of this study was the linkage of two prospective psoriasis registries with Medicare data. To our knowledge, this study is the first to link a

registry to Medicare data and utilize registry variables to predict disease severity. Prizment *et al*. linked women with psoriasis in the Iowa Women's Health Study (IWHS) to Medicare data to investigate possible associations between psoriasis and incident cancer.[33] However, their study was not able to control for psoriasis severity and utilized the surrogate measure of "number of dermatologist visits with a psoriasis diagnostic claim".

One of the limitations for our study is the overall small number of observations compared to the vast number of predictors. Increasing the number of predictors in our model would provide improved model classification ability, but could lead to spurious predictors as well as overly wide confidence intervals.[34] We used both *a priori* and statistical methods for variable selection to provide the most salient predictors for our model. The distribution of patients with severe psoriasis (41.1%) was relatively even compared to the comparator group, those patients with mild-to-moderate psoriasis (58.9%). This relatively even distribution between the two comparator groups, with the lower prevalence of the outcome reflected in the decreased positive predictive value.

3.8 Conclusions

To our knowledge, this is the first claims-based algorithm for psoriasis severity using clinical BSA data as the gold standard. The results indicate moderate classification and suggest that a claims-based algorithm for psoriasis disease severity to address confounding in claims data is possible. Our score may serve as a potentially important tool in adjusting for psoriasis disease severity in

pharmacoepidemiology studies, as the number of biologic and small molecules therapies approved for psoriasis continue to grow.

3.9 Conflicts of Interest

SARS, AB, and JM have no conflicts of interest to declare. JRC has received research funding for unrelated work from AbbVie, Amgen, BMS, Corrona, Eli Lilly, Janssen, Myriad, Pfizer, Regeneron, Roche, and UCB. JRC has consultancies with AbbVie, Amgen, BMS, Corrona, Eli Lilly, Janssen, Myriad, Novartis, Pfizer, Regeneron, Roche, Samsung, and UCB. KLW has received research funding for unrelated work from BMS and Pfizer. KLW has consultancies with AbbVie, Eli Lilly, Galapagos, GSK, and Pfizer.

3.10 Conference Presentations

This research has been accepted for presentation in poster form at the Society of Investigative Dermatology in Arizona, US, in May 2020.

3.11 Acknowledgments

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Chapter 4: Comparative Infectious Risk of Biologic Therapies for Psoriasis Among Real-World Users in Medicare

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4.1 Abstract

4.1.1 Purpose: To investigate whether initiation of biologic therapies for psoriasis (tumor necrosis factor-alpha (TNF-α), interleukin (IL)-12/23, IL-17, and IL-23 blockers) is associated with an increased risk of hospitalized infections in Medicare patients.

4.1.2 Methods: A retrospective cohort utilizing Medicare data from 2006-2017 was assessed. Exposure was defined as initiation of a TNF-α , an IL-12/23, an IL-17, or an IL-23 blocker for psoriasis. The outcome was hospitalized infections after initiation of biologic therapy. Incidence rates per 100 person-years were calculated, and hazard ratios with 95% confidence intervals were estimated using Cox proportional hazards regression models, utilizing a psoriasis severity score, and adjusted for the inverse probability of treatment-weighted propensity scores.

4.1.3 Results: There were a total of 26,333 treatment episodes of biologic therapies that met eligibility criteria. There were 2,463 hospitalized infections with 18,753 person-years of follow-up. Incidence rates were similar between patients using TNF-α or IL-17 blockers, and were higher than those using an IL-12/23 inhibitor. After propensity score weighting and adjustment for covariates, there was a decrease in risk of hospitalized infection in patients on either IL-17 (HR = 0.74; 95% CI: 0.60, 0.90) or IL-12/23 (HR = 0.83; 95% CI: 0.75, 0.91) inhibitors compared to those on TNF-α inhibitors. There was no significant difference for patients on IL-12/23 blockers (HR = 0.97; 95% CI: 0.80, 1.17) compared to those on IL-17 blockers.

4.1.4 Conclusions: Compared to TNF-α inhibitors, use of both IL-17 and IL-12/23 inhibitors were associated with reduced risks of hospitalized infection in Medicare patients with psoriasis.

4.2 Introduction

Psoriasis is estimated to affect about 3-4% of the United States population.[1-3] Over the past decade, new biologic therapies have been approved by the United States Food and Drug Administration (FDA) for the treatment of psoriasis, including the interleukin-12/23 (IL-12/23) inhibitor ustekinumab, IL-17 antagonists (secukinumab, ixekizumab, brodalumab), and IL-23 antagonists (guselkumab, tildrakizumab, risankizumab). There are likely risk differences between older biologics for psoriasis (TNF-α blockers) and these new therapy classes, given their mechanisms of action are considerably different from one another.[4] Thus, it is important to understand the potential risk of infection associated with each of these biologic classes.

Due to dysregulation of their immune systems, patients with psoriasis are at increased risk for infection.[5-9] Recent registry studies with ability to control for disease severity have shown that the risk of infection may also increase due to the use of biologic therapies.[10-12] Paradoxically, several registry studies and analyses on administrative databases have shown that the use of biologic treatment does not affect the risk of infection in those with psoriasis.[13-16] One potential reason for this contradiction is the inability to control for the effect of psoriasis disease severity in administrative data. Previously, we validated a score to control for psoriasis disease severity in administrative databases. Using national Medicare data for adults diagnosed with psoriasis between 2006-2017, along with a psoriasis severity score, we examined the comparative risk of

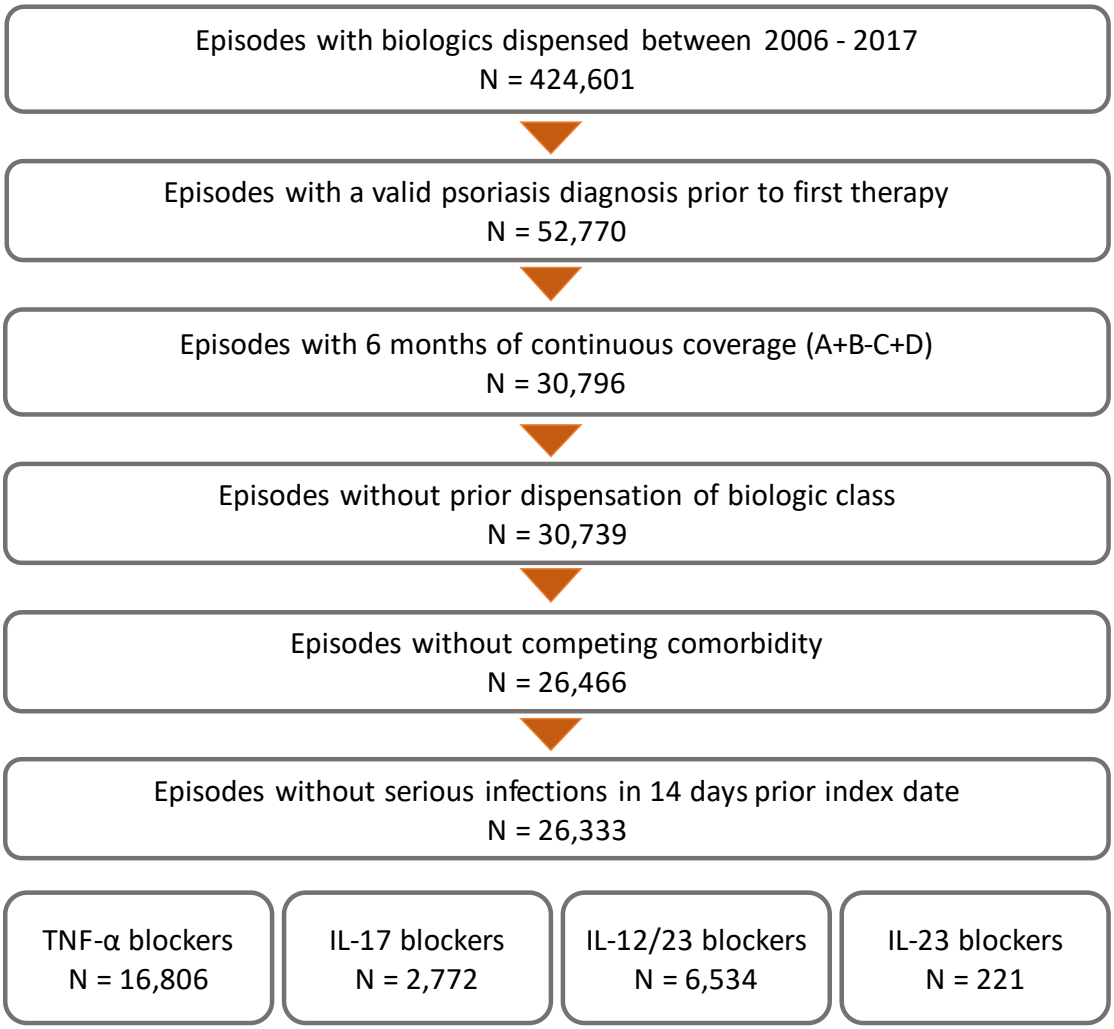
hospitalized and opportunistic infections in persons who started on biologic therapy.

4.3 Methods

4.3.1 Patient population

We utilized the complete Medicare dataset, including Parts A, B, and D from January 1, 2006, through December 31, 2017 to identify and characterize patients with psoriasis. Within this time frame, we identified a cohort of patients where all biologic therapies were either prescribed, or a procedural claim was recorded, to treat psoriasis. Our index date was defined as the date of biologic initiation. Patients were first defined as having psoriasis if they had ≥ 1 dermatologist-assigned diagnosis code for psoriasis (ICD-9 code 696.1 or ICD code L40.9) during an office visit. We then identified those who had either a prescription dispensation or procedure code for at least one biologic therapy. We defined an index date as the date of the first dispensing of any biologic therapy of interest. Patients had to have at least 6 months of continuous enrollment in Medicare. We additionally excluded patients who had a hospitalized infection within 14 days prior to the index date (**Figure 4.1**).

Figure 4.1. Cohort selection process.



We allowed for 90 days of non-overlap between discrete prescriptions as a period of continuous therapy. Biologics prescribed for self-administration were coded from pharmacy claims using the National Drug Codes (NDC). Biologics that were given via infusion were identified from procedural codes in medical claims, using the Healthcare Common Procedure Coding System (HCPCS). Medical claims based on HCPCS procedural codes do not contain information on days of supply. To address this issue, we assigned the length of each treatment period based on the dosage regimen. This method has been described in detail elsewhere.[17]

4.3.4 Outcome

We defined our outcome as hospitalized infection, which required a hospitalization encounter with an inpatient diagnosis code for infection at any position (primary or non-primary). Patients were followed from initiation of a biologic therapy until their first hospitalized infection, or were censored from the analysis if they discontinued their biologic therapy (defined as either a treatment gap of at least 90 days, or switching to a new biologic therapy class),[18] lost continuous Medicare coverage, died, or had ongoing therapy as of December 31, 2017, whichever came first.

4.3.5 Covariates

We evaluated covariates 6 months prior to the index date. Covariates included patient variables, select comorbidities (e.g., BMI), and health services utilization, including the number of prior hospitalizations. We also explored the effect between those patients who were biologic naïve (those episodes in which patients contributed their first exposure episode) and those with prior biologic experience (those episodes in which patients switched to a different biologic therapy class). We performed stratified analyses based on these two groups. For the number of prior biologics, all available data were used to determine each prior therapy status.

We utilized a unique severity score that was developed via linking two psoriasis registries to Medicare data: the Center for Excellence in Psoriasis and Psoriatic Arthritis (CEPPA), which is housed at Oregon Health & Science University (OHSU), and the Corrona Psoriasis Registry, which is a national registry. The CEPPA cohort[19] and the Corrona Psoriasis Registry have both been previously

described.[20] The development of our psoriasis severity score has been described elsewhere. Briefly, our severity score included 17 covariates that cover 6 unique domains: diagnoses, procedural or prescription therapies, a combination of diagnoses and procedural codes, healthcare utilization, surgical or outpatient procedures, and patient demographics. The severity score was used as a dichotomized covariate in the final model.

4.3.6 Propensity score

We computed propensity scores for each pairwise comparison to adjust for differences in baseline demographic and clinical characteristics between groups, which may confound the likelihood of initiating a specific biologic agent. Propensity scores were calculated based on the probability of starting anti-TNF-α biologic therapy. We used inverse probability of treatment weighting (IPTW) to calculate the average treatment effect.[21] Propensity scores were calculated based on the propensity of being prescribed to either TNF-α or a non-TNF-α inhibitor. Propensity scores were re-calculated for each of the stratified analyses of biologic naïve or prior biologic treatment status. Propensity score weights were trimmed to include only those with values from 1.0 to 10.0, excluding those individuals outside of this range to minimize the influence of outliers.[22]

4.3.7 Statistical analysis

We calculated the incidence rate (IR) of hospitalized infections by 100 person-years for each therapy type, with 95% confidence intervals (CI) computed using Poisson models. We performed Cox proportional hazard modeling to estimate the hazard ratios (HRs) and corresponding 95% CI for the risk of hospitalized

infection. Due to patients being able to contribute to multiple treatment episodes across classes, we calculated the corrected standard errors that were clustered at the patient-level. We used trimmed IPTW weighting of the propensity scores in the Cox proportional hazard model, and adjusted for covariates, including our severity score. We performed three pairwise comparisons in our analysis, comparing TNF-α, IL-17, and IL-12/23 blockers to each other.

4.4 Results

There were a total of 424,601 treatment episodes of biologic therapies being dispensed between January 1, 2006 and December 31, 2017 in 409,807 people. Of these, 26,333 episodes met eligibility criteria for inclusion in our analysis: 64% used TNF-α blockers, 11% used IL-17 blockers, 25% used an IL-12/23 blocker, and 1% used IL-23 blockers (Figure 1). Overall, the population had a mean age 58.5 (std 13.6) years and 58.8% were females. The severity score distribution varied little across the drug exposure groups. Psoriasis patients on IL-23 inhibitors had a the most individuals classified as having severe psoriasis (70%) and psoriasis patients on TNF-α inhibitors had the fewest classified as having severe psoriasis (61%) (**Table 4.1**).

Table 4.1. Demographic and Clinical Characteristics of New Users of Biologic Therapy Class at the time of Therapy Ini

Charactersitic	TNF-α blockers (n=16,806)	IL-17 blockers (n=2,772)	IL-12/23 blockers (n=6,534)	IL-23 blockers (n=221)
Age, years (std)	59.4 (13.4)	55.2 (13.5)	57.8 (13.8)	54.8 (14.9)
Female sex, n (%)	9,999 (60%)	1,614 (58%)	3,756 (57%)	115 (52%)
Race				
White	13,538 (81%)	2,191 (79%)	5,287 (81%)	170 (77%)
African American	1,068 (6%)	160 (6%)	396 (6%)	19 (9%)
Asian	455 (3%)	95 (3%)	184 (3%)	<11
American Indian or Alaska Native	123 (1%)	31 (1%)	55 (1%)	<11
Other	143 (1%)	31 (1%)	48 (1%)	<11
Unknown	1,479 (9%)	263 (9%)	564 (9%)	20 (9%)
Number of previous biologics				
0	16,465 (98%)	553 (20%)	2,693 (41%)	36 (16%)
1	338 (2%)	1172 (42%)	2,613 (40%)	97 (44%)
2 or more	3 (<1%)	1,047 (38%)	1,228 (19%)	88 (40%)
Number of previous DMARDs				
0	8,928 (53%)	1,169 (42%)	3,548 (54%)	99 (45%)
1	6,625 (39%)	1,093 (39%)	2,444 (37%)	83 (38%)
2 or more	1,253 (7%)	510 (18%)	542 (8%)	39 (18%)
Topical steroids in the past 6 months (%)	11,658 (69%)	1,890 (68%)	4,614 (71%)	156 (71%)
Phototherapy in the past 6 months (%)	1,397 (8%)	130 (5%)	473 (7%)	11 (5%)
Hospitalized in the past 6 months (%)	7,344 (44%)	1,518 (55%)	3,378 (52%)	126 (57%)
Severe psoriasis per severity score (%)	10,270 (61%)	1,811 (65%)	4,120 (63%)	154 (70%)
Diangosis during 6 months period prior to the index date				
Anxiety	2,096 (12%)	482 (17%)	888 (14%)	33 (15%)
Cardiovascular disease*	10644 (63%)	1730 (62%)	4094 (63%)	137 (62%)
Cardiac dysrhythmia	258 (2%)	34 (1%)	108 (2%)	<11
Chronic kidney disease	685 (4%)	168 (6%)	351 (5%)	22 (10%)
COPD	2,653 (16%)	461 (17%)	972 (15%)	49 (22%)
Depression	4,078 (24%)	734 (26%)	1,616 (25%)	52 (23%)
Diabetes (types 1 and 2)	6,054 (36%)	1,130 (41%)	2469 (44%)	94 (43%)
Fatty liver	568 (3%)	148 (5%)	251 (4%)	12 (5%)
Heart failure	157 (1%)	26 (1%)	72 (1%)	<11
Inflammatory bowel disease	524 (3%)	18 (1%)	184 (3%)	<11
Overweight (25 ≤ BMI <30)	200 (1.2%)	42 (1.5%)	72 (1.1%)	<11
Obese (BMI ≥ 30)	2,495 (14.9%)	603 (21.8%)	1,128 (17.3%)	53 (24.0%)
Osteoarthritis	1,452 (9%)	197 (7%)	418 (6%)	<11
Psoriatic arthritis	5,398 (32%)	626 (23%)	1,653 (25%)	23 (10%)
Rheumatoid arthritis	2,742 (16%)	263 (9%)	542 (8%)	<11
Systemic lupus erythematosus	171 (1%)	19 (1%)	75 (1%)	<11

*Includes any diagnosis of agnina, hypertension, myocardial infarction, stroke, congestive heart disease, atherosclerosis, or peripheral vascular disease.
DMARD: disease modifying antirheumetic drug; COPD: chronic obstructive pulmonary disease; BMI: body mass index.

4.4.1 Incidence rate of hospitalized infections

For our overall cohort, we found 2,463 hospitalized infections, which accounted for 9.4% of all treatment episodes, after the initiation of the biologic therapies of interest. The most commonly diagnosed hospitalized infections were urinary tract infection, pneumonia, and sepsis (**Table 4.2**). Hospitalized infections are broken out by biologic therapy class exposure in **Table 4.3** below.

Table 4.2. ICD codes for the most frequent hospitalized infections for new users of biologic therapy in Medicare 2007-2017

Code	Description	Frequency N (%)
All therapies (N=12,606)		
N390	Urinary tract infection, site not specified	1,953 (15.5%)
J189	Pneumonia, organism unspecified	1,715 (13.6%)
A419	Sepsis	1,600 (12.7%)
L03119	Cellulitis and abscess of leg, except foot	777 (6.2%)
R6520	Severe sepsis	369 (2.9%)
J209	Acute bronchitis	319 (2.5%)
B9620	Other and unspecified Escherichia coli	311 (2.5%)
L0390	Cellulitis and abscess of unspecified sites	245 (1.9%)
K5732	Diverticulitis of colon (without mention of hemorrhage)	218 (1.7%)
R7881	Bacteremia	175 (1.4%)
	Other types of hospitalized infections	4,924 (39.1%)

Table 4.3. ICD codes for the most frequent hospitalized infections for new users of biologic therapy in Medicare 2007-2017, by therapy type

Code	Description	Frequency N (%)
	TNF-α (N=9,689)	
N390	Urinary tract infection, site not specified	1,504 (15.5%)
J189	Pneumonia, organism unspecified	1,357 (14.0%)
A419	Sepsis	1,213 (12.5%)
L03119	Cellulitis and abscess of leg, except foot	633 (6.5%)
R6520	Severe sepsis	289 (3.0%)
J209	Acute bronchitis	233 (2.4%)
B9620	Other and unspecified Escherichia coli	224 (2.3%)
L0390	Cellulitis and abscess of unspecified sites	175 (1.8%)
K5732	Diverticulitis of colon (without mention of hemorrhage)	174 (1.8%)
J159	Unspecified bacterial pneumonia	128 (1.3%)
	Other types of hospitalized infections	3,759 (38.8%)
	Il-23 (N=13)	
A419	Sepsis	<11
J209	Acute bronchitis	<11
N390	Urinary tract infection, site not specified	<11
B9561	Methicillin susceptible staphulococcus aureus infection as the cause of disease classified elsewhere	<11
I96	Gangrene, not elsewhere classified	<11
J13	Pneumonia due to streptococcus pneumoniae	<11
J189	Pneumonia, organism unspecified	<11
L0390	Cellulitis and abscess of unspecified sites	<11
R6520	Severe sepsis without septic shock	<11
T814XXA	Infection following a procedure, initial encounter	<11

Table 4.3. (Continuted) ICD codes for the most frequent hospitalized infections for new users of biologic therapy in Medicare 2007-2017, by therapy type

Code	Description	Frequency N (%)
	Il-17 (N=497)	
N390	Urinary tract infection, site not specified	76 (15.3%)
A419	Sepsis	62 (12.5%)
J189	Pneumonia, organism unspecified	49 (9.9%)
B9620	Other and unspecified Escherichia coli	23 (4.6%)
J209	Acute bronchitis	18 (3.6%)
B9562	Methicillin resistant staphulococcus aureus infection as the cause of disease classified elsewhere	17 (6.4%)
L03119	Cellulitis and abscess of leg, except foot	14 (2.8%)
L0390	Cellulitis and abscess of unspecified sites	14 (2.8%)
R7881	Bacteremia	12 (2.4%)
R6520	Severe sepsis without septic shock	11 (2.2%)
	Other types of hospitalized infections	201 (40.4%)
	Il-12/23 (N=2,407)	
N390	Urinary tract infection, site not specified	371 (15.4%)
A419	Sepsis	323 (13.4%)
J189	Pneumonia, organism unspecified	308 (12.8%)
L03119	Cellulitis and abscess of leg, except foot	130 (5.4%)
R6520	Severe sepsis without septic shock	68 (2.8%)
J209	Acute bronchitis	66 (2.7%)
B9620	Other and unspecified Escherichia coli	64 (2.7%)
L0390	Cellulitis and abscess of unspecified sites	55 (2.3%)
K5732	Diverticulitis of colon (without mention of hemorrhage)	37 (1.5%)
B9562	Methicillin resistant staphulococcus aureus infection as the cause of disease classified elsewhere	35 (1.5%)
	Other types of hospitalized infections	1,457 (60.5%)

The crude incidence rates of hospitalized infection for the cohort was 9.2 (95% CI: 8.8, 9.5) per 100 p-y, with the rates being higher in patients using TNF-α or IL-17 blockers as compared to those using an IL-12/23 inhibitor. The incidence rate of hospitalized infections in patients using an IL-23 blocker was high, 28.2 (95% CI: 14.7, 54.2) per 100 p-y. This is due to the low number of individuals on IL-23 inhibitors. Our stratified analyses found that the incidence rates were higher for

those with prior biologic exposure, as compared to those who were biologic naïve. Patients on an IL-12/23 blocker were the exception, as the incidence rates were very similar between these two strata (**Table 4.4**).

Table 4.4. Crude incidence rates of hospitalized infections among biologic users

	All biologics	TNF-α blockers	IL-17 blockers	IL-12/23 blockers	IL-23 blockers
Total cohort					
Total number of treatment episodes	26,333	16,806	2,772	6,534	221
Total person-years of follow-up	26,893.1	18,516.3	1,781.1	529.0	31.9
Incident serious infections, n (%)	2,463 (9.4)	1,710 (10.2)	168 (6.1)	546 (8.4)	<11
Incidence rates (95% CI), per 100 p-y	9.2 (8.8, 9.5)	9.3 (8.9, 9.7)	9.4 (8.1, 11.0)	8.6 (7.9, 9.4)	-
Biologic naïve					
Total number of treatment episodes	19,748	16,465	554	2,693	36
Total person-years of follow-up	21,358.6	18,516.3	315.9	2,521.4	4.9
Incident serious infections, n (%)	1,955 (9.9)	1,710 (10.4)	27 (4.9)	218 (8.1)	<11
Incidence rates (95% CI), per 100 p-y	9.2 (8.8, 9.6)	9.2 (8.8, 9.7)	8.6 (5.9, 12.5)	8.7 (7.6, 9.9)	-
Prior biologic exposure					
Total number of treatment episodes	6,585	341	2,218	3,841	185
Total person-years of follow-up	5,534.50	235.5	1,465.1	3,806.00	26.9
Incident serious infections, n (%)	508 (7.7)	30 (8.8)	141 (6.4)	328 (8.5)	<11
Incidence rates (95% CI), per 100 p-y	9.2 (8.4, 10.0)	12.7 (8.9, 18.2)	9.6 (8.2, 11.4)	8.6 (7.7, 9.6)	-

4.4.2 Adjusted risk of hospitalized infections

After propensity score weighting, trimming, and adjustment for covariates, there was a decrease in risk of hospitalized infection in patients using IL-12/23 inhibitors compared to those on TNF-α inhibitors (HR = 0.83; 95% CI: 0.75, 0.91). There was no significant difference in risk for patients on IL-17 or IL-12/23 blockers (HR = 0.97; 95% CI: 0.80, 1.17). Similarly, patients on IL-17 inhibitors did not exhibit a significant difference in risk of infection as compared to those on TNF-α inhibitors (HR = 0.88; 95% CI: 0.64, 1.19) (**Table 4.5**). Due to low counts, we were unable to calculate HRs for any comparisons with IL-23 inhibitors. Similarly, the unbalanced variability between the stratified propensity scores made us unable to calculate HRs for the stratified comparisons.

Table 4.5. Hazard ratios with 95% confidence intervals of risk of hospitalized infection among new users of biologic therapies, by therapy class

	Unadjusted model	Partially Adjusted Model[1]	Fully Adjusted Model
Total cohort			
IL-12/23 vs TNF-α blockers	**0.89 (0.81, 0.99)**	**0.90 (0.81, 0.99)**	**0.87 (0.76, 0.99)**[2a]
IL-17 vs TNF-α blockers	**0.80 (0.67, 0.97)**	**0.82 (0.68, 0.98)**	0.86 (0.63, 1.18)[2b]
IL-12/23 vs IL-17 blockers	0.94 (0.78, 1.14)	0.94 (0.78, 1.13)	0.95 (0.78, 1.15)[2c]

[1]Model covariate includes severity score only.

[2a]Model covariates include age, BMI (categorical: <25 or ≥25), number of prior biologic therapies, number of rheumatology visits, procedures for inflammatory markers, psoriatic arthritis, rheumatoid arthritis, sex, and propensity score weighting.

[2b]Model covariates include age, anxiety, BMI (categorical: <25 or ≥25), chronic heart disease, Crohn's disease, dactylitis, diabetes, inflammatory bowel disease, non-melanoma skin cancer, number of prior biologic therapies, procedures for liver function testing, psoriatic arthritis, rheumatoid arthritis, race, sex, ulcerative colitis, and propensity score weighting.

[2c]Model covariates include age, anxiety, BMI (categorical: <25 or ≥25), chronic heart disease, Crohn's disease, dactylitis, inflammatory bowel disease, non-melanoma skin cancer, number of prior biologic therapies, number of rheumatology visits, procedures for inflammatory markers, region, sex, and propensity score weighting.

4.4.3 Severity score

The severity score did not vary between the different exposure groups when adjusting for severity alone as compared to an unadjusted model with IPTW weighting. The distribution of severe psoriasis as classified by the severity score does not change significantly across the different treatment classes (**Table 4.1**)

An analysis of the sex- and age-adjusted HRs for risk of hospitalized infection by psoriasis severity for each pairwise therapy comparison showed an increase in risk for those individuals classified as having severe psoriasis, when comparing to those classified with mild-to-moderate psoriasis. This potential trend towards an increased risk was observed in the IL-12/23 vs. TNF-α inhibitors and IL-17 vs. TNF-α inhibitors comparisons, However, a similar increase in risk of hospitalized infection by psoriasis severity was not observed in the IL-12/23 vs. IL-17 inhibitor analysis (**Table 4.6**).

Table 4.6. Age- and sex-adjusted hazard ratios with 95% confidence intervals of risk of hospitalized infection among nes users of biologic therapies, by psoraisis severity and therapy class

	Adjusted Model
Total cohort	
IL-12/23 vs TNF-α blockers	
Mild-to-moderate psoriasis	0.84 (0.72, 0.98)
Severe psoriasis	0.95 (0.83, 1.08)
IL-17 vs TNF-α blockers	
Mild-to-moderate psoriasis	0.77 (0.56, 1.05)
Severe psoriasis	0.88 (0.70, 1.11)
IL-12/23 vs IL-17 blockers	
Mild-to-moderate psoriasis	0.93 (0.69, 1.26)
Severe psoriasis	0.94 (0.75, 1.19)

4.3 Discussion

Due to the increasing number of biologic therapies approved to treat psoriasis, understanding the comparative risk of hospitalized infection associated with different biologic therapies is of upmost importance. Here, we observed a decreased risk of hospitalized infection when patients started an IL-12/23 blocker, as compared to those treated with TNF-α blockers. Recent studies have shown a decreased risk of hospitalized infection in patients initiating IL-12/23 inhibitors in comparison to non-biologic therapies.[11,23] Li *et al.* also found a decreased risk of serious infection for patients with psoriasis initiating an IL-12/23 blocker when compared to those treated with TNF-α blockers.[24]

We did not see a decreased risk of hospitalized infection when patients initiated IL-17 blockers compared to TNF-α. Previous real-world literature has not found a protective relationship between IL-17 inhibitor initiation and the risk of serious infections, when compared to other biologic therapies. Our results a very similar

to Li *et al.* who also found that there was no decreased risk of hospitalized infection with IL-17 compared to TNF-α. [24] Our results may be due to the small sample size for the IL-17 exposure group, due to the relatively new FDA approval for the majority of these therapies. These results may also speak to potential changes in prescribing patterns with newly approved biologic therapies.

We found that the incidence of hospitalized infection to be similar in those patients initiating TNF-α or IL-17 blockers. Those who started IL-12/23 blockers had a low incidence of hospitalized infection, though not significantly. The higher incidence rates for those with prior biologic exposure compared to those who are biologic naïve is not surprising. Individuals with prior biologic exposure are more likely to have moderate-to-severe disease, which would increase the incidence of hospitalized infections. Data from our analyses add important information regarding the serious infection rate of newer biologic therapies, such as IL-17 and IL-12/23 inhibitors, and will assist practitioners in choosing therapies among available therapeutic options.

Hospitalized infections were common across our three therapy classes. Our observed rates were similar to those reported by a prior analysis performed on multiple U.S. claims and health administrative data.[18] Grijalva *et al.* identified incidence rates of serious infection in patients with psoriasis or spondyloarthropathies of 5.41 per 100 p-y. However, some previous studies have reported lower incidence rates for hospitalized infections. Schneeweiss *et al.* included individuals on Medicare Advantage in their analysis, potentially including individuals who had fewer comorbidities than those without Medicare Advantage.

Additionally, this study had a limited follow-up time of 6 months, which could have artificially reduced the number of events, and therefore the incidence rate of hospitalized infections.[25] A previous study looking at the Medicare population of patients with parts A, B, and D (without part C) also found lower incidence rates of hospitalized infection.[15] This study used older data, and our results may show a potential trend towards increasing comorbidities leading to hospitalization in older individuals.

We built a population-based cohort of patients with psoriasis and, utilizing our severity score, compared the risk of hospitalized infections between three biologic therapies. Inability to control for underlying psoriasis disease severity is a concern for analyses utilizing healthcare or administrative databases.[4] Some studies have utilized indirect measures including therapy utilization patterns,[18,26] or the number of hospital visits to determine disease severity.[27] We did not observe substantial differences when including or excluding the dichotomized severity variable from the model. The computed univariate association between our dichotomized severity variable and our outcome of hospitalized infection was significant (χ^2= 48.9, p-value < 0.0001). All individuals in our cohort were treated with biologic therapy, and therefore these populations were more likely to have severe psoriasis as classified by our severity score. As such, the severity score may not provide additional information out of the propensity score.

The use of the dichotomized severity variable also introduces the potential for residual confounding in our analyses. Clinician use psoriasis severity categorization to guild treatment decisions and BSA is a method to standardize

psoriasis severity. The broad categorization of psoriasis severity into a binary variable allows for residual confounding to exist in the association, and may account for some of the association that was observed. We posit that the effect of residual confounding is small in our study, as analyses including and excluding the severity variable did not appreciably change our effect measures.

A key strength of this study was the use of propensity scores to ensure that comparison groups were similar with regards to factors associated with therapy choice. Our analyses also included data for several recently-approved IL-17 and IL-23 blockers, which have not been previously well-characterized in real-world data studies. Regarding limitations of this work, comparisons were limited by statistical power, as there were very few individuals prescribed IL-23 inhibitors. Similarly, we had limited numbers in certain strata of previous biologic therapy use. ICD codes that were used to define hospitalized infections were derived from several validation studies of patients with inflammatory arthritis,[28] and feedback from clinicians. Finally, our estimates may be biased due to unmeasured confounding as propensity scores only balance variables that are available and measured. We postulate that estimates from our analysis would be minimally biased, as our estimates mirror the direction and magnitude of results from similar analyses utilizing different sources of data.[24]

In summary, we evaluated the risk of hospitalized infections among a nationwide cohort of Medicare patients in the U.S. using a severity score. Our results found relatively high rates of hospitalized infections in biologic users, with patients on IL-12/23 inhibitors exhibiting a numerically lower rate when compared to those on

either TNF-α or IL-17 inhibitors. There was a significantly decreased relative risk for patients initiating an IL-12/23 blocker as compared to those who initiated TNF-α blockers. This relationship was not seen for those patients initiating an IL-17 blocker as compared to those starting TNF-α blockers. These data add to the growing body of evidence regarding the risk of hospitalized infections by therapy type for individuals being treated for psoriasis.

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Chapter 5: Comparative Risk of All-cause and Infection-Specific Mortality by Therapy for Psoriasis in Medicare data linked to the National Death Index

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5.1 Abstract

5.1.1 Purpose: To investigate whether initiation of either biologic systemic therapies for psoriasis (tumor necrosis factor-alpha (TNF-α) or interleukin (IL)-12/23 blockers) is associated with an increased risk of infection-specific mortality in Medicare patients.

5.1.2 Methods: A retrospective cohort utilizing Medicare data linked to the National Death Index from 2006-2015 was assessed. Exposure was defined as initiation of a TNF-α or an IL-12/23 blocker for psoriasis. The outcome was infection-related mortality after initiation of therapy. Incidence rates per 1,000 person-years were calculated, and hazard ratios with 95% confidence intervals were estimated using Cox proportional hazards regression models, utilizing a psoriasis severity score, and adjusted for the inverse probability of treatment-weighted propensity scores.

5.1.3 Results: There were a total of 14,385 patients that met eligibility criteria. There were 122 all-cause cases of mortality, or which 7% were infection-related mortality cases. For the all-cause mortality, there were 15,103 person-years of follow-up. Incidence rates were similar between patients using TNF-α inhibitor or an IL-12/23 inhibitor for both all-cause death and infection-specific death. After propensity score weighting and adjustment for covariates, there was no significant difference in risk of infection-related mortality for patients on IL-12/23 (HR = 0.45; 95% CI: 0.09, 2.19) inhibitors compared to those on TNF-α inhibitors.

5.1.4 Conclusions: Overall mortality, and mortality due to infection, are both low in our cohort. There was no significant decrease in risk of infection-specific mortality for users on IL-12/23 blockers, in comparison to those on TNF- α blockers.

5.2 Introduction

Psoriasis has not historically been considered a disease associated with increased risk of mortality. Previous studies have found an increased risk of mortality in patients with psoriasis as compared to the general population.[1-3] Recent population-based studies corroborated these results, finding that patients with severe psoriasis requiring systemic treatment are at greater risk of both cardiovascular, and overall mortality.[4-9] All of these studies do not directly evaluate how psoriasis disease severity influence mortality, instead using indirect measures such as initiation of biologic treatment as a proxy for severe psoriasis. Additional studies have found a dose-response with disease severity increased risks in mortality,[10,11] further illustrating the need to objectively account for disease severity.

The association between mortality and treatment type in the population of individuals with psoriasis has not yet been studied, and thus it is unknown whether different psoriasis therapies affect risk for mortality. Recent literature has shown a link to objectively measured psoriasis severity and mortality.[12] The U.S., cause of death is documented on death certificates, which are coded according to the *International Classification of Diseases 10th Revisions* (ICD-10) for deaths beginning in 1999.[13] The NDI recodes ICD codes into different classifications. To assess the cause of morality, identifiers within Medicare can linked with the National Death Index (NDI).[14] It is possible that biologic therapies may confer risks that would increase the risk of mortality and, perhaps just as likely, that these medications would decrease risk of mortality by decreasing

overall inflammation within the body. Our objective was to determine the risk of infection-specific mortality by psoriasis therapy type in a cohort of individuals within the Medicare database, adjusting for psoriasis severity using a novel psoriasis severity index.

5.3 Methods

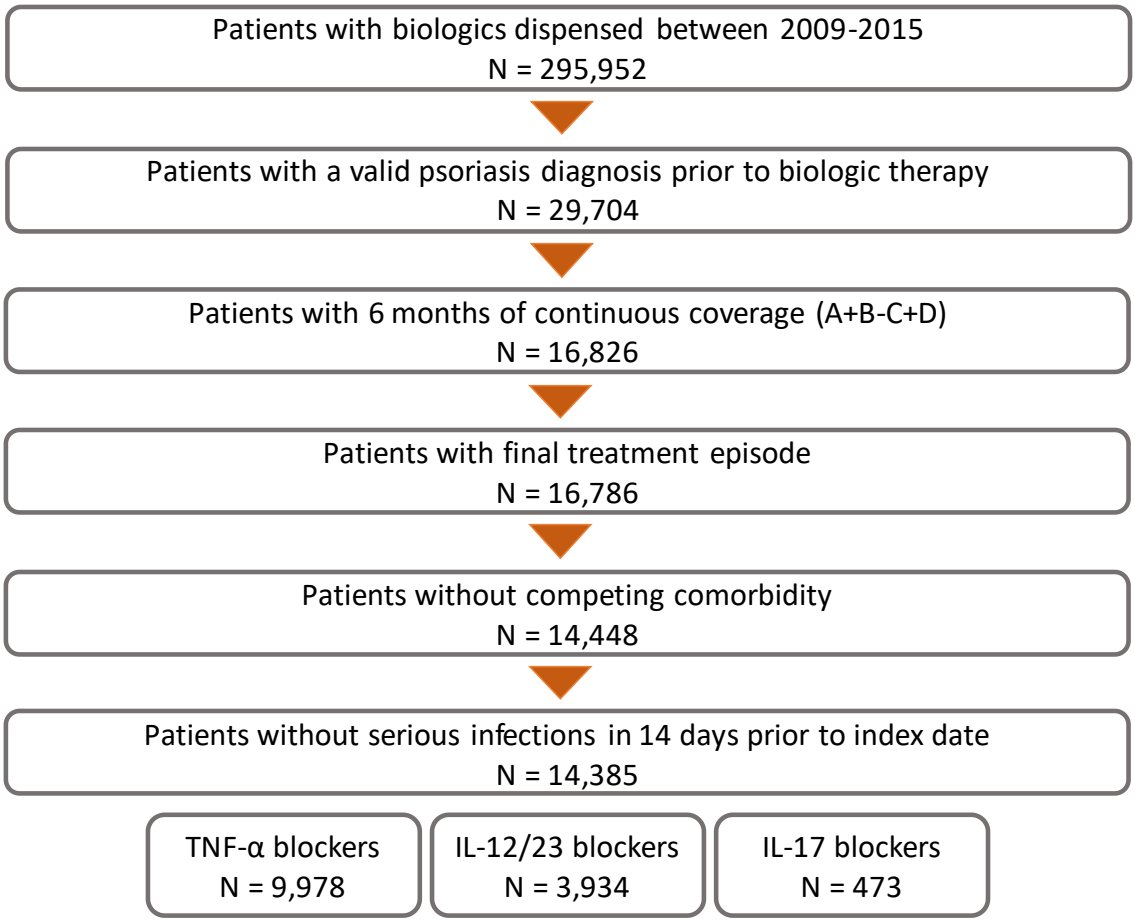
5.3.1 Patient population

We utilized the complete Medicare dataset, including Parts A, B, and D from January 1, 2009, through December 31, 2015 to identify and characterize patients with psoriasis. These data were linked with the National Death Index (NDI), which is a centralized database of death record information on file in state vital statistics offices.

Within this period, we identified a cohort of patients with prescribed, or a procedural claim was recorded, for biologic therapies to treat psoriasis. Our index date was defined as the date of psoriasis therapy initiation. Patients were first defined as having psoriasis if they had ≥ 1 dermatologist-assigned diagnosis code for psoriasis (ICD-9 code 696.1 or ICD code L40.9) during an office visit. We then identified those who had either a prescription dispensation or procedure code for at least one biologic therapy. We defined an index date as start of the last episode of any biologic of interest prior to death. Patients had to have at least 6 months of continuous enrollment in Medicare, while not being enrolled in a Medicare Advantage (Part C) plan prior to the index date. We excluded individuals who were prescribed two therapies at the same time. We also

excluded patients with the following diagnoses within the 24 months prior to the index date: human immunodeficiency virus, organ transplant, cancer other than non-melanoma skin cancer, chronic lymphocytic leukemia, or non-Hodgkin's lymphoma. We additionally excluded patients who had a hospitalized infection within 14 days prior to the index date (**Figure 5.1**).

Figure 5.1. Cohort selection process.



5.3.2 Exposure

We defined three exposure groups based on biologic therapies: TNF-α blockers, IL-12/23 blocker, and IL-17 blockers. Each treatment episode was defined as the initiation of a new therapy without a previous claim for that specific therapy class.

We allowed for 90 days of non-overlap between discrete prescriptions as a period of continuous therapy. Biologics prescribed for self-administration were coded from pharmacy claims using the National Drug Codes (NDC). Biologics that were given via infusion were identified from procedural codes in medical claims, using the Healthcare Common Procedure Coding System (HCPCS). Medical claims based on HCPCS procedural codes do not contain information on days of supply. To address this issue, we assigned the length of each treatment period based on the dosage regimen. This method has been described in detail elsewhere.[15]

5.2.3 Outcome

The outcome of interest is all-cause and mortality due to infection. These deaths were identified via the NDI's recoding of ICD-10 code cause of death into 358 categories. Codes for infection as a cause of death were used as the variable of interest (**Table A5.1**).

5.3.4 Covariates

We evaluated covariates 6 months prior to the index date. Covariates included patient variables, select comorbidities (e.g., BMI), and health services utilization, including the number of prior hospitalizations. We also explored the effect between those patients who were biologic naïve and those with prior biologic experience. For the number of prior biologics, all available data were used to determine each prior therapy status.

We utilized a unique severity score that was developed via linking two psoriasis registries to Medicare data: the Center for Excellence in Psoriasis and Psoriatic Arthritis (CEPPA), which is housed at Oregon Health & Science University (OHSU), and the Corrona Psoriasis Registry, which is a national registry. The CEPPA cohort[16] and the Corrona Psoriasis Registry have both been previously described.[17] The development of our psoriasis severity score has been described elsewhere. Briefly, our severity score included 17 covariates that cover five unique domains: diagnoses, procedural or prescription therapies, a combination of diagnoses or procedural codes, healthcare utilization, surgical or outpatient procedures, and patient demographics. The severity score was used as a dichotomized covariate in the final model.

5.3.5 Propensity score

We computed propensity scores for the pairwise comparison to adjust for differences in baseline demographic and clinical characteristics between groups, which may confound the likelihood of initiating a specific biologic agent. Propensity scores were calculated based on the probability of starting biologic therapy compared to non-biologic therapy. We used inverse probability of treatment weighting (IPTW) to calculate the average treatment effect.[18] Propensity score weights were trimmed to include only those with values from 1.0 to 10.0, excluding those individuals outside of this range, to minimize the influence of outliers.[19]

5.3.6 Statistical analysis

We calculated the incidence of mortality associated by infection for each therapy

class. We performed Cox proportional hazard modeling to estimate the hazard ratios (HRs) and corresponding 95% CI for the risk of infection-related mortality. We used trimmed IPTW weighting of the propensity scores in the Cox proportional hazard model, and adjusted for imbalanced covariates, including our severity score. We performed two pairwise comparisons in our analysis, comparing MTX to TNF-α blockers, and MTX to IL-12/23 blockers.

5.4 Results

There were a total of 295,952 patients with biologic therapies being dispensed between January 1, 2009 and December 31, 2015. Of these, 14,385 patients met eligibility criteria for inclusion in our analysis: 69% TNF-α blockers, 27% IL-12/23, and 3% in the IL-17 group, respectively (**Figure 5.1**). Overall, the population was mean age 61.2 (std 13.7) years and 59.0% females. The severity score varied little across the drug exposure groups. IL-17 and TNF-α blockers both had a mean severity score of 0.52 (std 0.19), and users of methotrexate had a mean severity score of 0.54 (std 0.18) (**Table 5.1**).

Table 5.1. Demographic and Clinical Characteristics of New Users of Biologic Therapy Class at the time of Therapy Initiation

Charactersitic	TNF-α blockers (n=9,978)	IL-12/23 blockers (n=3,934)	IL-17 blockers (n=473)
Age, years (std)	61.7 (13.6)	60.2 (14.1)	59.1 (13.6)
Female sex, n (%)	5,928 (59%)	2,282 (58%)	270 (57%)
Race			
White	8,079 (81%)	3,162 (80%)	383 (81%)
African American	606 (6%)	245 (6%)	31 (7%)
Asian	265 (3%)	103 (3%)	17 (4%)
American Indian or Alaska Native	65 (1%)	33 (1%)	<11
Other	90 (1%)	31 (1%)	<11
Unknown	873 (9%)	360 (9%)	37 (8%)
Number of previous biologics			
0	9,780 (98%)	1,392 (35%)	89 (19%)
1	198 (2%)	1,633 (42%)	194 (41%)
2 or more	<11	909 (23%)	190 (40%)
Number of previous DMARDs			
0	5,253 (53%)	2,226 (57%)	219 (46%)
1	3,968 (40%)	1,475 (37%)	199 (42%)
2 or more	125 (1%)	233 (6%)	55 (12%)
Topical steroids in the past 6 months (%)	6,874 (69%)	2,887 (73%)	349 (74%)
Phototherapy in the past 6 months (%)	866 (9%)	325 (8%)	25 (5%)
Hospitalized in the past 6 months (%)	4,592 (46%)	2,008 (51%)	243 (51%)
Severe psoriasis per severity score (%)	5,912 (59%)	2,433 (62%)	298 (63%)
Diangosis during 6 months period prior to the index date			
Anxiety	1,183 (12%)	506 (13%)	72 (15%)
Cardiovascular disease*	1,681 (17%)	653 (17%)	69 (15%)
Cardiac dysrhythmia	160 (2%)	66 (2%)	<11
Chronic kidney disease	395 (4%)	158 (4%)	<11
COPD	1,552 (16%)	598 (15%)	91 (19%)
Depression	2,424 (24%)	1,006 (26%)	137 (29%)
Diabetes (types 1 and 2)	3,583 (36%)	1,475 (37%)	208 (44%)
Fatty liver	335 (3%)	143 (4%)	31 (7%)
Heart failure	113 (1%)	63 (2%)	13 (3%)
Inflammatory bowel disease	317 (3%)	63 (2%)	<11
Overweight (25 ≤ BMI <30)	139 (1%)	41 (1%)	11 (2%)
Obese (BMI ≥ 30)	1,477 (15%)	684 (17%)	130 (27%)
Osteoarthritis	862 (9%)	225 (6%)	19 (4%)
Psoriatic arthritis	3,662 (37%)	1,234 (31%)	159 (34%)
Rheumatoid arthritis	1,803 (18%)	363 (9%)	41 (9%)
Systemic lupus erythematosus	115 (1%)	62 (2%)	<11

*Includes any diagnosis of agnina, hypertension, myocardial infarction, stroke, congestive heart disease, atherosclerosis, or peripheral vascular disease.

DMARD: disease modifying antirheumetic drug; COPD: chronic obstructive pulmonary disease; BMI: body mass index.

5.4.1 Incidence of mortality and infection-specific mortality

We found a total of 162 deaths due to infection, which accounted for 8.4% of all deaths of those who initiated a biologic therapy of interest (**Table 5.2**). Incidence of mortality was similar between IL-12/23 and TNF-α inhibitors, 10.1 (95% CI: 7.5, 13.8) per 1,000 person-years and 7.3 (95% CI: 5.9, 9.1) per 1,000 person-years, respectively. Patients on IL-17 inhibitors had small counts for overall mortality and the incidence rate of mortality was not calculated. Similarly, the overall numbers for infection-specific mortality were very low, with incidence rates for infection-specific mortality similar between TNF-α and IL-12/23 blockers, 0.6 (95% CI: 0.3, 1.3) and 0.5 (95% CI: 0.1, 2.0), respectively. Of the infection-specific deaths, 89% occurred within hospital. (**Table 5.2**).

Table 5.2. Crude incidence rates of mortality due to infection among users of biologic therapies in a Medicare-National Death Index linked database from 2009-2015

	TNF-α blockers	IL-12/23 blockers	IL-17 blockers
Total cohort - Overall mortality			
Total number of patients	9,978	3,934	473
Total person-years of follow-up	10,924.2	4,032.70	146.2
Mortality, n (%)	80	41	<11
Incidence rates of mortality (95% CI), per 1,000 p-y	7.3 (5.9, 9.1)	10.1 (7.5, 13.8)	-
Infection-specific mortality, n (%)	<11	<11	<11
Incidence rates of infection mortality (95% CI), per 1,000 p-y	0.6 (0.3, 1.3)	0.5 (0.1, 2.0)	-

There were 122 deaths within our cohort. Overall, the five most common causes of death were diabetes mellitus (7%), acute myocardial infarction (7%), atherosclerotic cardiovascular disease, so described (7%), all other forms of chronic ischemic heart disease (7%), and other chronic obstructive pulmonary disease (6%), data not shown. Among the therapy class exposure groups, the most common causes of death for users of TNF-α blockers were diabetes

mellitus (10%), acute myocardial infarction (9%), atherosclerotic cardiovascular disease, so described (8%), all other forms of chronic ischemic heart disease (6%), and other chronic obstructive pulmonary disease (5%). For users of IL-12/23 blockers, the most common causes of death were other chronic obstructive pulmonary disease (10%), malignant neoplasms of trachea, bronchus and lung (7%), obesity and other hyperalimentation (7%), acute myocardial infarction (7%), and accidental poisoning by and exposure to drugs and other biological substances (7%). The only cause of death reported for users of IL-17 blocker was acute myocardial infarction (**Table 5.3**).

Table 5.3. National Death Index codes of the most common cause of death among a cohort of 14,385 in a Medicare-National Death Index linked database from 2009-2015, by therapy type

Code	Description and associated ICD code(s)	Count (%)
TNF-α blockers deaths (N=80)		
15900	Diabetes mellitus (E10-E14)	<11
21100	Acute myocardial infarction (I21-I22)	<11
21400	Atherosclerotic cardiovascular disease, so described (I25.0)	<11
21500	All other forms of chronic ischemic heart disease (I20, I25.1-I25.9)	<11
26700	Other chronic obstructive pulmonary disease (J44)	<11
42000	Accidental poisoning by and exposure to drugs and other biological substances (X40-X44)	<11
09300	Malignant neoplasms of trachea, bronchus and lung (C33-C34)	<11
16900	Obesity and other hyperalimentation (E65-E68)	<11
25700	Pneumonia due to other or unspecified organisms (J16, J18)	<11
27800	All other diseases of respiratory system (J80-J84, J93-J98)	<11
	All other causes of death	56 (70%)
IL-12/23 blocker deaths (N=41)		
26700	Other chronic obstructive pulmonary disease (J44)	<11
09300	Malignant neoplasms of trachea, bronchus and lung (C33-C34)	<11
16900	Obesity and other hyperalimentation (E65-E68)	<11
21100	Acute myocardial infarction (I21-I22)	<11
42000	Accidental poisoning by and exposure to drugs and other biological substances (X40-X44)	<11
17300	Other metabolic disorders (E70-E83, E85, E88)	<11
21400	Atherosclerotic cardiovascular disease, so described (I25.0)	<11
22700	Cardiomyopathy (I42)	<11
27800	All other diseases of respiratory system (J80-J84, J93-J98)	<11
39300	Occupant of car, pickup truck or van involved in collision with other motor vehicle (V42-V44, V49, V52-V54, V59)	<11
	All other causes of death	15 (37%)
IL-17 blockers deaths (N<11)		
21100	Acute myocardial infarction (I21-I22)	<11

Among the reported deaths, 7% were infectious-related deaths. For both users of IL-12/23 and TNF-α blockers, the causes of infectious-related death were pneumonia due to other or unspecified organisms (56%), septicemia (22%), urinary tract infection, site not specified (11%), and infections of skin subcutaneous tissue (11%) (**Table 5.4**).

Table 5.4. National Death Index codes of infectious-related causes of death among a cohort of 14,385 in a Medicare-National Death Index linked database from 2009-2015, overall and by therapy type

Code	Description	Count (%)
Total cohort infection-specific deaths (N<11)		
25700	Pneumonia due to other or unspecified organisms (J16, J18)	<11
02300	Septicemia (A40-A41)	<11
33000	Urinary tract infection, site not specified (N39.0)	<11
30800	Infections of skin subcutaneous tissue (L00-L08)	<11
TNF-α blockers infection-specific deaths (N<11)		
25700	Pneumonia due to other or unspecified organisms (J16, J18)	<11
02300	Septicemia (A40-A41)	<11
33000	Urinary tract infection, site not specified (N39.0)	<11
IL-12/23 blocker infection-specific deaths (N<11)		
25700	Pneumonia due to other or unspecified organisms (J16, J18)	<11
30800	Infections of skin subcutaneous tissue (L00-L08)	<11

5.4.2 Adjusted risk of mortality and infection-specific mortality

After propensity score weighting and trimming, there was a significant increase in risk of all-cause mortality for patients initiating IL-12/23 compared to those initiating TNF-α inhibitors (aHR = 1.41; 95% CI: 1.03, 1.93). The risk increased when the analysis was limited to those patients who did not have a history of biologic therapy use in Medicare data (aHR = 1.68; 95% CI: 1.22, 2.31) (**Table 5.5**). Due to low counts, we were unable to calculate HRs for any comparisons with IL-17 inhibitors.

Table 5.5. Hazard ratios with 95% confidence intervals of all-cause mortality due to infection among those on biologic therapy in 2009-2015 Medicare data

	Unadjusted model	Partially adjusted Model[1]	Fully Adjusted Model
Total cohort			
IL-12/23 vs TNF-α blockers	**1.35 (1.05, 1.75)**	**1.35 (1.05, 1.75)**	**1.41 (1.03, 1.93)**[2a]
Biologic naïve users			
IL-12/23 vs TNF-α blockers	**1.80 (1.31, 2.48)**	**1.80 (1.31, 2.48)**	**1.68 (1.22, 2.31)**[2b]

[1]Model covariate includes severity score and propensity weighting.

[2a]Covariates include age, BMI (categorical: <25 or ≥25), number of biologics, sex, and propensity score weighting.

[2b]Covariates include age, BMI (categorical: <25 or ≥25), sex, and propensity score weighting.

TNF: tumor necrosis factor; IL: interleukin.

5.5 Discussion

Previous real-world literature has not investigated the relationship between therapy type, or class, and risk of mortality for individuals with psoriasis. However, due to the innate immune-mediation of biologic therapies, there is a need to understand the risk of all-cause and infection-specific mortality for individuals with psoriasis by therapy. Here, we observed a significant increased risk of mortality when patients initiated an IL-12/23 inhibitor when compared to those who initiated a TNF-α inhibitor. This association was strengthened when the analysis was kept to those who had no previous history of biologic therapies.

These results are counter to our previous hypothesis, which was that those initiating IL-12/23 blockers would be at decreased risk of mortality, as compared to those initiating TNF-α blockers. We hypothesize that IL-12/23 blockers themselves do not increase the risk, but those individuals on IL-12/23 blockers are more likely to have risk factors for serious infections, or have had prior serious infections. These patients could be channeled to a presumably safer

therapy due to these risk factors. In addition, patients on IL-12/23 blockers may have failed TNF-α blockers in the distant past, and may have had many treatments prior to their enrollment in Medicare. However, if there have not been any psoriasis therapy changes after enrollment into Medicare, these patients appear to be biologic therapy naïve, even though they may have a higher risk of mortality.

We found that the incidence of infection-specific mortality to be similar in those patients using methotrexate or TNF-α blockers. Those who were prescribed IL-12/23 inhibitors had a lower incidence of infection-specific mortality, though not significantly. Our sample size was relatively low, which may have contributed to our comparisons being non-significant, and one of the limitations of our study. A large proportion of patients were removed from our cohort due to comorbidities that increase the risk of infection. The exclusion criteria reduces the potential for confounding in the association between therapy type and infection-specific mortality, but reduces our sample size and power to detect a potentially significant association.

The majority of existing mortality literature has focused on comparisons between individuals with psoriasis and those without.[4,6-8] These studies also analyzed the effect of psoriasis disease severity on the risk of mortality, and have found the risk increases as severity does. However, these studies have used indirect proxy measures to account for disease severity. Noe *et al*. recently performed a study of the association between psoriasis disease severity and mortality. The authors were able to use an objective measure of psoriasis disease severity, body

surface area (BSA) affected, to show that those with severe psoriasis (defined as ≥10% BSA) were 1.79 times more likely to die than those without psoriasis, after controlling for independent risk factors for mortality.[12] Our study utilized a dichotomized psoriasis severity variable to control for disease severity, though we did not see a substantial difference when the severity score was included in covariate adjustment. The percentage of individuals classified with severe psoriasis did not vary between the different treatment groups, 59% for users of TNF-α, 62% for IL-12/23, and 63% for IL-17 inhibitors. It may be that for this particular population, the effect of severe psoriasis as measured by our dichotomized variable may be reflected by the propensity score.

The use of the dichotomized severity variable also introduces the potential for residual confounding in our analyses. Clinician use psoriasis severity categorization to guild treatment decisions and BSA is a method to standardize psoriasis severity. The broad categorization of psoriasis severity into a binary variable allows for residual confounding to exist in the association, and may account for some of the association that was observed. We posit that the effect of residual confounding is small in our study, as analyses including and excluding the severity variable did not appreciably change our effect measures.

A strength of our study is the use of the NDI as a source of vital statistics, which has been shown to be more accurate than other administrative databases for documentation of death.[20,21] A potential concern is bias in terms of reporting cause of death. Patients with severe psoriasis will be more likely to have visible lesions at time of death, which may bias the determination of cause of death;

however, it is unlikely that the individual making the determination of cause of death would preferentially determine infection-related mortality if the individual was on a certain therapy. Therefore, any potential misclassifications for our outcome would be non-differential, and would bias our results towards the null.

In summary, we investigated the risk of all-cause and infection-specific mortality utilizing a linkage between two national cohorts, Medicare and the National Death Index. Our results found that overall death due to infection is low in our cohort. There was a trend towards decrease in risk of infection-specific mortality for both TNF-α and IL-12/23 blockers, in comparison to methotrexate therapy. These data add to the literature regarding the risks of infectious outcomes, specifically mortality due to infection, by therapy type for individuals being treated for psoriasis.

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Chapter 6: Synthesis of Research

6.1 Overview

The primary goal of this dissertation research was to understand the association between psoriasis therapy type and infectious risk. Clinical trial data provide incomplete understanding of these associations, as relatively healthy individuals are typically selected to participate. There is a dearth of real-world data regarding the infectious risk of individuals with psoriatic disease who are taking biologic therapies.[1,2] The three research aims of this dissertation focused on different aspects of the relationship between therapy type and infectious risk.

In Aim 1 (Chapter 3), I used data from two national registries linked to Medicare to develop and validate a severity score to account for psoriasis disease activity. The registries, Corrona and CEPPA, contained the gold standard measure of BSA affected as the outcome, and the healthcare claims data served as the predictors in my model.

In Aim 2 (Chapter 4), I used a larger set of Medicare data to explore the association between different therapies prescribed for the treatment of psoriasis and risk of developing hospitalized infections. Due to the increasing number of biologic therapies recently approved to treat psoriasis, this aim focused on different biologic therapy types, including TNF-α, IL-12/23, IL-17, and IL-23 inhibitors. I hypothesized that patients prescribed non-TNF-α inhibitors (IL-17, IL-12/23, or IL-23 inhibitors) will have reduced risk of hospitalized infections when as compared to patients prescribed TNF-α inhibitors.

In Aim 3 (Chapter 5), I evaluated the association between different psoriasis treatments and all-cause and infection-specific mortality, utilizing Medicare data linked to the National Death Index. Biologic therapies (TNF-α, IL-12/23, IL-17 inhibitors) were used as exposure groups. I hypothesized that patients prescribed non-TNF-α inhibitors (IL-17 or IL-12/23 inhibitors) will have reduced rate of infection-specific mortality when as compared to patients prescribed TNF-α inhibitors.

6.2 Significance and contributions of this research

Patients with psoriasis have dysregulated immune system functions, which are responsible for the initiation and maintenance of disease pathogenesis. Biologic therapies disrupt different immunologic pathways, which often leads to skin clearance; however, many of these immune pathways are also responsible for protecting the body from fungal and bacterial infections.[3] Therefore, patients with psoriasis are at increased infectious risk from both their disease and at least some of theirmedications.

The effect of disease severity has not been directly controlled for in analyses utilizing administrative claims. As disease severity is associated with both prescribing patterns as well as independent risk of infectious outcomes.[4] It is necessary to include clinical assesments, such as BSA affected, to accurately control for psoriasis severity; however, real-world data such as claims data, do not include these clinical assessments. Additionally, the Centers for Disease Control and Prevention (CDC) highlights the need for understanding of the

prevalence of psoriasis severity and how it relates to comorbidities and treatments, and this study will help to fill this gap in knowledge.

In Aim 1, I developed and validated a disease severity score based on claims-based variables to predict BSA affected. Due to the large number of potential variables to test, I used strict selection criteria to narrow the number of variables for model building. I employed LASSO regression paired with k-fold cross-validation to construct and validate a predictive model. The severity score had moderate classification, and a good positive predictive value. However, a concern with the use of a severity score index build from a self-selected group of individuals is the potential lack of generaliability to the larger Medicare population. Additional testing of the severity score within Medicare would provide key information to improve upon this proposed index.

Aim 2 focused on understanding the association between therapy and hospitalized infections. Recently approved biologic therapies for psoriasis may increase infectious risk for patients, although this risk is likely to vary across drugs with different mechanisms of action.[2] To account for the differences in prescribing, I developed a propensity score based on the propensity to be prescribed TNF-α inhibitors vs. non-TNF-α inhibitors. I used an incident user group design to reduce bias in my observational dataset.[5] Inverse probability of treatment weighting was used to develop a sample of the covariates independent of their exposure group. I performed a Cox proportional hazards ratio analysis using the propensity score weighting, as well as adjusting for and psoriasis disease severity any covariates that remained unbalaned. The results found that

IL-12/23 inhibitors exhibited a protective effect on developing a hospitalized infection when compared to TNF-α inhibitors. These results supported our hypothesis, since both IL-17 and IL-12/23 inhibitors more specifically target psoriatic inflammation when compared to TNF- α inhibitors, which target inflammation in general.[3] As newer biologic treatments become more widely utilized, it will be imperative to evaluate their safety in the context of real-world data.

Few studies have evaluated the risk of infection-related mortality in patients with psoriasis,[6] and none have reported on infection-specific mortality by therapy type. To explore this association in Aim 3, I worked with Medicare data linked to the National Death Index, which houses causes of death based on individual state's vital statistics. Building on knowledge from Aim 2, I again developed a propensity score based on the propensity to be prescribed TNF-α inhibitors vs. non-TNF-α inhibitors. Inverse probability of treatment weighting was used in conjuction with Cox proportional hazards ratio analyses and an incident user study design. Interestingly, initiation of IL-12/23 inhibitors were found to increase risk of mortality when compared to initiation of TNF-α inhibitors. A limitation was the sample size and date range of the available data, as user of IL-17 inhibitors were relatively low and there was sparse mortality data on this exposure group.

In summary, the data could be interpreted to indicate that IL-12/23 inhibitors appear to have increased risk of all-cause mortality in the Medicare population when compared to patients with psoriasis treated with TNF-α inhibitors. However, these results need to be seen through the lens of channeling bias and

the likelihood that patients receiving IL-12/23 inhibitors are more likely to be at risk for developing hospitalized infections due to historic medical data, none of which appears to be fully accounted for in Medicare data. My research adds another piece of evidence to better understand the potential infectious risks for newer psoriasis biologic therapies.

These findings could be used to direct treatment choice, as decisions on medication must be tethered to evidence-based observations for patient safety. To date, these research findings provide the most rigorous evidence on how therapy type affected risk of infection or infection-specific mortality. Collectively, this research provides novel evidence for the degree of infectious risk for a variety of psoriasis therapies with different mechanisms of action.

6.3 Future directions

While significant effort went into the development of the psoriasis severity score, my work underscores the need to better understand the role of psoriasis disease severity in determining infectious associations. This could be accomplished by continual accural of participants into registries and linking them with claims databases such as Medicare. Additionally, utilizing longitudinal data collected via registries may better allow for the time-varying effects of teatment to be studied. Although k-fold cross-validation allows for a single dataset to act as both the testing and training dataset with internal validation, improvements on a psoriasis severity score could be made by using external datasets for validation.

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APPENDICES

Appendix 1. Institutional Review Board Documentation

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

March 1, 2017

Dear Investigator:

On 3/1/2017, the IRB reviewed the following submission:

IRB ID:	STUDY00016822
Type of Review:	Initial Study
Title of Study:	Association between treatment type and psoriasis-related morbidity and mortality
Principal Investigator:	Kevin Winthrop
Funding:	None
IND, IDE, or HDE:	None
Documents Reviewed:	• Limited Data Sharing Agreement OHSU Investigator Research signed1 - signed.pdf • WoA • PPQ • Protocol • DUA RSCH-2014-27432_Sig Add_Siegel with modified Exec Sum_VKZ-978-55662.pdf • 01_Amend_Rqst Ltr_VKZ-978-55662.PDF

The IRB granted final approval on 3/1/2017. The study is approved until 2/28/2018.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

January 29, 2018

Dear Investigator:

On 1/29/2018, the IRB reviewed the following submission:

IRB ID:	STUDY00016822	MOD or CR ID:	MODCR00004741
Type of Review:	Modification and Continuing Review		
Title of Study:	Association between treatment type and psoriasis-related morbidity and mortality		
Title of modification	Annual CRQ 2018		
Principal Investigator:	Kevin Winthrop		
Funding:	None		
IND, IDE, or HDE:	None		
Documents Reviewed:	• 01_Amend_Rqst Ltr_VKZ-978-55662.PDF • Limited Data Sharing Agreement OHSU Investigator Research signed1 - signed.pdf • WoA • DUA RSCH-2014-27432_Sig Add_Siegel with modified Exec Sum_VKZ-978-55662.pdf • PPQ • Protocol		

The IRB granted final approval on 1/29/2018. The study is approved until 1/28/2019.

Review Category: Expedited Category #5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

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(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

January 11, 2019

Dear Investigator:

On 1-11-2019 the IRB reviewed the following submission:

IRB ID:	STUDY00016822	MOD or CR ID:	MODCR00008674
Type of Review:	Modification and Continuing Review		
Title of Study:	Association between treatment type and psoriasis-related morbidity and mortality		
Title of modification	Annual CRQ 2019		
Principal Investigator:	Kevin Winthrop		
Funding:	None		
IND, IDE, or HDE:	None		
Documents Reviewed:	• DUA RSCH-2014-27432_Sig Add_Siegel with modified Exec Sum_VKZ-978-55662.pdf • Siegel SID 2019 Psoriasis Disease Severity.pdf • Protocol • PPQ • 01_Amend_Rqst Ltr_VKZ-978-55662.PDF • Limited Data Sharing Agreement OHSU Investigator Research signed1 - signed.pdf • WoA		

The IRB granted final approval on 1/11/2019. The study is approved until 1/10/2020.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

IRB MEMO

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APPROVAL OF SUBMISSION

December 12, 2019

Dear Investigator:

On 12/12/2019, the IRB reviewed the following submission:

IRB ID:	STUDY00016822	MOD or CR ID:	MODCR00012054
Type of Review:	Modification and Continuing Review, Study Closure or Check-in		
Title of Study:	Association between treatment type and psoriasis-related morbidity and mortality		
Title of modification	Annual 2020 CRQ		
Principal Investigator:	Kevin Winthrop		
Funding:	None		
IND, IDE, or HDE:	None		
Documents Reviewed:	• DUA RSCH-2014-27432_Sig Add_Siegel with modified Exec Sum_VKZ-978-55662.pdf • Siegel SID 2019 Psoriasis Disease Severity.pdf • Protocol • PPQ • 01_Amend_Rqst Ltr_VKZ-978-55662.PDF • Limited Data Sharing Agreement OHSU Investigator Research signed1 - signed.pdf • 2019 Siegel SID Poster.pdf • WoA		

The IRB granted final approval on 12/12/2019. The study is approved until 12/11/2020.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Appendix 2. Supplemental materials for "Development of a Psoriasis Severity Score for Clinical Measures in a Claims Database"

Appendix 2 Tables

Table A2.1. List of potential predictors for the psoriasis severity score

Potential Predictors	Reason to exclude
Baseline diagnosis or procedure: influenza vaccination	**Included**
Baseline diagnosis: advanced kidney disease	not significant at 0.20 level
Baseline diagnosis: advanced liver disease	not significant at 0.20 level
Baseline diagnosis: angina	not significant at 0.20 level
Baseline diagnosis: ankylosing spondylitis	not significant at 0.20 level
Baseline diagnosis: anxiety	not significant at 0.20 level
Baseline diagnosis: body mass index equal to, or greater than 25	not significant at 0.20 level
Baseline diagnosis: cancer	not significant at 0.20 level
Baseline diagnosis: cardiovascular screening	not significant at 0.20 level
Baseline diagnosis: chronic heart disease	not significant at 0.20 level
Baseline diagnosis: chronic obstructive pulmonary disease	not significant at 0.20 level
Baseline diagnosis: connective tissue disease	not significant at 0.20 level
Baseline diagnosis: Crohn's disease	not significant at 0.20 level
Baseline diagnosis: dactylitis	<3% prevalence
Baseline diagnosis: deep vein thrombosis	not significant at 0.20 level
Baseline diagnosis: depression	**Included**
Baseline diagnosis: diabetes	not significant at 0.20 level
Baseline diagnosis: diagnoses for endoscopy	not significant at 0.20 level
Baseline diagnosis: diverticulitis	not significant at 0.20 level
Baseline diagnosis: end stage renal disease	<3% prevalence
Baseline diagnosis: enthesitis	<3% prevalence
Baseline diagnosis: extra-articular manifestations	not significant at 0.20 level
Baseline diagnosis: failure to thrive	not significant at 0.20 level
Baseline diagnosis: fatty liver	not significant at 0.20 level
Baseline diagnosis: fibromyalgia	**Included**
Baseline diagnosis: fistula abscess	not significant at 0.20 level
Baseline diagnosis: fracture	not significant at 0.20 level
Baseline diagnosis: fracture due to balance	not significant at 0.20 level
Baseline diagnosis: fracture due to fall	not significant at 0.20 level
Baseline diagnosis: fracture due to stroke	not significant at 0.20 level
Baseline diagnosis: GI perforation	not significant at 0.20 level
Baseline diagnosis: gout	not significant at 0.20 level
Baseline diagnosis: heart failure	not significant at 0.20 level
Baseline diagnosis: hemorrhagic stroke	<3% prevalence
Baseline diagnosis: hepatitis B	not significant at 0.20 level

Baseline diagnosis: hepatitis C	<3% prevalence
Baseline diagnosis: herpes simplex	<3% prevalence
Baseline diagnosis: herpes simplex complex	<3% prevalence
Baseline diagnosis: herpes simplex uncomplicated	not significant at 0.20 level
Baseline diagnosis: human immunodeficiency virus	not significant at 0.20 level
Baseline diagnosis: hypertension	not significant at 0.20 level
Baseline diagnosis: infection in the inpatient setting	**Included**
Baseline diagnosis: infection in the outpatient setting	**Included**
Baseline diagnosis: infectious mononucleosis	not significant at 0.20 level
Baseline diagnosis: inflammatory bowel disease	not significant at 0.20 level
Baseline diagnosis: influenza vaccination	not significant at 0.20 level
Baseline diagnosis: injury	<3% prevalence
Baseline diagnosis: interstitial lung disease	not significant at 0.20 level
Baseline diagnosis: ischemic stroke	<3% prevalence
Baseline diagnosis: joint surgery	not significant at 0.20 level
Baseline diagnosis: leukemia	not significant at 0.20 level
Baseline diagnosis: liver failure	not significant at 0.20 level
Baseline diagnosis: long-term drug use	**Included**
Baseline diagnosis: lower back pain	**Included**
Baseline diagnosis: lung failure	not significant at 0.20 level
Baseline diagnosis: Lyme disease	not significant at 0.20 level
Baseline diagnosis: lymphoma	not significant at 0.20 level
Baseline diagnosis: mammogram	<3% prevalence
Baseline diagnosis: metabolic syndrome	not significant at 0.20 level
Baseline diagnosis: multiple sclerosis	not significant at 0.20 level
Baseline diagnosis: myocardial stroke	**Included**
Baseline diagnosis: non-melanoma skin cancer (any)	not significant at 0.20 level
Baseline diagnosis: non-melanoma skin cancer (basal)	not significant at 0.20 level
Baseline diagnosis: non-melanoma skin cancer (squamous)	not significant at 0.20 level
Baseline diagnosis: organ transplant	not significant at 0.20 level
Baseline diagnosis: osteoarthritis	not significant at 0.20 level
Baseline diagnosis: Papanicolaou test	not significant at 0.20 level
Baseline diagnosis: polymyositis	not significant at 0.20 level
Baseline diagnosis: prior myocardial infarction	correlated
Baseline diagnosis: progressive multifocal leukoencepalitis	not significant at 0.20 level
Baseline diagnosis: prostrate-specific antigen	not significant at 0.20 level
Baseline diagnosis: psoriasis	correlated
Baseline diagnosis: psoriatic arthritis	not significant at 0.20 level
Baseline diagnosis: pulmonary embolism	not significant at 0.20 level
Baseline diagnosis: reactive arthritis	not significant at 0.20 level
Baseline diagnosis: rheumatoid arthritis	not significant at 0.20 level
Baseline diagnosis: scleroderma	not significant at 0.20 level
Baseline diagnosis: sleep apnea	not significant at 0.20 level

Baseline diagnosis: smoking	not significant at 0.20 level
Baseline diagnosis: solid cancer	correlated
Baseline diagnosis: stroke	<3% prevalence
Baseline diagnosis: suicide	<3% prevalence
Baseline diagnosis: systemic lupus erythematosus	not significant at 0.20 level
Baseline diagnosis: transient ischemic attack	not significant at 0.20 level
Baseline diagnosis: tuberuclosis	not significant at 0.20 level
Baseline diagnosis: ulcerative colitis	not significant at 0.20 level
Baseline diagnosis: ulcers	not significant at 0.20 level
Baseline diagnosis: uveitis	not significant at 0.20 level
Baseline diagnosis: zoster	not significant at 0.20 level
Baseline diagnsosi: Sjogren's disease	not significant at 0.20 level
Baseline prescription: zoster vaccination	not significant at 0.20 level
Baseline procedue: rehabilitation visit	not significant at 0.20 level
Baseline procedure: barium swallow for colon	not significant at 0.20 level
Baseline procedure: barium swallow for upper GI	not significant at 0.20 level
Baseline procedure: chronic heart disease	not significant at 0.20 level
Baseline procedure: cidofovir	not significant at 0.20 level
Baseline procedure: end stage renal disease	<3% prevalence
Baseline procedure: endoscopy	not significant at 0.20 level
Baseline procedure: fistula abscess	not significant at 0.20 level
Baseline procedure: fracture due to balance issue	not significant at 0.20 level
Baseline procedure: hormone replacement	not significant at 0.20 level
Baseline procedure: inflammatory marker	not significant at 0.20 level
Baseline procedure: infliximab	correlated
Baseline procedure: intra-articular injection	not significant at 0.20 level
Baseline procedure: intralestional injection	correlated
Baseline procedure: joint surgery	not significant at 0.20 level
Baseline procedure: lipid lab testing	correlated
Baseline procedure: liver function testing	not significant at 0.20 level
Baseline procedure: mammogram	correlated
Baseline procedure: organ transplant	not significant at 0.20 level
Baseline procedure: Papanicolaou test	correlated
Baseline procedure: parenteral therapy	not significant at 0.20 level
Baseline procedure: physical therapy	not significant at 0.20 level
Baseline procedure: platelet testing	not significant at 0.20 level
Baseline procedure: skilled nursing facility	not significant at 0.20 level
Baseline procedure: tuberculosis screening	not significant at 0.20 level
Baseline procedure: zoster vaccination	not significant at 0.20 level
Baseline procedures: any drug or biologic	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription abatacept	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription adalimumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription anakinra	not significant at 0.20 level

Baseline to 3 months therapy: either procedure or prescription apremilast	correlated
Baseline to 3 months therapy: either procedure or prescription azathioprine	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription belimumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription canakinumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription certolizumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription cyclophosphamide	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription cyclosporine	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription efalizumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription golimumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription hydroxychloroquine	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription infliximab	correlated
Baseline to 3 months therapy: either procedure or prescription methotrexate	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription rituximab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription secukinumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription sulfasalazine	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription tacrolimus	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription thiomalate	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription tocilizumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription tofacitinib	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription ustekinumab	not significant at 0.20 level
Baseline to 3 months therapy: either procedure or prescription vedolizumab	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription abatacept	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription adalimumab	**Included**
Baseline to 6 months therapy: either procedure or prescription azathioprine	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription certolizumab	not significant at 0.20 level

Baseline to 6 months therapy: either procedure or prescription cyclosporine	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription etanercept	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription golimumab	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription hydroxychloroquine	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription infliximab	<3% prevalence
Baseline to 6 months therapy: either procedure or prescription leflunomide	<3% prevalence
Baseline to 6 months therapy: either procedure or prescription methotrexate	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription minocycline	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription penicillamine	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription rituximab	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription secukinumab	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription sulfasalazine	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription tocilizumab	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription tofacitinib	not significant at 0.20 level
Baseline to 6 months therapy: either procedure or prescription ustekinumab	not significant at 0.20 level
Baseline to forty-two days prescription: zoster vaccination	not significant at 0.20 level
Baseline to forty-two days: zoster vaccination	not significant at 0.20 level
Baseline to fourteen days prescription: antibiotics	not significant at 0.20 level
Baseline to fourteen days: antibiotics	not significant at 0.20 level
Baseline to six months: biologic therapy	not significant at 0.20 level
Baseline to six months: infection in the inpatient setting	not significant at 0.20 level
Baseline to six months: number of therapy classes	not significant at 0.20 level
Baseline to three months: biologic therapy	not significant at 0.20 level
Baseline to twenty-eight days procedure: intrarticular injection	not significant at 0.20 level
Baseline: Charlson Comorbidity Index	not significant at 0.20 level
Baseline: chronic heart disease (any)	not significant at 0.20 level
Baseline: chronic obstructive pulmonary disease (any)	not significant at 0.20 level
Baseline: either procedure or diagnosis cardiovascular screening	correlated
Baseline: either procedure or diagnosis high-risk mammography screening	not significant at 0.20 level
Baseline: either procedure or diagnosis joint surgery	not significant at 0.20 level

Baseline: either procedure or prescription etanercept	not significant at 0.20 level
Baseline: either procedure or prescription golimumab	not significant at 0.20 level
Baseline: either procedure or prescription hydroxychloroquine	not significant at 0.20 level
Baseline: either procedure or prescription infliximab	correlated
Baseline: end stage renal disease (any)	<3% prevalence
Baseline: endoscropy	not significant at 0.20 level
Baseline: influenza vaccination	not significant at 0.20 level
Baseline: number of therapy classes	not significant at 0.20 level
Baseline: procedure or diagnosis any fistula abscess	not significant at 0.20 level
Baseline: procedure or diagnosis fracture	not significant at 0.20 level
Baseline: procedure or diagnosis organ transplant	not significant at 0.20 level
Baseline: procedure or diagnosis Papanicolaou test	not significant at 0.20 level
Baseline: procedure or diagnosis prostate-antigen test	not significant at 0.20 level
Baseline: tuberuclosis screening	not significant at 0.20 level
Baseline: tuberuclosis screening	not significant at 0.20 level
Baseline: zoster vaccination	not significant at 0.20 level
Demographic: age	not significant at 0.20 level
Demographic: female sex	**Included**
Demographic: Hispanic (Y/N)	not significant at 0.20 level
Demographic: race	not significant at 0.20 level
Demographic: rural	not significant at 0.20 level
Fourteen days: parenteral therapy	not significant at 0.20 level
Fourty-two days procedure: zoster vaccination	not significant at 0.20 level
History diagnosis: advanced kidney disease	not significant at 0.20 level
History diagnosis: advanced liver disease	not significant at 0.20 level
History diagnosis: angina	not significant at 0.20 level
History diagnosis: ankylosing spondylitis	not significant at 0.20 level
History diagnosis: anxiety	not significant at 0.20 level
History diagnosis: any cancer	not significant at 0.20 level
History diagnosis: any injury	correlated
History diagnosis: any late effects of injury	not significant at 0.20 level
History diagnosis: any type of fistual abscess	not significant at 0.20 level
History diagnosis: any type of fracture	not significant at 0.20 level
History diagnosis: any type of stroke	not significant at 0.20 level
History diagnosis: BMI ≥30	not significant at 0.20 level
History diagnosis: breast cancer	not significant at 0.20 level
History diagnosis: cancer	not significant at 0.20 level
History diagnosis: cardiovascular disease screening	not significant at 0.20 level
History diagnosis: chronic heart disease	correlated
History diagnosis: Chronic obstructive pulmonary disorder	not significant at 0.20 level
History diagnosis: colonrectal cancer	not significant at 0.20 level
History diagnosis: connective tissue disease	not significant at 0.20 level
History diagnosis: Crohn's disease	not significant at 0.20 level

History diagnosis: deep vein thrombosis	not significant at 0.20 level
History diagnosis: depression	correlated
History diagnosis: diagnoses for endoscopic procedure	not significant at 0.20 level
History diagnosis: diagnoses for joint surgery	not significant at 0.20 level
History diagnosis: diverticulitis	not significant at 0.20 level
History diagnosis: dyslipidemia	**Included**
History diagnosis: end-stage renal failure	<3% prevalence
History diagnosis: extra-articular manifestations	not significant at 0.20 level
History diagnosis: failure to grow/thrive	not significant at 0.20 level
History diagnosis: fatty liver disease	not significant at 0.20 level
History diagnosis: fibromyalgia	correlated
History diagnosis: GI perforation	not significant at 0.20 level
History diagnosis: gout	not significant at 0.20 level
History diagnosis: heart failure	not significant at 0.20 level
History diagnosis: hemorrhagic stroke	not significant at 0.20 level
History diagnosis: hepatitis B	not significant at 0.20 level
History diagnosis: herpes simplex	not significant at 0.20 level
History diagnosis: herpes simplex complicated	not significant at 0.20 level
History diagnosis: herpes simplex uncomplicated	not significant at 0.20 level
History diagnosis: high-risk mammography screening	not significant at 0.20 level
History diagnosis: human immunodeficieny virus	not significant at 0.20 level
History diagnosis: hypertension	not significant at 0.20 level
History diagnosis: infection in the inpatient setting	not significant at 0.20 level
History diagnosis: infection in the outpatient setting	not significant at 0.20 level
History diagnosis: infectious mononucleosis	not significant at 0.20 level
History diagnosis: interstital lung disease	not significant at 0.20 level
History diagnosis: ischemic stroke	not significant at 0.20 level
History diagnosis: leukemia	not significant at 0.20 level
History diagnosis: liver failure	not significant at 0.20 level
History diagnosis: long-term drug use	correlated
History diagnosis: lung cancer	not significant at 0.20 level
History diagnosis: lung failure	not significant at 0.20 level
History diagnosis: Lyme disease	not significant at 0.20 level
History diagnosis: lymphoma	not significant at 0.20 level
History diagnosis: melanoma	not significant at 0.20 level
History diagnosis: metabolic syndromes	not significant at 0.20 level
History diagnosis: multiple sclerosis	not significant at 0.20 level
History diagnosis: myocardial infarction	not significant at 0.20 level
History diagnosis: non-melanoma skin cancer	not significant at 0.20 level
History diagnosis: non-melanoma skin cancer, basal cell	<3% prevalence
History diagnosis: non-melanoma skin cancer, squamous cell	correlated
History diagnosis: non-tuberculosis opportunistic infection	not significant at 0.20 level
History diagnosis: organ transplant	not significant at 0.20 level

History diagnosis: osteoarthritis	**Included**
History diagnosis: Paget's disease	<3% prevalence
History diagnosis: pancreatic cancer	not significant at 0.20 level
History diagnosis: Papanicolaou test	not significant at 0.20 level
History diagnosis: polymyositis	not significant at 0.20 level
History diagnosis: prescribed a DMARD	not significant at 0.20 level
History diagnosis: prior myocardial infarction	**Included**
History diagnosis: progressive multifocal leukoencepalitis	not significant at 0.20 level
History diagnosis: prostate cancer	not significant at 0.20 level
History diagnosis: prostate-specific antigen	not significant at 0.20 level
History diagnosis: psoriasis	correlated
History diagnosis: psoriatic arthritis	correlated
History diagnosis: pulmonary embolism	not significant at 0.20 level
History diagnosis: reactive arthritis	not significant at 0.20 level
History diagnosis: rheumatoid arthritis	not significant at 0.20 level
History diagnosis: scleroderma	not significant at 0.20 level
History diagnosis: Sjögren's syndrome	not significant at 0.20 level
History diagnosis: sleep apnea	not significant at 0.20 level
History diagnosis: smoking	not significant at 0.20 level
History diagnosis: solid cancer	not significant at 0.20 level
History diagnosis: stomach ulcer	not significant at 0.20 level
History diagnosis: suicide	not significant at 0.20 level
History diagnosis: systemic lupus erythematosus	not significant at 0.20 level
History diagnosis: transient ischemic attack	not significant at 0.20 level
History diagnosis: tubercolosis	<3% prevalence
History diagnosis: tubercolosis screening	not significant at 0.20 level
History diagnosis: ulcerative colitis	not significant at 0.20 level
History diagnosis: uveitis	not significant at 0.20 level
History diagnosis: zoster	not significant at 0.20 level
History diagnsosi: diabetes	not significant at 0.20 level
History prescription: statins	correlated
History procedure: liver function tests	not significant at 0.20 level
History procedure: organ transplant	not significant at 0.20 level
History procedure: any drug or biologic	not significant at 0.20 level
History procedure: cardiovascular disease screening	not significant at 0.20 level
History procedure: done at rehabilitory visit	not significant at 0.20 level
History procedure: done at skilled nursing facility	**Included**
History procedure: joint surgery	not significant at 0.20 level
History procedure: Papanicolaou test	not significant at 0.20 level
History procedure: parenteral therapy	not significant at 0.20 level
History procedure: phototherapy	not significant at 0.20 level
History procedure: physical therapy	not significant at 0.20 level
History procedure: platelet tests	not significant at 0.20 level
History procedure: tuberculosis screening	not significant at 0.20 level

History procedure: wheelchair use	not significant at 0.20 level
History procedure: zoster vaccination	not significant at 0.20 level
History: abatacept	not significant at 0.20 level
History: acyclovir	not significant at 0.20 level
History: adalimumab	not significant at 0.20 level
History: advanced kidney disease or end-stage renal disease	not significant at 0.20 level
History: anticoagulants	not significant at 0.20 level
History: antidepressants	not significant at 0.20 level
History: any form of stroke	not significant at 0.20 level
History: any influenza vaccination	not significant at 0.20 level
History: any non-melanoma skin cancer	not significant at 0.20 level
History: apremilast	not significant at 0.20 level
History: aurothioglucose	not significant at 0.20 level
History: azathioprine	not significant at 0.20 level
History: certolizumab	not significant at 0.20 level
History: chronic pulmonary obstructive disease and oral steroid use	not significant at 0.20 level
History: cidofovir	not significant at 0.20 level
History: cyclophosphamide	not significant at 0.20 level
History: cyclosporine	not significant at 0.20 level
History: dactylitis	not significant at 0.20 level
History: depression and use of antidepressants	not significant at 0.20 level
History: diabetes and BMI ≥ 30	not significant at 0.20 level
History: dyslipidemia and statin use	correlated
History: efalizumab (any)	not significant at 0.20 level
History: either depression or anxiety	not significant at 0.20 level
History: either diagnosis or procedure for joint surgery	not significant at 0.20 level
History: either fibromyalgia or lower back pain	correlated
History: either fibromyalgia or lower back pain and NSAID use	correlated
History: either tuberculosis or non-TB opportunistic infection	not significant at 0.20 level
History: enthesitis	<3% prevalence
History: etanercept	not significant at 0.20 level
History: etanercept (any)	not significant at 0.20 level
History: fatty liver and BMI ≥ 30	not significant at 0.20 level
History: golimumab	not significant at 0.20 level
History: golimumab (any)	not significant at 0.20 level
History: hepatitis C	<3% prevalence
History: hydroxychloroquine	<3% prevalence
History: hypertension and beta blocker use	not significant at 0.20 level
History: inflammatory bowel disease	<3% prevalence
History: inflammatory bowel disease, ulcerative colitis, or Crohn's disease	<3% prevalence

History: inflammatory bowel syndrome and oral steroid use	<3% prevalence
History: inflammatory marker test	not significant at 0.20 level
History: infliximab	not significant at 0.20 level
History: influenza vaccination (any)	not significant at 0.20 level
History: intralestional injection	correlated
History: lower back pain	correlated
History: methotrexate	not significant at 0.20 level
History: minocycline	not significant at 0.20 level
History: mycophenolate	not significant at 0.20 level
History: myocardial infarction, chronic heart disease, heart failure, prior myocardial infarction, stroke due to myocardial infarction, or chronic heart disease	not significant at 0.20 level
History: no visits for diagnoses of myocardial infarction, congestive heart disease, peripheral vascular disorder, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, or acquired immunodeficiency syndrome	**Included**
History: number of biologics (any)	not significant at 0.20 level
History: number of DMARD episodes	not significant at 0.20 level
History: number of infliximab episodes	not significant at 0.20 level
History: prescribed a biologic	not significant at 0.20 level
History: rheumatoid arthritis and DMARD use	not significant at 0.20 level
History: rilonacept	not significant at 0.20 level
History: rituximab	not significant at 0.20 level
History: secukinumab	<3% prevalence
History: sulfasalazine	not significant at 0.20 level
History: ustekinumab	not significant at 0.20 level
Six to twelve months prescription: abatacept	not significant at 0.20 level
Six to twelve months prescription: adalimumab	not significant at 0.20 level
Six to twelve months prescription: anakinra	not significant at 0.20 level
Six to twelve months prescription: antibiotics	not significant at 0.20 level
Six to twelve months prescription: anticoagulants	not significant at 0.20 level
Six to twelve months prescription: antidepressants	not significant at 0.20 level
Six to twelve months prescription: apremilast	not significant at 0.20 level
Six to twelve months prescription: auranofin	not significant at 0.20 level
Six to twelve months prescription: azathioprine	not significant at 0.20 level
Six to twelve months prescription: belimumab	not significant at 0.20 level
Six to twelve months prescription: beta blockers	not significant at 0.20 level
Six to twelve months prescription: bisphosphonates	not significant at 0.20 level

Six to twelve months prescription: canakinumab	not significant at 0.20 level
Six to twelve months prescription: certolizumab	not significant at 0.20 level
Six to twelve months prescription: cyclophosphamide	not significant at 0.20 level
Six to twelve months prescription: cyclosporine	not significant at 0.20 level
Six to twelve months prescription: efalizumab	not significant at 0.20 level
Six to twelve months prescription: etanercept	not significant at 0.20 level
Six to twelve months prescription: golimumab	not significant at 0.20 level
Six to twelve months prescription: hydroxychloroquine	not significant at 0.20 level
Six to twelve months prescription: infliximab	not significant at 0.20 level
Six to twelve months prescription: leflunomide	not significant at 0.20 level
Six to twelve months prescription: mercaptopurine	not significant at 0.20 level
Six to twelve months prescription: methotrexate	not significant at 0.20 level
Six to twelve months prescription: minocycline	not significant at 0.20 level
Six to twelve months prescription: narcotics	**Included**
Six to twelve months prescription: nonsteroidal anti-inflammatory drug, cox inhibitor	not significant at 0.20 level
Six to twelve months prescription: nonsteroidal anti-inflammatory drug, noncox inhibitor	not significant at 0.20 level
Six to twelve months prescription: oral steroids	not significant at 0.20 level
Six to twelve months prescription: penicillamine	not significant at 0.20 level
Six to twelve months prescription: rituximab	not significant at 0.20 level
Six to twelve months prescription: secukinumab	not significant at 0.20 level
Six to twelve months prescription: statins	**Included**
Six to twelve months prescription: tofacitinib	<3% prevalence
Six to twelve months prescription: topical steroids	not significant at 0.20 level
Six to twelve months prescription: ustekinumab	not significant at 0.20 level
Six to twelve months prescription: vedolizumab	not significant at 0.20 level
Six to twelve months prescription: zoster vaccination	not significant at 0.20 level
Six to twelve months procedure: abatacept	not significant at 0.20 level
Six to twelve months procedure: adalimumab	not significant at 0.20 level
Six to twelve months procedure: alefacept	not significant at 0.20 level
Six to twelve months procedure: anakinra	not significant at 0.20 level
Six to twelve months procedure: auranofin	not significant at 0.20 level
Six to twelve months procedure: aurothioglucose	not significant at 0.20 level
Six to twelve months procedure: azathioprine	not significant at 0.20 level
Six to twelve months procedure: canakinumab	not significant at 0.20 level
Six to twelve months procedure: certolizumab	not significant at 0.20 level
Six to twelve months procedure: cyclophosphamide	not significant at 0.20 level
Six to twelve months procedure: cyclosporine	not significant at 0.20 level
Six to twelve months procedure: efalizumab	not significant at 0.20 level
Six to twelve months procedure: etanercept	not significant at 0.20 level
Six to twelve months procedure: golimumab	not significant at 0.20 level
Six to twelve months procedure: hydroxychloroquine	not significant at 0.20 level
Six to twelve months procedure: infliximab	not significant at 0.20 level
Six to twelve months procedure: leflunomide	not significant at 0.20 level

Six to twelve months procedure: mercaptopurine	not significant at 0.20 level
Six to twelve months procedure: methotrexate	not significant at 0.20 level
Six to twelve months procedure: minocycline	not significant at 0.20 level
Six to twelve months procedure: mycophenolate	not significant at 0.20 level
Six to twelve months procedure: penicillamine	not significant at 0.20 level
Six to twelve months procedure: rilonacept	not significant at 0.20 level
Six to twelve months procedure: rituximab	not significant at 0.20 level
Six to twelve months procedure: sulfasalazine	not significant at 0.20 level
Six to twelve months procedure: tacrolimus	not significant at 0.20 level
Six to twelve months procedure: thiomalate	not significant at 0.20 level
Six to twelve months procedure: tocilizumab	not significant at 0.20 level
Six to twelve months procedure: tofacitinib	not significant at 0.20 level
Six to twelve months procedure: ustekinumab	<3% prevalence
Six to twelve months: biologic therapy	not significant at 0.20 level

Table A2.2. International Classification of Diseases (ICD), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes for covariate definition.

Variable	Notes	Proposed Definition
Age		Age at enrollment into Registry
BMI		
BMI ≥30		**ICD-9:** 278.00, 278.01, 793.91, V85.3, V85.4; **ICD-10:** E66.01, E66.9, R93.9, Z68.3, Z68.4
BMI 25-29		**ICD-9:** 278.02, V85.2; **ICD-10:** E66.3, Z68.2
Abdominal imaging		**ICD-9 Procedure Codes:** 88.01, 88.95, 88.97; **ICD-10 Procedure Codes:** B83.5Y0Z, B83.5YZZ, 83.5ZZZ, B83.6Y0Z, B83.6YZZ, B83.6ZZZ, B83.7Y0Z, B83.7YZZ, 83.7ZZZ, BF3.5Y0Z, BF3.5YZZ, BF3.5ZZZ, BF3.6Y0Z, BF3.6YZZ, BF3.6ZZZ BF3.7Y0Z, BF3.7YZZ, BF3.7ZZZ, BH3.DY0Z, BH3.DYZZ, BH3.DZZZ, BT3.0Y0Z, BT3.0YZZ, BT3.0ZZZ, BT3.1Y0Z, BT3.1YZZ, BT3.1ZZZ, BT3.2Y0Z, BT3.2YZZ, BT3.2ZZZ, BT3.3Y0Z, BT3.3YZZ, BT3.3ZZZ, BT3.9Y0Z, BT3.9YZZ, BT3.9ZZZ, BV3.3Y0Z, BV3.3YZZ, BV3.3ZZZ, BW2.000Z, BW2.00ZZ, BW2.010Z, BW2.01ZZ, BW2.0Y0Z, BW2.0YZZ, BW2.0ZZZ, BW3.GY0Z, BW3.GYZZ, BW3.GZZZ, BW3.8Y0Z, BW3.8YZZ, BW3.8ZZZ, BW3.FY0Z, BW3.FYZZ, BW3.FZZZ; **CPT and HCPCS Codes**: 72191 - 72198, 74150, 74160, 74170, 74175, 74181 - 74183, 74185
Ankylosing spondylitis		**ICD-9:** 720.0; **ICD-10:** M45.9
Anxiety		**ICD-9:** 293.84, 300.00, 300.02, 300.20; **ICD-10:** F06.4, F40.9, F41.1, F41.9
Dactylitis		**ICD-9:** 039.0, 686.09, 686.8, 686.9, 910.1, 910.3, 910.5, 910.7, 910.9, 911.1, 911.3, 911.5, 911.7, 911.9, 912.1, 912.3, 912.5, 912.7, 912.9, 913.1, 913.3, 913.5, 913.7, 913.9, 914.1, 914.3, 914.5, 914.7, 915.1, 915.3, 915.5, 915.7, 915.9, 916.1, 916.3, 916.5, 916.7, 916.9, 917.1, 917.3, 917.5, 917.7, 917.9, 919.1, 919.3, 919.5, 919.7, 919.9; **ICD-10:** L08.0, L08.1, L08.89, L08.9
Dermatology visits (count)	Ambulatory visits	Encounter type = "AV" and Provider Type = "07"
Depression		**ICD-9:** 296.20-296.82, 300.4, 300.9, 311.XX; **ICD-10:** F30.8, F31.10-F31.13, F31.2, F31.73, F31.74, F31.30-F31.32, F31.4, F31.5, F31.75, F31.76, F31.60-F31.64, F31.77, F31.78, F31.9,

		F32.0-F32.5, F32.8, F32.9, F33.0-F33.3, F33.41, F33.42, F33.9, F34.1, F48.9, F99
Diabetes (type I or II)		**ICD-9:** 250; **ICD-10:** E10.10, E10.11, E10.21, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.648, E10.65, E10.8, E10.9, E11.00, E11.01, E11.21, E11.29, E11.311, E11.319, E11.36, E11.39, E11.40, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9
Diverticulitis		**ICD-9:** 562; **ICD-10:** K57.10, K57.11, K57.12, K57.13, K57.30, K57.31, K57.32, K57.33
Dyslipidemia		**ICD-9:** 272.4; **ICD-10:** E78.4, E78.5
Endoscopic procedures (count)		**ICD-9 Procedure Codes:** 4524; **ICD-10 Procedures Codes:** 0DJ.D8ZZ; **CPT and HCPCS Codes:** 45300, 45303, 45305, 45307, 45308, 45309, 45315, 45317, 45320, 45321, 45327, 45330, 45331, 45332, 45333, 45334, 45335, 45337, 45338, 45339, 45340, 45341, 45342, 45345, G0104
End stage renal disease		ICD-9: V56, V45.11, V45.12, 585.6; ICD-10: N18.6, Z49.01, Z49.02, Z49.31, Z49.32, Z91.15, Z99.2
Endoscopic screening		**CPT and HCPCS Codes:** G0104, G0105, G0121
Enthesitis		**ICD-9:** 714.30, 714.31, 714.32, 714.33; **ICD-10:** M08.00, M08.3, M08.40
Fatty liver		**ICD-9:** 5718; **ICD-10:** K76.0, K76.89
Fecal occult blood testing	Individuals ≥50 years	**CPT and HCPCS Codes:** 82270-82274, G0107, G0328
Fibromyalgia		**ICD-9:** 729.1; **ICD-10:** M60.9, M79.1, M79.7
Fracture		**ICD-9 Codes:** 332.0, 334, 342.90, 386, 438.20, 438.40, 733.1, 780.4, 781.2, 781.3, 800.00 - 829.99, E 88.89, V15.88; **ICD-10 Codes:** G20, G81.90, I69.949, I69.959, R26.0, R26.1, R26.89, R26.9, R27.0, R27.8, R27.9, R42, S02.0XXA, S02.0XXB, S06.330A - S06.339A, S06.4X0A - S06.4X9A, S06.5X0A - S06.5X9A, S06.6X0A - S06.6X9A, S06.360A - S06.369A, S06.890A - S06.899A, S06.9X0A - S06.9X2A, S06.9X4A - S06.9X9A, S42.009A, S42.009B, S42.013A, S42.016A, S42.019A,

		S42.023A, S42.026A, S42.033A, S42.036A, S42.013B, S42.016B, S42.019B, S42.023B, S42.026B, S42.033B, S42.036B, Z77.9, Z91.81, Z92.89; **CPT and HCPCS Codes:** E0100, E0105, E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E1013, E1035, E1036, E1037, E1038, E1039, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1092, E1093, E1100, E1110, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228, E1229, E1230, E1231, E1232, E1233, E1234, E1235, E1236, E1237, E1238, E1239, E1240, E1250, E1260, E1270, E1280, E1285, E1290, E1295, E1296, E1297, E1298
Gastrointestinal perforations		**ICD-9:** 530.40, 531.10, 531.11, 531.20, 531.21, 531.50, 531.51, 531.60, 531.61, 532.10, 532.11, 532.20, 532.21, 532.50, 532.51, 532.60, 532.61, 533.10, 533.11, 533.20, 533.21, 533.50, 533.51, 533.60, 533.61, 534.10, 534.20, 534.21, 534.50, 534.51, 534.60, 534.61, 540.00, 562.00, 562.01, 562.02, 562.03, 562.10, 562.11, 562.12, 569.83; **ICD-10:** K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K35.2, K57.10, K57.11, K57.12, K57.13, K57.30, K57.31, K57.32, K63.1
Gout		**ICD-9:** 274.00 - 274.03, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9; **ICD-10:** M10.00, M10.30, M10.40, M10.9, M1A00X1, M1A20X1, M1A30X1, M1A40X1, M1A9XX0, M1A9XX1, N20.0
Herpes zoster		**ICD-9:** 053; **ICD-10:** B02.1, B02.21, B02.22, B02.23, B02.24, B02.29, B02.32, B02.33, B02.39, B02.8, B02.9
Inflammatory bowel disease (includes Crohn's and ulcerative colitis)		**ICD-9:** 555.0 - 555.2, 555.9, 556.0 - 556.6, 556.8, 556.9; **ICD-10:** K50.00, K50.10, K50.80, K50.90, K51.00, K51.20, K51.30, K51.40, K51.50, K51.80, K51.90
Influenza vaccination		**ICD-9:** V04.81, V06.6; **ICD-9 Procedure Codes:** 99.52; **ICD-10:** Z23; **ICD-10 Procedure Codes:** 3E0.134Z; **CPT and HCPCS Codes:** 4037F, 90659, 90660, 90656, 90658, G0008
Inpatient visits coded for all reasons, excluding infection (count)	Within 3 months of index date	Encounter type = "IP" for all visits, excluding those involving an infection

Inpatient visits coded for infection (count)	Within 3 months of index date	Encounter type = "IP" for a visit involving an infection
Intralesional injection		**CPT and HCPCS Codes:** 119.00, 119.01, J3301 **ICD-9 Codes:** 718.4, 718.5, 724.9, 738.5; **ICD-10 Codes:** M43.8X9, M53.9, M99.83, M99.84; **ICD-9 Procedure Codes:** 800 - 804, 806 - 809, 811, 812, 814, 815, 817 - 819; **ICD-10 Procedure Codes:** 0LQ.10ZZ, 0LQ.13ZZ, 0LQ.14ZZ, 0LQ.20ZZ, 0LQ.23ZZ, 0LQ.24ZZ, 0P8.H0ZZ, 0P8.H3ZZ, 0P8.H4ZZ, 0P8.J0ZZ, 0P8.J3ZZ, 0P8.J4ZZ, 0P8.K0ZZ, 0P8.K3ZZ, 0P8.K4ZZ, 0P8.L0ZZ, 0P8.L3ZZ, 0P8.L4ZZ, 0PB.H0ZZ, 0PB.H3ZZ, 0PB.H4ZZ, 0PB.J0ZZ, 0PB.J3ZZ, 0PB.J4ZZ, 0PB.K0ZZ, 0PB.K3ZZ, 0PB.K4ZZ, 0PB.L0ZZ, 0PB.L3ZZ, 0PB.L4ZZ, 0PC.H0ZZ, 0PC.H3ZZ, 0PC.H4ZZ, 0PC.J0ZZ, 0PC.J3ZZ, 0PC.J4ZZ, 0PC.K0ZZ, 0PC.K3ZZ, 0PC.K4ZZ, 0PC.L0ZZ, 0PC.L3ZZ, 0PC.L4ZZ, 0PH.H04Z, 0PH.H05Z, 0PH.H06Z, 0PH.H0BZ, 0PH.H0CZ, 0PH.H0DZ, 0PH.H34Z, 0PH.H35Z, 0PH.H36Z, 0PH.H3BZ, 0PH.H3CZ, 0PH.H3DZ, 0PH.H44Z, 0PH.H45Z, 0PH.H46Z, 0PH.H4BZ, 0PH.H4CZ, 0PH.H4DZ, 0PH.J04Z, 0PH.J05Z, 0PH.J06Z, 0PH.J0BZ, 0PH.J0CZ, 0PH.J0DZ, 0PH.J34Z, 0PH.J35Z, 0PH.J36Z, 0PH.J3BZ, 0PH.J3CZ, 0PH.J3DZ, 0PH.J44Z, 0PH.J45Z, 0PH.J46Z, 0PH.J4BZ, 0PH.J4CZ, 0PH.J4DZ, 0PH.K04Z, 0PH.K05Z, 0PH.K06Z, 0PH.K0BZ, 0PH.K0CZ, 0PH.K0DZ, 0PH.K34Z, 0PH.K35Z, 0PH.K36Z, 0PH.K3BZ, 0PH.K3CZ, 0PH.K3DZ, 0PH.K44Z, 0PH.K45Z, 0PH.K46Z, 0PH.K4BZ, 0PH.K4CZ, 0PH.K4DZ, 0PH.L04Z, 0PH.L05Z, 0PH.L06Z, 0PH.L0BZ, 0PH.L0CZ, 0PH.L0DZ, 0PH.L34Z, 0PH.L35Z, 0PH.L36Z, 0PH.L3BZ, 0PH.L3CZ, 0PH.L3DZ, 0PH.L44Z, 0PH.L45Z, 0PH.L46Z, 0PH.L4BZ, 0PH.L4CZ, 0PH.L4DZ, 0PN.H0ZZ, 0PN.H3ZZ, 0PN.H4ZZ, 0PN.J0ZZ, 0PN.J3ZZ, 0PN.J4ZZ, 0PN.K0ZZ, 0PN.K3ZZ, 0PN.K4ZZ, 0PN.L0ZZ, 0PN.L3ZZ, 0PN.L4ZZ, 0PQ.H0ZZ, 0PQ.H3ZZ, 0PQ.H4ZZ, 0PQ.J0ZZ, 0PQ.J3ZZ, 0PQ.J4ZZ, 0PQ.K0ZZ, 0PQ.K3ZZ, 0PQ.K4ZZ, 0PQ.L0ZZ, 0PQ.L3ZZ, 0PQ.L4ZZ, 0PR.H07Z, 0PR.H0JZ, 0PR.H0KZ, 0PR.H37Z, 0PR.H3JZ, 0PR.H3KZ, 0PR.H47Z, 0PR.H4JZ, 0PR.H4KZ, 0PR.J07Z, 0PR.J0JZ, 0PR.J0KZ, 0PR.J37Z, 0PR.J3JZ, 0PR.J3KZ, 0PR.J47Z, 0PR.J4JZ, 0PR.J4KZ, 0PR.K07Z, 0PR.K0JZ, 0PR.K0KZ, 0PR.K37Z, 0PR.K3JZ, 0PR.K3KZ,
Joint surgery		

0PR.K47Z, 0PR.K4JZ, 0PR.K4KZ, 0PR.L07Z, 0PR.L0JZ, 0PR.L0KZ, 0PR.L37Z, 0PR.L3JZ, 0PR.L3KZ, 0PR.L47Z, 0PR.L4JZ, 0PR.L4KZ, 0PS.H04Z, 0PS.H05Z, 0PS.H06Z, 0PS.H0BZ, 0PS.H0CZ, 0PS.H0DZ, 0PS.H0ZZ, 0PS.H34Z, 0PS.H35Z, 0PS.H36Z, 0PS.H3BZ, 0PS.H3CZ, 0PS.H3DZ, 0PS.H44Z, 0PS.H45Z, 0PS.H46Z, 0PS.H4BZ, 0PS.H4CZ, 0PS.H4DZ, 0PS.J04Z, 0PS.J05Z, 0PS.J06Z, 0PS.J0BZ, 0PS.J0CZ, 0PS.J0DZ, 0PS.J0ZZ, 0PS.J34Z, 0PS.J35Z, 0PS.J36Z, 0PS.J3BZ, 0PS.J3CZ, 0PS.J3DZ, 0PS.J44Z, 0PS.J45Z, 0PS.J46Z, 0PS.J4BZ, 0PS.J4CZ, 0PS.J4DZ, 0PS.K04Z, 0PS.K05Z, 0PS.K06Z, 0PS.K0BZ, 0PS.K0CZ, 0PS.K0DZ, 0PS.K0ZZ, 0PS.K34Z, 0PS.K35Z, 0PS.K36Z, 0PS.K3BZ, 0PS.K3CZ, 0PS.K3DZ, 0PS.K44Z, 0PS.K45Z, 0PS.K46Z, 0PS.K4BZ, 0PS.K4CZ, 0PS.K4DZ, 0PS.L04Z, 0PS.L05Z, 0PS.L06Z, 0PS.L0BZ, 0PS.L0CZ, 0PS.L0DZ, 0PS.L0ZZ, 0PS.L34Z, 0PS.L35Z, 0PS.L36Z, 0PS.L3BZ, 0PS.L3CZ, 0PS.L3DZ, 0PS.L44Z, 0PS.L45Z, 0PS.L46Z, 0PS.L4BZ, 0PS.L4CZ, 0PS.L4DZ, 0PT.H0ZZ, 0PT.J0ZZ, 0PT.K0ZZ, 0PT.L0ZZ, 0PU.H07Z, 0PU.H0JZ, 0PU.H0KZ, 0PU.H37Z, 0PU.H3JZ, 0PU.H3KZ, 0PU.H47Z, 0PU.H4JZ, 0PU.H4KZ, 0PU.J07Z, 0PU.J0JZ, 0PU.J0KZ, 0PU.J37Z, 0PU.J3JZ, 0PU.J3KZ, 0PU.J47Z, 0PU.J4JZ, 0PU.J4KZ, 0PU.K07Z, 0PU.K0JZ, 0PU.K0KZ, 0PU.K37Z, 0PU.K3JZ, 0PU.K3KZ, 0PU.K47Z, 0PU.K4JZ, 0PU.K4KZ, 0PU.L07Z, 0PU.L0JZ, 0PU.L0KZ, 0PU.L37Z, 0PU.L3JZ, 0PU.L3KZ, 0PU.L47Z, 0PU.L4JZ, 0PU.L4KZ, 0RB.E0ZZ, 0RB.E3ZZ, 0RB.E4ZZ, 0RB.F0ZZ, 0RB.F3ZZ, 0RB.F4ZZ, 0RB.G0ZZ, 0RB.G3ZZ, 0RB.G4ZZ, 0RB.H0ZZ, 0RB.H3ZZ, 0RB.H4ZZ, 0RB.J0ZZ, 0RB.J3ZZ, 0RB.J4ZZ, 0RB.K0ZZ, 0RB.K3ZZ, 0RB.K4ZZ, 0RB.L0ZZ, 0RB.L3ZZ, 0RB.L4ZZ, 0RB.M0ZZ, 0RB.M3ZZ, 0RB.M4ZZ, 0RN.E0ZZ, 0RN.E3ZZ, 0RN.E4ZZ, 0RN.F0ZZ, 0RN.F3ZZ, 0RN.F4ZZ, 0RN.G0ZZ, 0RN.G3ZZ, 0RN.G4ZZ, 0RN.H0ZZ, 0RN.H3ZZ, 0RN.H4ZZ, 0RN.J0ZZ, 0RN.J3ZZ, 0RN.J4ZZ, 0RN.K0ZZ, 0RN.K3ZZ, 0RN.K4ZZ, 0RN.L0ZZ, 0RN.L3ZZ, 0RN.L4ZZ, 0RN.M0ZZ, 0RN.M3ZZ, 0RN.M4ZZ, 0RS.E04Z, 0RS.E0ZZ, 0RS.F04Z, 0RS.F0ZZ, 0RS.G04Z, 0RS.G0ZZ, 0RS.H04Z, 0RS.H0ZZ, 0RS.J04Z, 0RS.J0ZZ, 0RS.K04Z, 0RS.K0ZZ, 0RS.L04Z, 0RS.L05Z, 0RS.L0ZZ, 0RS.M04Z, 0RS.M05Z, 0RS.M0ZZ, 0RT.E0ZZ, 0RT.F0ZZ, 0RT.G0ZZ, 0RT.H0ZZ, 0RT.J0ZZ, 0RT.K0ZZ, 0RT.L0ZZ, 0RT.M0ZZ;

	CPT and HCPCS Codes: 22532, 22808, 23802, 25443, 26357, 26842, 27440, 28086, 28730, 29838, 22533, 22810, 23929, 25444, 26358, 26843, 27441, 28088, 28735, 29840, 22534, 22812, 24102, 25445, 26370, 26844, 27442, 28260, 28737, 29844, 22548, 22818, 24360, 25446, 26372, 26850, 27443, 28261, 28740, 29845, 22554, 22819, 24361, 25447, 26373, 26852, 27445, 28262, 28750, 29848, 22556, 22840, 24362, 25800, 26418, 26860, 27446, 28264, 28755, 29860, 22558, 22841, 24363, 25805, 26420, 26861, 27447, 28270, 28760, 29861, 22585, 22842, 24365, 25810, 26426, 26862, 27580, 28272, 28899, 29863, 22590, 22843, 24366, 25820, 26428, 26863, 27599, 28290, 29805, 29870, 22595, 22844, 24800, 25825, 26432, 26989, 27625, 28292, 29806, 29873, 22600, 22845, 24802, 25830, 26433, 27054, 27626, 28293, 29820, 29875, 22610, 22846, 24999, 25999, 26434, 27130, 27700, 28294, 29821, 29876, 22612, 22847, 25105, 26130, 26437, 27284, 27702, 28296, 29822, 29884, 22614, 22851, 25118, 26135, 26530, 27286, 27703, 28297, 29823, 29895, 22630, 22899, 25119, 26140, 26531, 27299, 27870, 28298, 29827, 29897, 22632, 23105, 25332, 26145, 26535, 27334, 27871, 28299, 29830, 29898, 22800, 23470, 25337, 26350, 26536, 27335, 27899, 28705, 29835, 29899, 22802, 23472, 25441, 26352, 26820, 27437, 28070, 28715, 29836, 29900, 22804, 23800, 25442, 26356, 26841, 27438, 28072, 28725, 29837, 29901 **ICD-9 Codes:** V81.0, V81.1, V81.2; **ICD-10 Codes:** Z13.6;
Lipid testing	**CPT and HCPCS Codes:** 80061, 82465, 83695, 83698, 83700, 83701, 83704, 83715, 83716, 83718, 83719, 83721, 84478, G8725
Liver function testing	**CPT and HCPCS Codes:** 80054, 80058, 80076
Long-term (current) use of other medications	**ICD-9:** V58.69; **ICD-10:** Z798.91, Z798.99

Lower back pain		**ICD-9:** 715, 721, 722, 724, 729; **ICD-10:** M4.716, M15.0, M15.1, M15.2, M15.3, M15.8, M15.9, M16.10, M16.9, M17.10, M17.5, M18.9, M19, M43.27, M43.8X9,M46.45, M46.47, M47.10, M47.12, M47.14, M47.812, M47.814, M47.817, M47.819, M48.00, M48.04, M48.06, M48.08, M48.10, M48.20, M48.30, M48.9,M50.00, M50.20, M50.30, M50.80, M50.90, M51.04, M51.05, M51.06, M51.07, M51.24, M51.25, M51.26, M51.27, M51.34, M51.35, M51.36, M51.37, M51.44, M51.45, M51.46, M51.47, M51.84, M51.85, M51.86, M51.87, M51.9, M53.2X7, M53.2X8, M53.3, M53.9, M54.08, M54.10, M54.14, M54.15, M54.16, M54.17, M54.3, M54.5, M54.6, M54.89, M54.9, M60.9, M70.98, M72.9, M79.0, M79.1, M79.2, M79.3, M79.4, M79.5, M79.609, M79.7, M79.81, M79.89, M79.9, M79.A19, M79.A3, M79.A9, M96.1, M533, M4328, MM46.40
Myocardial infarction	Encounter type = "IP"	**ICD-9:** 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91; **ICD-10:** I21.09, I21.19, I21.111, I21.119, I21.29, I21.3, I21.4
Rheumatology visits (count)	Ambulatory visits	Encounter type = "AV" and Provider Type = "66", "300", "450"
Old myocardial infarction		**ICD-9:** 412; **ICD-10:** I25.2
Osteoporosis		**ICD-9:** 733.0; **ICD-10:** M81.0, M81.8
Outpatient visit for infection		Encounter type = "AV", "ED", "ER", "NH", or "HH" for a visit involving an infection
Physical therapy		**CPT and HCPCS Codes:** 29540, 97001, 97002, 97003, 97004, 97110, 97112, 97113, 97116, 97530, 97535, 97750
Psoriatic arthritis		**ICD-9:** 696.6; **ICD-10:** L405.4, L405.9
Respiratory failure		**ICD-9:** 518.81, 518.83, 518.84; **ICD-10:** J96.00, J96.10, J96.20, J96.90
Rheumatoid arthritis		**ICD-9:** 714; **ICD-10:** M05.00, M05.10, M05.30, M05.60, M06.1, M06.4, M06.9, M08.00, M08.3, M08.40, M12.00
Screening mammogram		**ICD-9:** V76.11, V76.12; **ICD-10:** Z12.31
Sex (female)		BENE_SEX_IDENT_CD = 2
Sjogren's syndrome		**ICD-9:** 710.2; **ICD-10:** M35.00, M35.01

Tuberculosis or tuberculosis screening	**ICD-9:** 010 - 018; **ICD-10:** A11.789, A15.0, A15.4, A15.5, A15.6, A15.7, A15.8, A17.0, A17.1, A17.81, A17.82, A17.9, A18.01, A18.02, A18.03, A18.10, A18.11, A18.12, A18.13, A18.14, A18.15, A18,16, A18.17, A18.18, A18.2, A18.31, A18.32, A18.39, A18.4, A18.50, A18.51, A18.52, A18.53, A18.54, A18.59, A18.6, A18.7, A18.81, A18.84, A18.85, A18.89, A19.2, A19.8, A19.9; **CPT and HCPCS Codes:** 3510F, 86480, 86580
Unstable angina	**ICD-9:** 41.1; **ICD-10:** I20.0

Table A2.3. Biologic, phototherapy, disease-modifying antirheumatic drug (DMARD), and other thapery codes for predictor definition.

Variable	**Code type**
Abatacept	NDC and HCPCS codes
Anticoagulants	NDC codes
Apremilast	NDC codes
Adalimumab	NDC and HCPCS codes
Certolizumab	NDC and HCPCS codes
Etanercept	NDC and HCPCS codes
Golimumab	NDC and HCPCS codes
Hydroxychloroquine	NDC codes
Infliximab	NDC and HCPCS codes
Methotrexate	NDC and HCPCS codes
Parenteral therapies	NDC and HCPCS codes
Phototherapy	CPT codes
Rituximab	NDC and HCPCS codes
Secukinumab	NDC codes
Sulfasalazine	NDC codes
Statins	NDC codes
Tocilizumab	NDC and HCPCS codes
Tofacitinib	NDC codes
Ustekinumab	NDC and HCPCS codes
	Variable type
Biologic therapies (count)	Continuous variable
DMARD therapies (count)	Continuous variable
Oral steroids dose	Continuous variable

Table A2.4. Coefficients between claims-based variables and mild-to-moderate BSA as selected via LASSO variable selection.

Claimes-based variables	Coefficient
Adalimumab, procedure or prescription within 6 month	1.39
Depression	0.06
Dyslipidemia, ever	-0.18
Female sex	-1.35
Fibromyalgia within 12 months	-1.97
Influenza vaccination, procedure or diagnosis within 12	-0.58
Long term drug use within 12 months	-0.02
Lower back pain within 12 months	-0.27
Myocardial infarction with stroke	1.53
No CCI visits, ever	0.85
Osteoarthritis, ever	-0.18
Prior myocardial infarction, ever	-3.11
Procedure in a skilled nursing facility	-0.33
Treatment with narcotics, within 6 to 12 months	0.67
Treatment with statins, within 6 to 12 months	-0.62
Visit for infection within 12 months, inpatient	1.10
Visit for infection within 12 months, outpatient	-0.16

CCI: Charlson Comorbidity Index. Visits of interest include those for the following diangoses: myocardial infarction, congestive heart disease, peripheral vascular disorder, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, acquired immunodeficieny syndrome

Appendix 2 Figures

Figure A2.1. Cohort selection process.

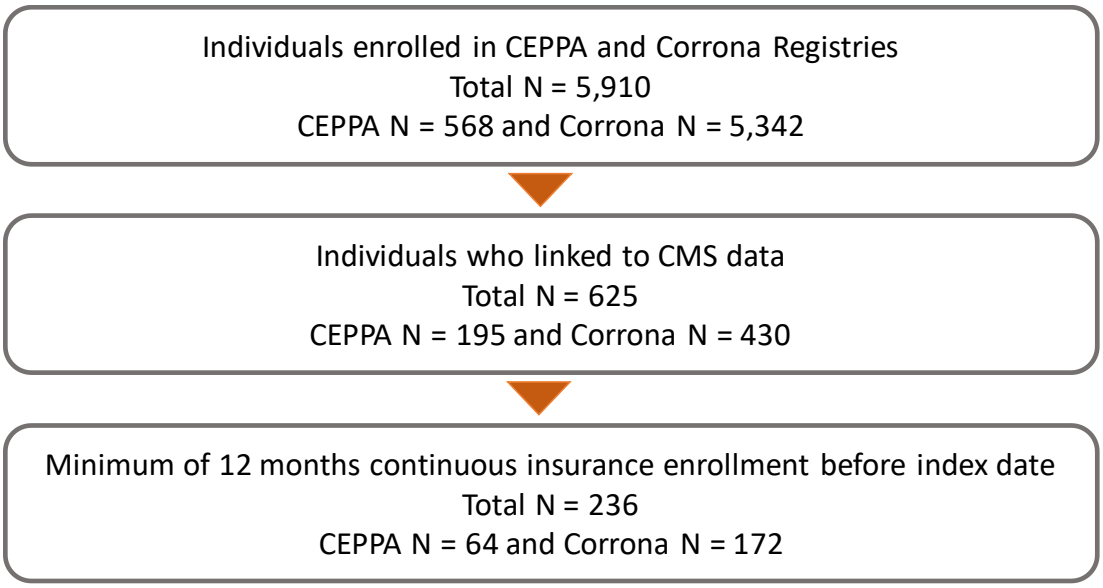


Figure A2.2. Plot of lambda values from cross-validation of LASSO regression and variable selection model.

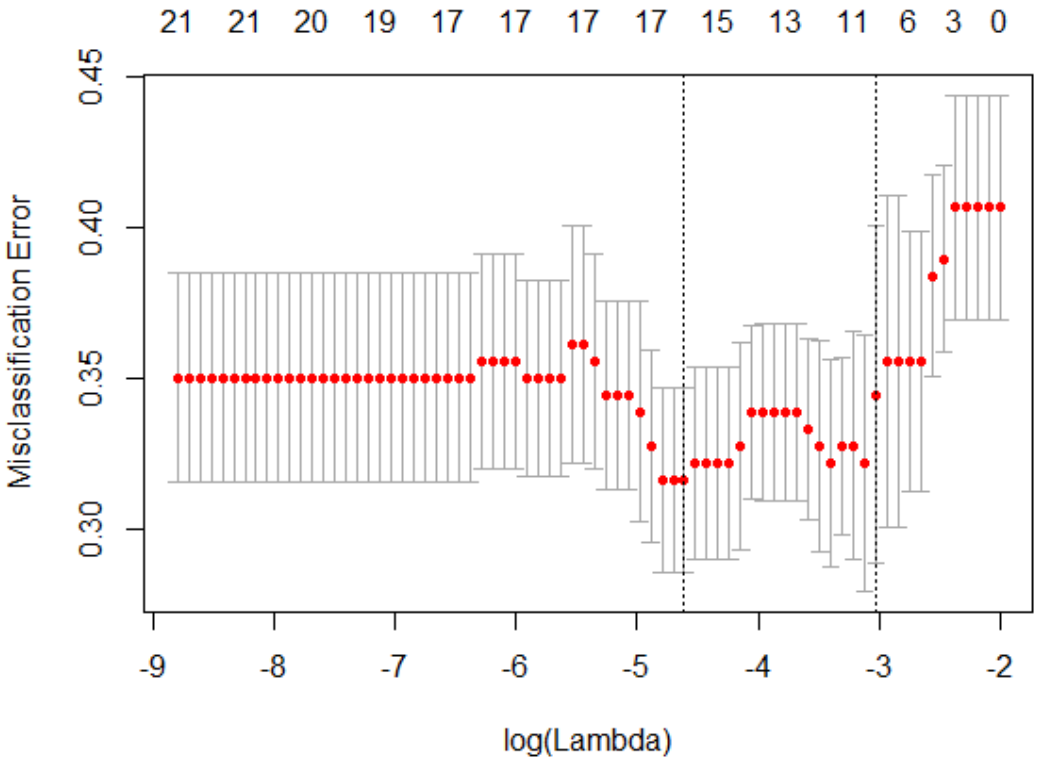
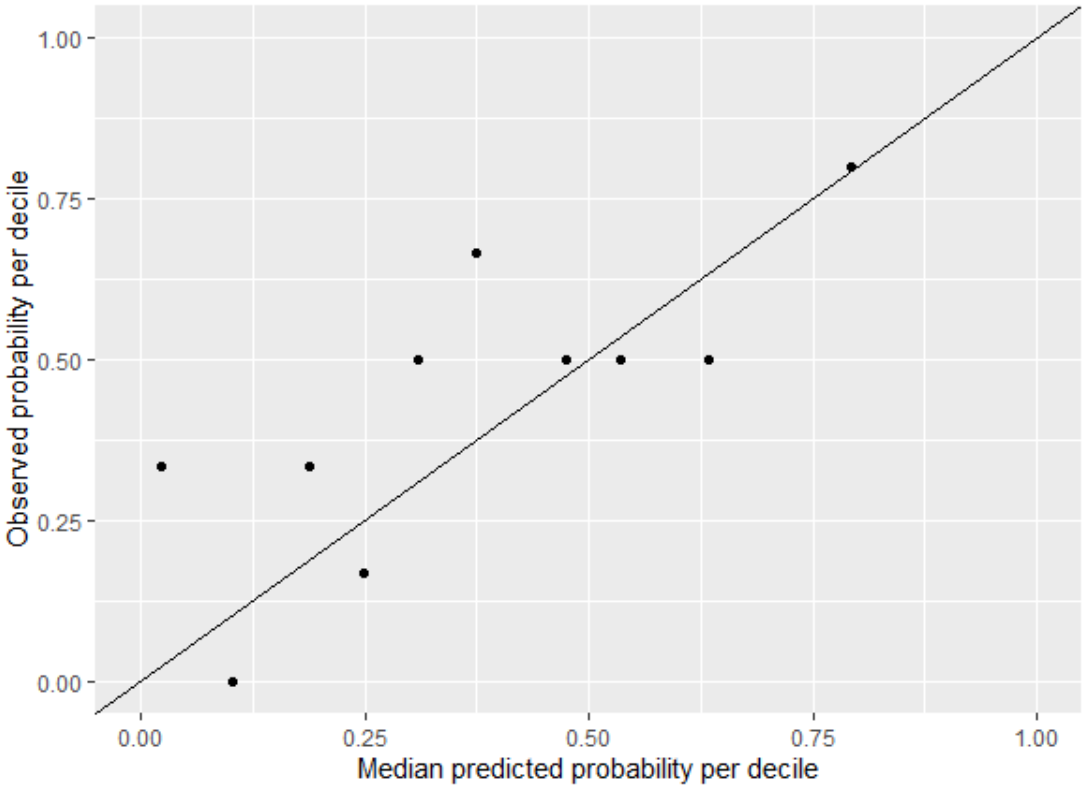


Figure A2.3. Calibration plot of the median observed probabilities per decile and the median predicted probabilities per decile for the severity score as a continuous variable.



Appendix 3. Supplemental materials for “Comparative Infectious Risk of Biologic Therapies for Psoriasis Among Real-World Users in Medicare”

Appendix 3 Tables

Table A3.1. Propensity score variables for TNF-α and IL-12/23 blockers compairson and their unweighted and weighted standardized differences.

Variable name	Unweighted standardized differences	Weighted standardized differences
Age	-0.1193	-0.0126
Ankylosing spondylitis	-0.0509	0.0016
Anxiety	0.0338	0.0076
BMI	0.097	0
Chronic heart disease	-0.0802	-0.0049
Crohn's disease	0.0231	0.0037
Dactylitis	0.0023	0.0009
Depression	0.0133	0.0148
Diabetes	0.0349	0.0005
Dyslipidemia	0.0194	-0.0027
Enthesitis	-0.0007	-0.0027
Flu vaccination	0.0569	-0.0061
Heart failure	0.0324	0.0019
Hepatitis B	0.0164	-0.0013
Hepatitis C	-0.0367	-0.0022
Topical steroid dose	0.0192	0.0016
Hypertension	0.0268	-0.0058
Inflammatory bowel disease	-0.0048	0.0018
Multiple sclerosis	0.0783	0.0002
Nonmelanoma skin cancer	-0.022	-0.0006
Number of dermatologist visits	0.2835	0.0108
Number of liver function tests	-0.0899	0.001
Number of medications	0.0308	-0.0018
Number of platelet tests	-0.0241	-0.0017
Number of rheumatologist visits	0.2517	-0.0013
Opportunistic infections	0.0209	0.001
Oral steroid dose	-0.0248	-0.0076
Procedure for inflammatory markers	-0.1006	-0.0073
Procedure for intralesional injection	-0.0163	0.0041
Procedure for lipid lab	0.0118	0.0006
Psoriatic arthritis	-0.108	0.0049
Race	0	0.0361
Region	0.0634	0.0329
Rheumatoid arthritis	-0.2099	-0.0103
Sex	0.0124	0.0028
Treatment for hypertension	0.0349	-0.0002
Treatment with antibiotics	-0.0195	0.0002
Treatment with beta blockers	0.0128	-0.0037
Treatment with statins	0.0396	-0.0024
Ulcerative colitis	-0.0232	0.0001

Table A3.2. Propensity score variables for TNF-α and IL-117 blockers compairson and their unweighted and weighted standardized differences.

Variable name	Unweighted standardized differences	Weighted standardized differences
Age	-0.3168	-0.0209
Ankylosing spondylitis	-0.0106	-0.0134
Anxiety	0.1471	0.0273
BMI	0.2333	0.024
Chronic heart disease	-0.2585	-0.0314
Crohn's disease	-0.1144	0.0261
Dactylitis	-0.0936	-0.0003
Depression	0.0641	0.0275
Diabetes	0.1006	-0.0091
Dyslipidemia	0.0131	0.0233
Enthesitis	0.0222	-0.0054
Flu vaccination	0.0478	0.0047
Heart failure	-0.0129	0.0312
Hepatitis B	0.0128	-0.004
Hepatitis C	-0.0279	-0.0007
Hypertension	0.0289	-0.0083
Inflammatory bowel disease	-0.1606	0.0263
Multiple sclerosis	0.0394	0.01
Nonmelanoma skin cancer	-0.1594	-0.0211
Number of dermatologist visits	0.2597	0.0197
Number of liver function tests	-0.1383	-0.0007
Number of medications	0.0604	-0.0055
Number of platelet tests	0.0283	-0.0037
Number of rheumatologist visits	0.2323	-0.0094
Opportunistic infection	-0.0114	-0.0118
Oral steroid dose	-0.0199	-0.0145
Procedure for inflammatory markers	0.0206	0.0037
Procedure for intralesional injection	0.0214	0.0096
Procedure for lipid lab	0.0081	-0.0053
Psoriatic arthritis	-0.0953	-0.0095
Race	0.0704	0
Region	0.1561	0.0276
Rheumatoid arthritis	-0.1603	-0.0015
Sex	0.0437	0.0206
Topical steroid dose	0.0281	0.007
Treatment for hypertension	0.021	-0.0192
Treatment with antibiotics	0.0007	-0.0009
Treatment with beta blockers	0.0251	0.0011
Treatment with statins	0.0334	-0.0016
Ulcerative colitis	-0.0807	0.0219

Table A3.3. Propensity score variables for IL-12/23 and IL-17 blockers compairson and their unweighted and weighted standardized differences.

Variable name	Unweighted standardized differences	Weighted standardized differences
Age	-0.1936	0.0026
Ankylosing spondylitis	0.0406	-0.0057
Anxiety	0.1134	0.0026
BMI	0.136	0
Chronic heart disease	-0.1787	-0.009
Crohn's disease	-0.133	0.0155
Dactylitis	-0.0958	0.0025
Depression	0.0508	0.0122
Diabetes	0.0656	0.0011
Dyslipidemia	-0.0063	0.0172
Enthesitis	0.0229	-0.0001
Flu vaccination	-0.009	0.0069
Heart failure	-0.0452	0.0128
Hepatitis B	-0.0037	0.0092
Hepatitis C	0.0089	-0.0006
Hypertension	0.002	0.0038
Inflammatory bowel disease	-0.1562	0.0172
Multiple sclerosis	-0.0412	0.0091
Nonmelanoma skin cancer	-0.1387	-0.0037
Number of dermatologist visits	0.1689	0.0019
Number of liver function tests	-0.0499	0.0028
Number of medications	0.0298	-0.0001
Number of platelet tests	0.0528	-0.003
Number of rheumatologist visits	0.3656	0.006
Opportunistic infection	-0.0324	-0.0103
Oral steroid dose	0.033	-0.0064
Procedure for inflammtory markers	0.1212	0.0072
Procedure for intralesional injection	0.0377	0.0042
Procedure for lipid lab	-0.0038	0.0052
Psoriatic arthritis	0.0127	0.0165
Race	0.0704	0.0361
Region	0.1463	0.0317
Rheumatoid arthritis	0.0498	0.0156
Sex	0.0315	0.0042
Topical steroid dose	0.0018	0.0033
Treatment for hypertension	-0.0138	-0.0037
Treatment with antibiotics	0.0202	-0.0038
Treatment with beta blockers	0.0123	0.0056
Treatment with statins	-0.0063	0.0005
Ulcerative colitis	-0.0584	0.0122

Table A3.4. Age- and sex-adjusted hazard ratios with 95% confidence intervals of risk of hospitalized infection among those with psoriasis, by severity score quartile and therapy class.

	Adjusted Model
IL-12/23 vs TNF-α blockers	
1st quartile of severity score	0.86 (0.72, 1.03)
2nd quartile of severity score	0.84 (0.68, 1.04)
3rd quartile of severity score	1.03 (0.84, 1.26)
4th quartile of severity score	0.86 (0.70, 1.06)
IL-17 vs TNF-α blockers	
1st quartile of severity score	0.76 (0.53, 1.08)
2nd quartile of severity score	0.70 (0.46, 1.06)
3rd quartile of severity score	1.28 (0.91, 1.80)
4th quartile of severity score	0.63 (0.42, 0.96)
IL-12/23 vs IL-17 blockers	
1st quartile of severity score	0.96 (0.68, 1.34)
2nd quartile of severity score	1.06 (0.71, 1.57)
3rd quartile of severity score	0.68 (0.48, 0.95)
4th quartile of severity score	1.31 (0.85, 2.01)

Appendix 3 Figures

Figure A3.1. Propensity scores for psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

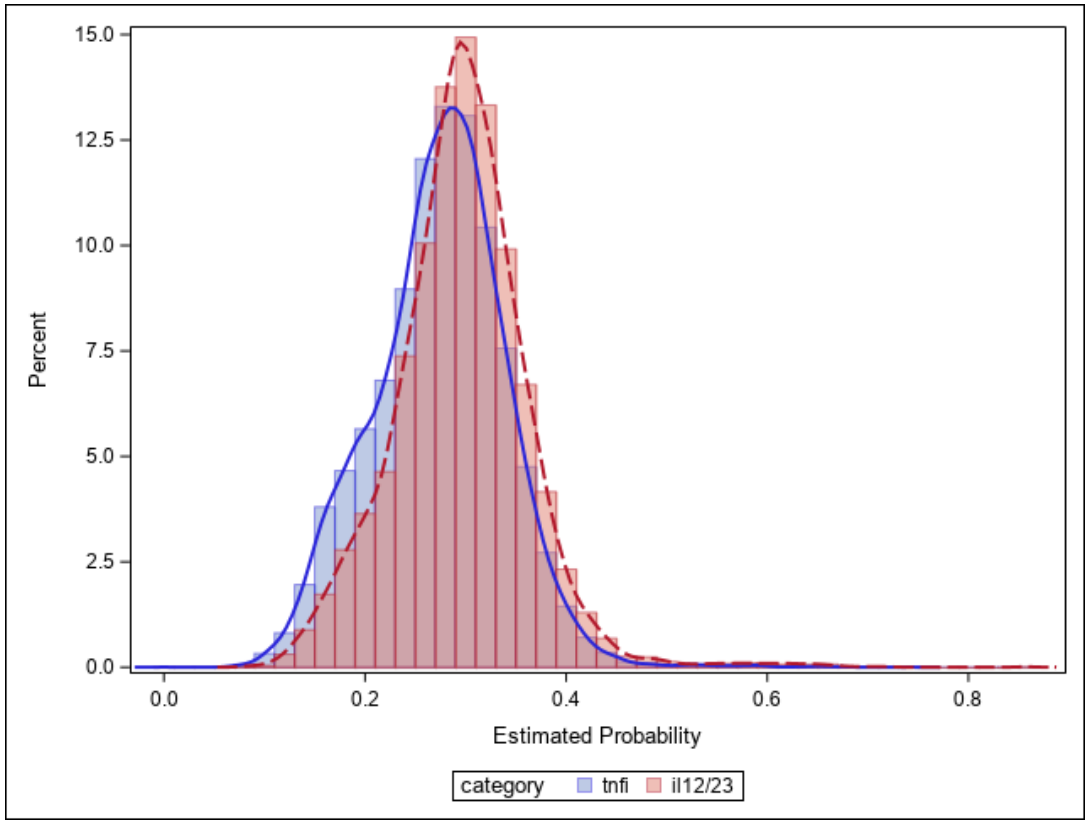


Figure A3.2. Weighted vs. unweighted Standardized Mean Differences for psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

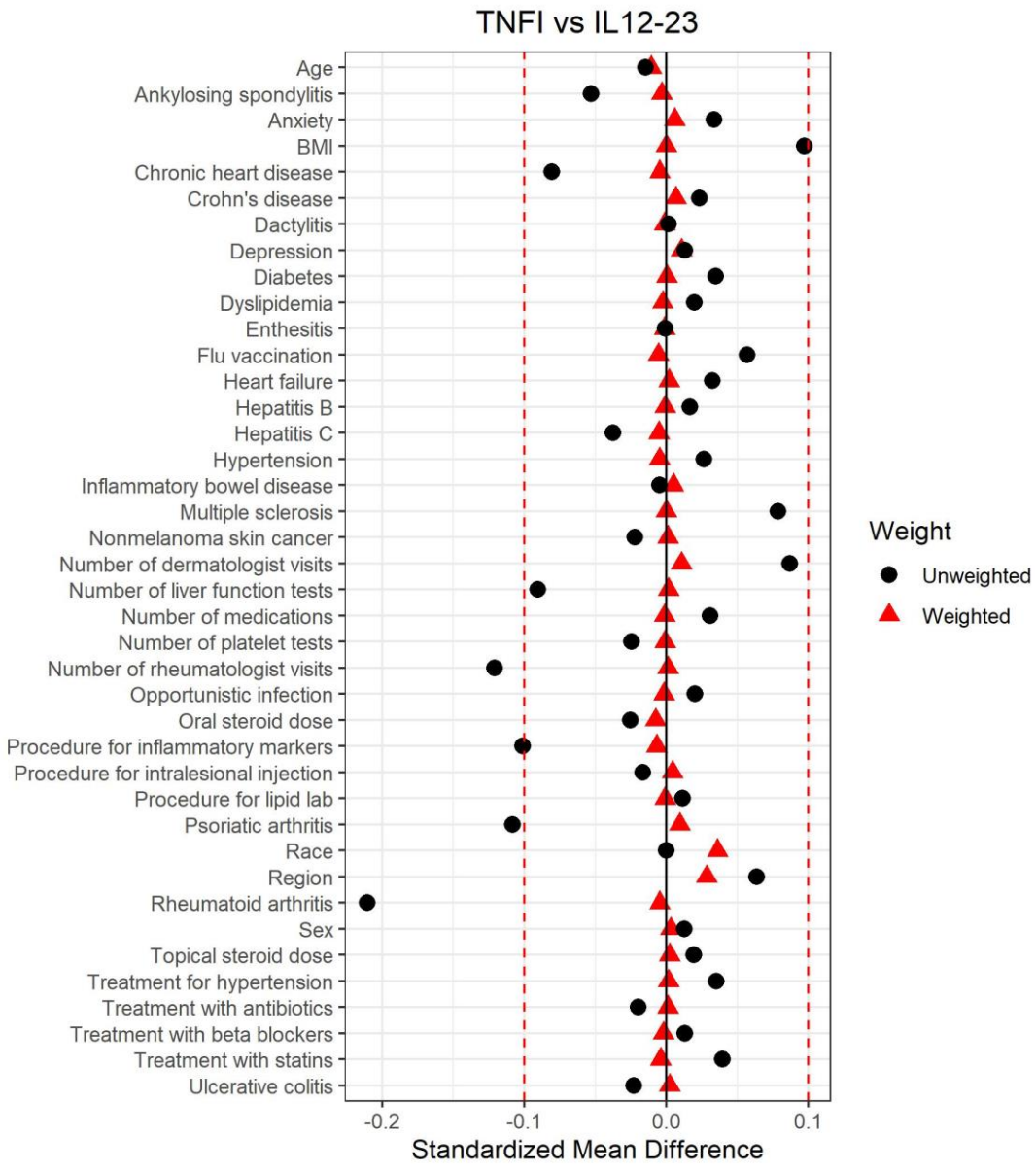


Figure A3.3. Propensity scores for biologic-naïve psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

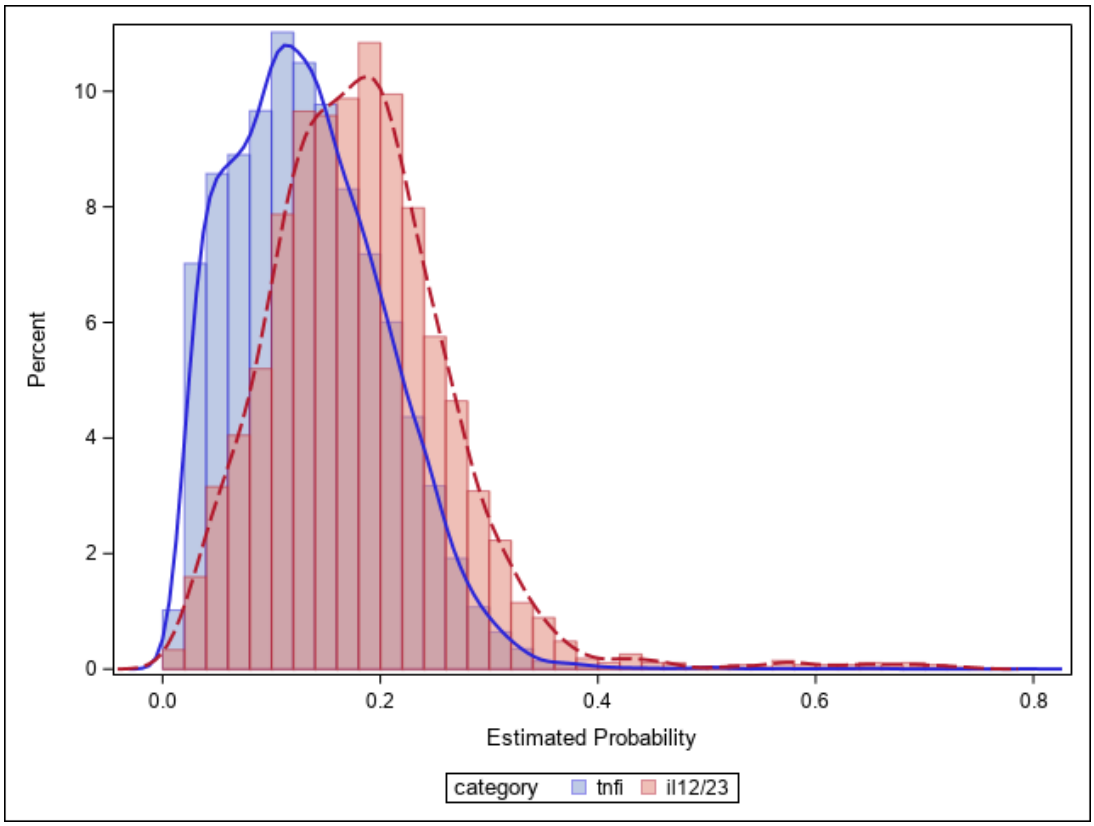


Figure A3.4. Weighted vs. unweighted Standardized Mean Differences for biologic-naïve psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

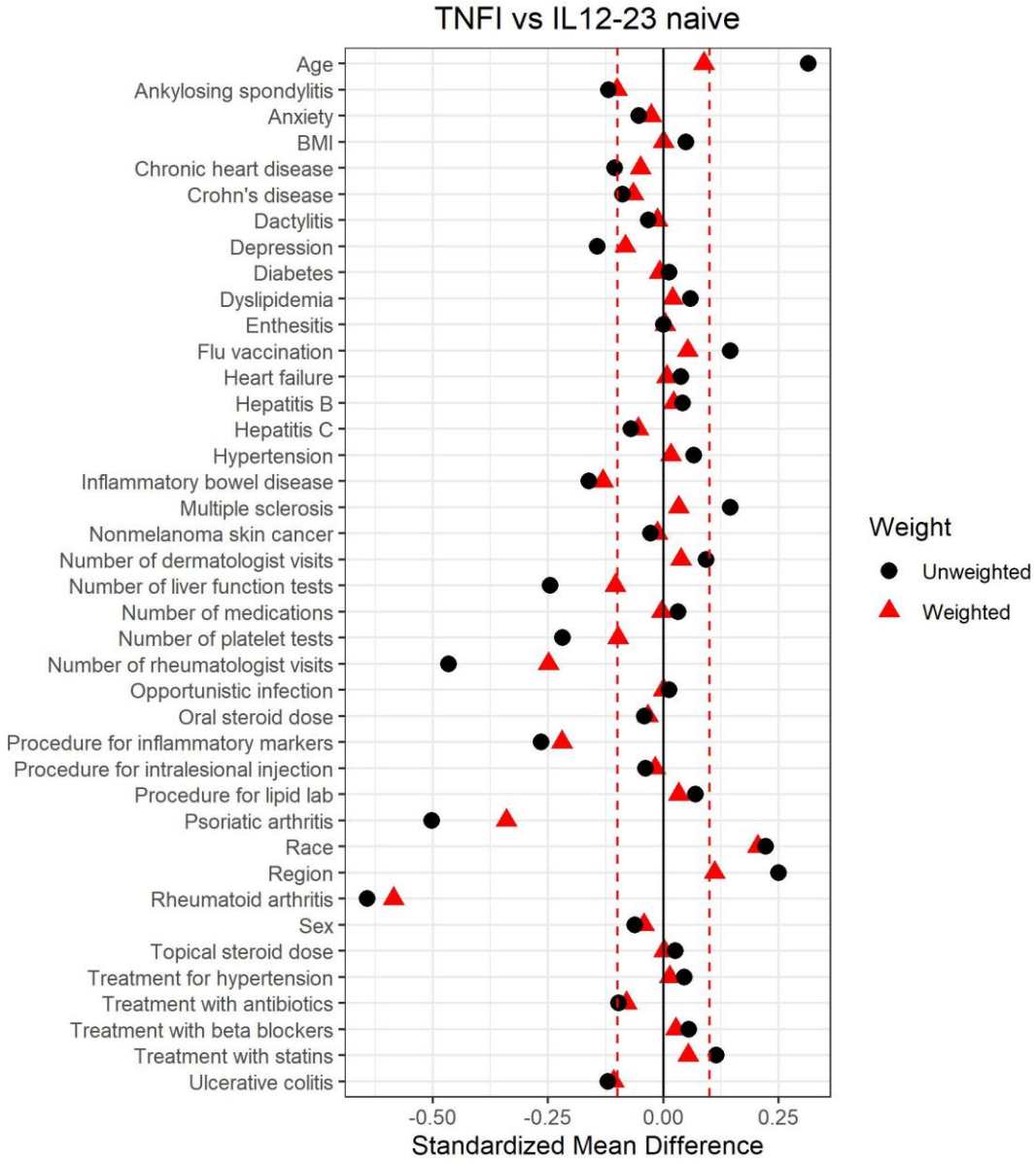


Figure A3.5. Propensity scores for biologic experienced psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

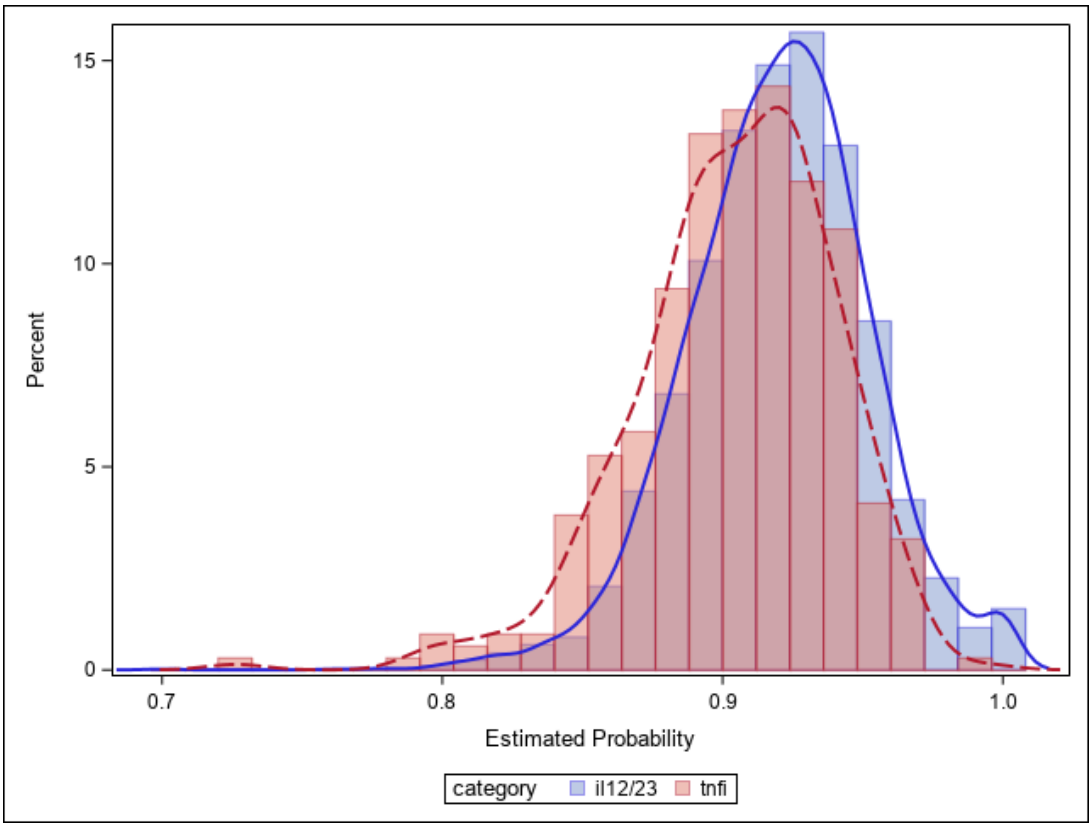


Figure A3.6. Weighted vs. unweighted Standardized Mean Differences for biologic experienced psoriasis patients initiating either TNF-α or IL-12/23 inhibitors.

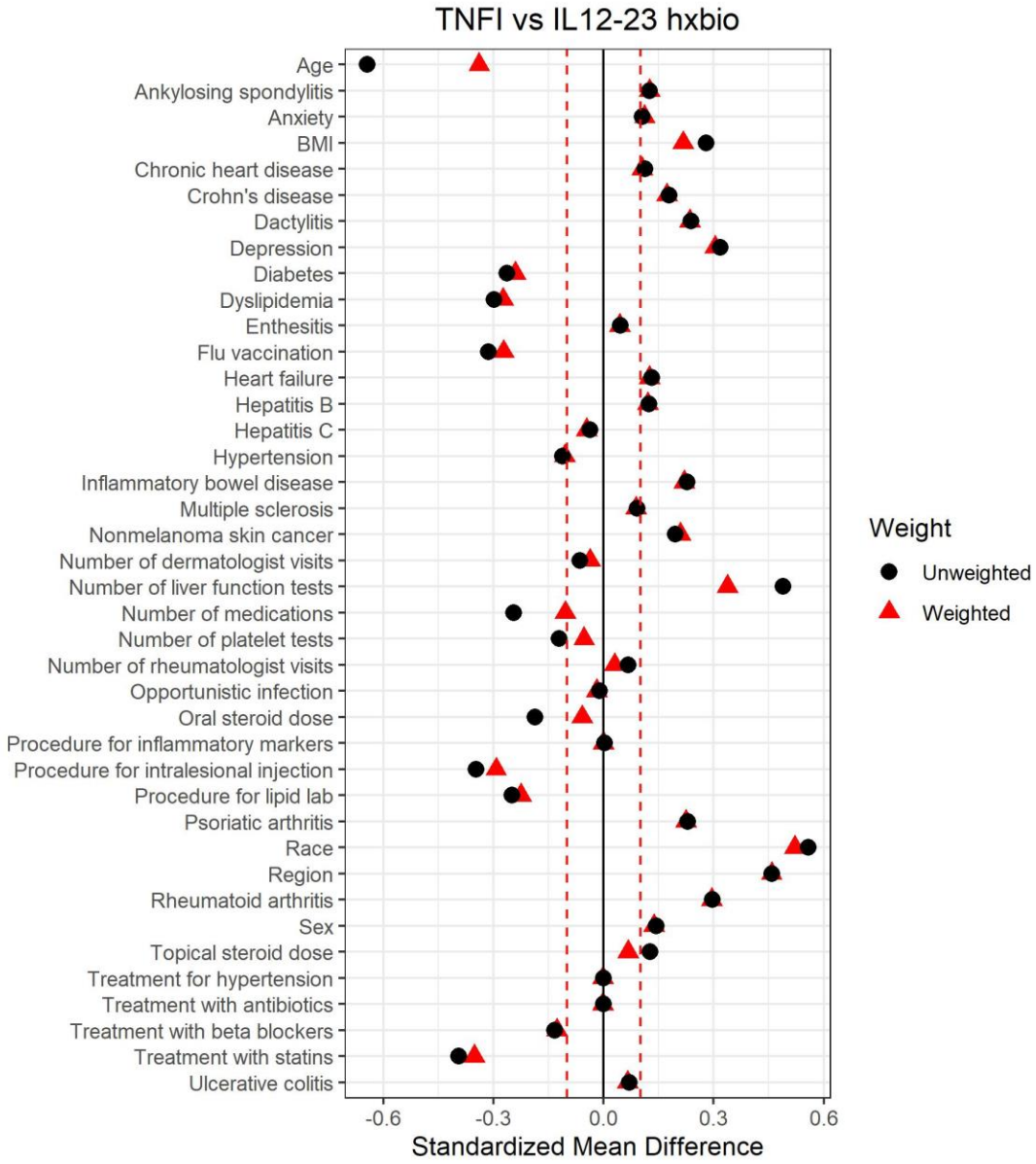


Figure A3.7. Propensity scores for psoriasis patients initiating either TNF-α or IL-17 inhibitors.

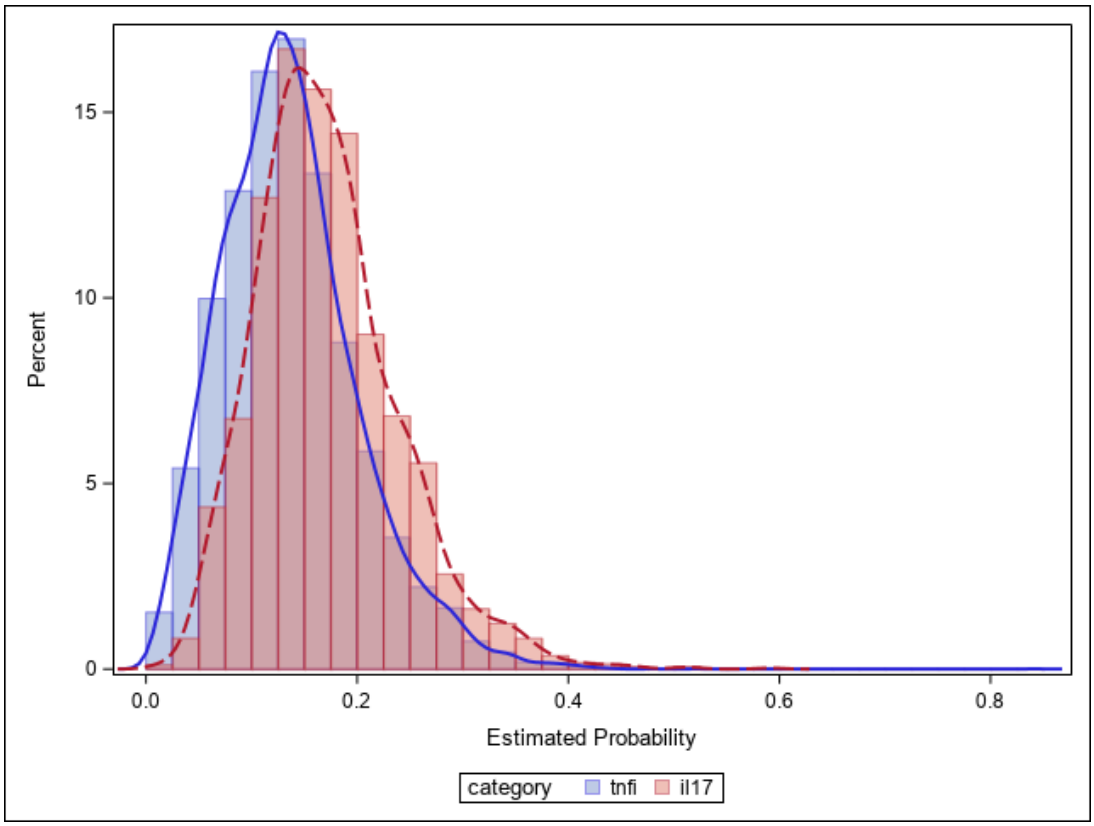


Figure A3.8. Weighted vs. unweighted standardized mean differences for psoriasis patients initiating either TNF-α or IL-17 inhibitors.

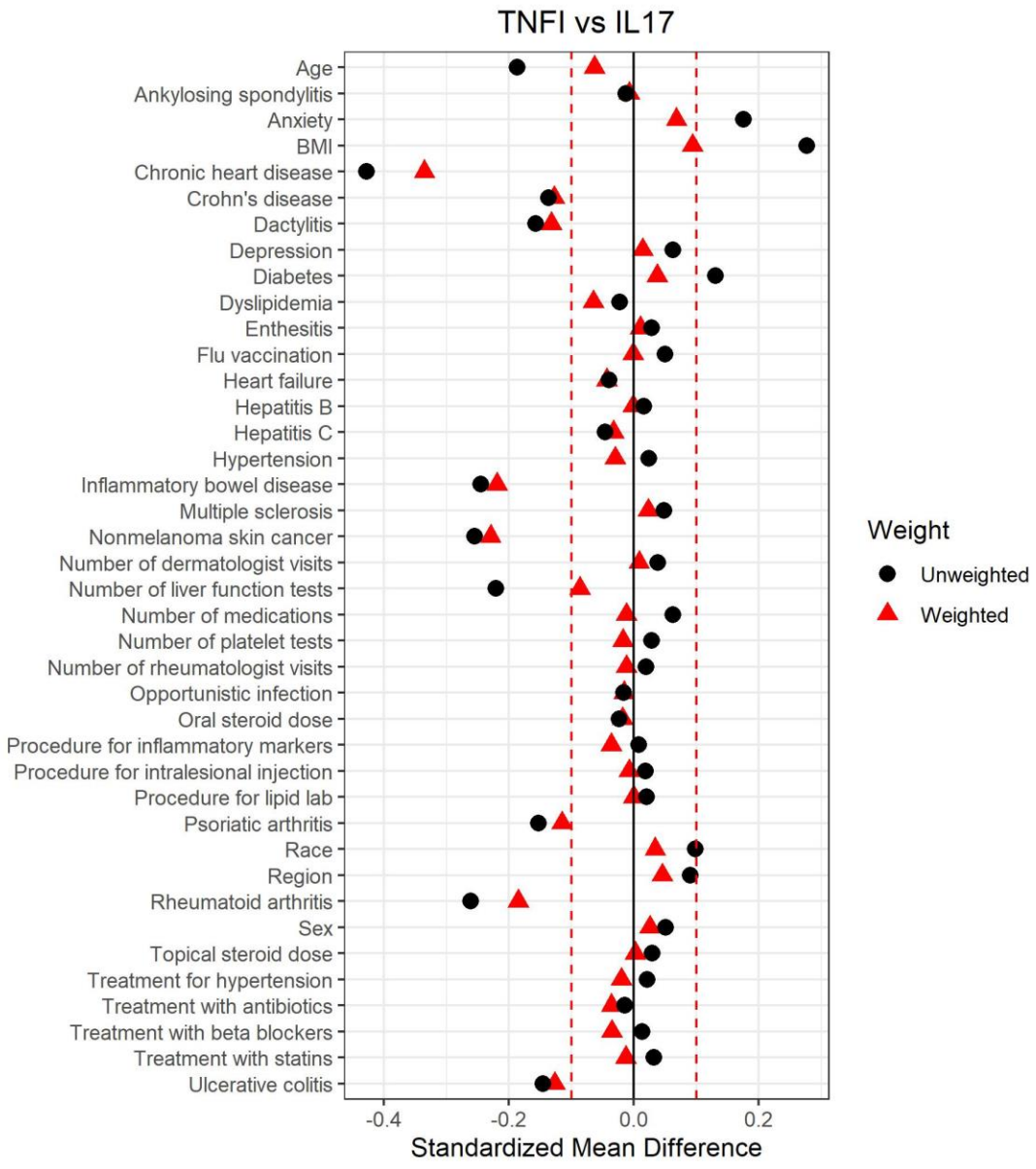


Figure A3.9. Propensity scores for biologic-naïve psoriasis patients initiating either TNF-α or IL-17 inhibitors.

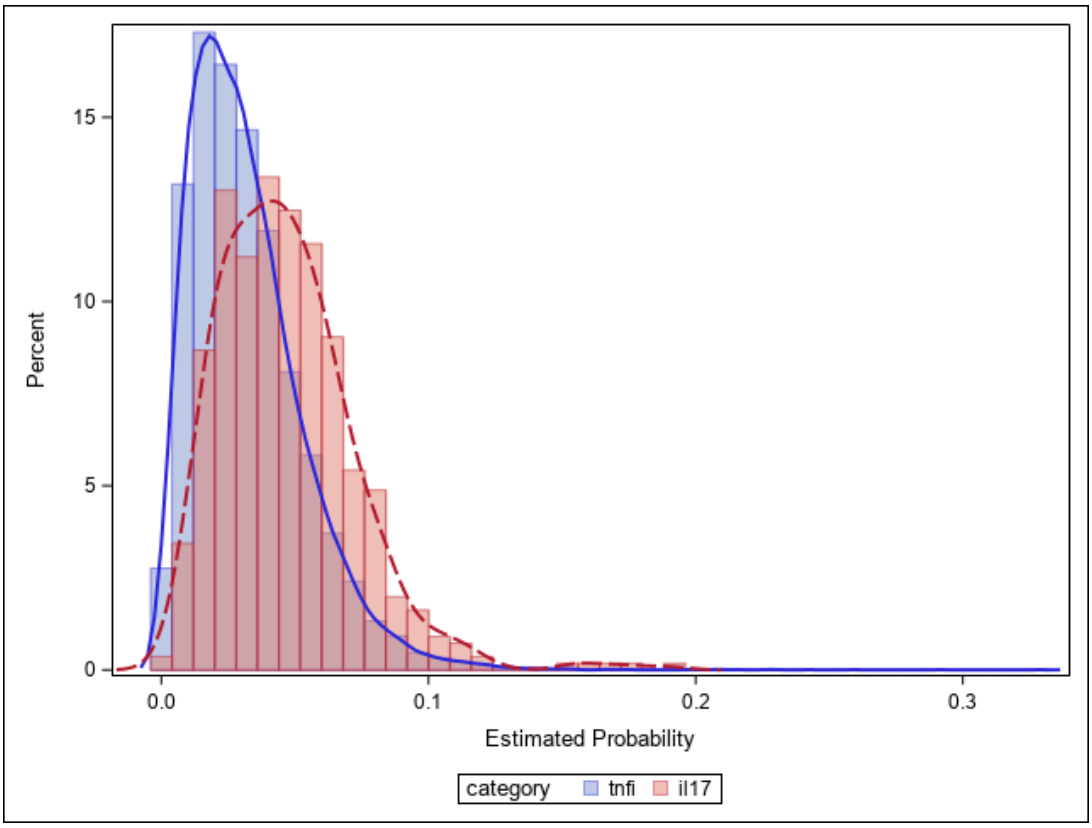


Figure A3.10. Weighted vs. unweighted standardized mean differences for biologic-naïve psoriasis patients initiating either TNF-α or IL-17 inhibitors.

Figure A3.11. Propensity scores for biologic experienced psoriasis patients initiating either TNF-α or IL-17 inhibitors.

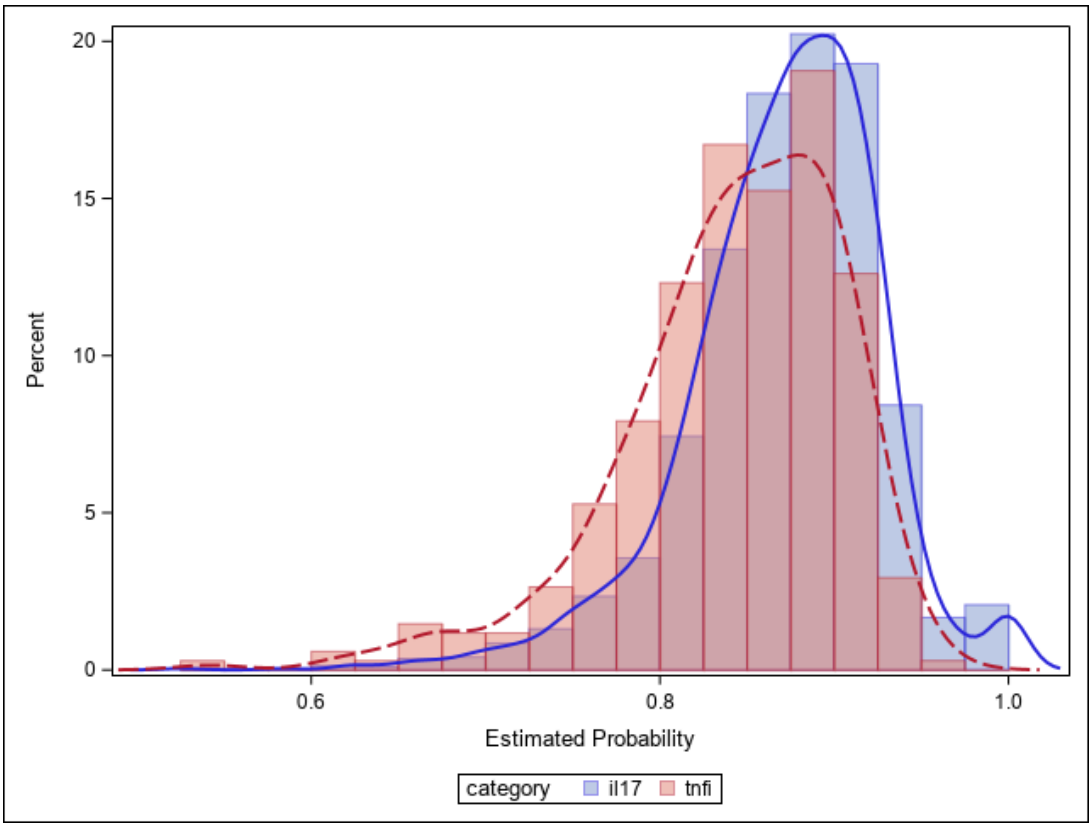


Figure A3.12. Weighted vs. unweighted standardized mean differences for biologic experienced psoriasis patients initiating either TNF-α or IL-17 inhibitors.

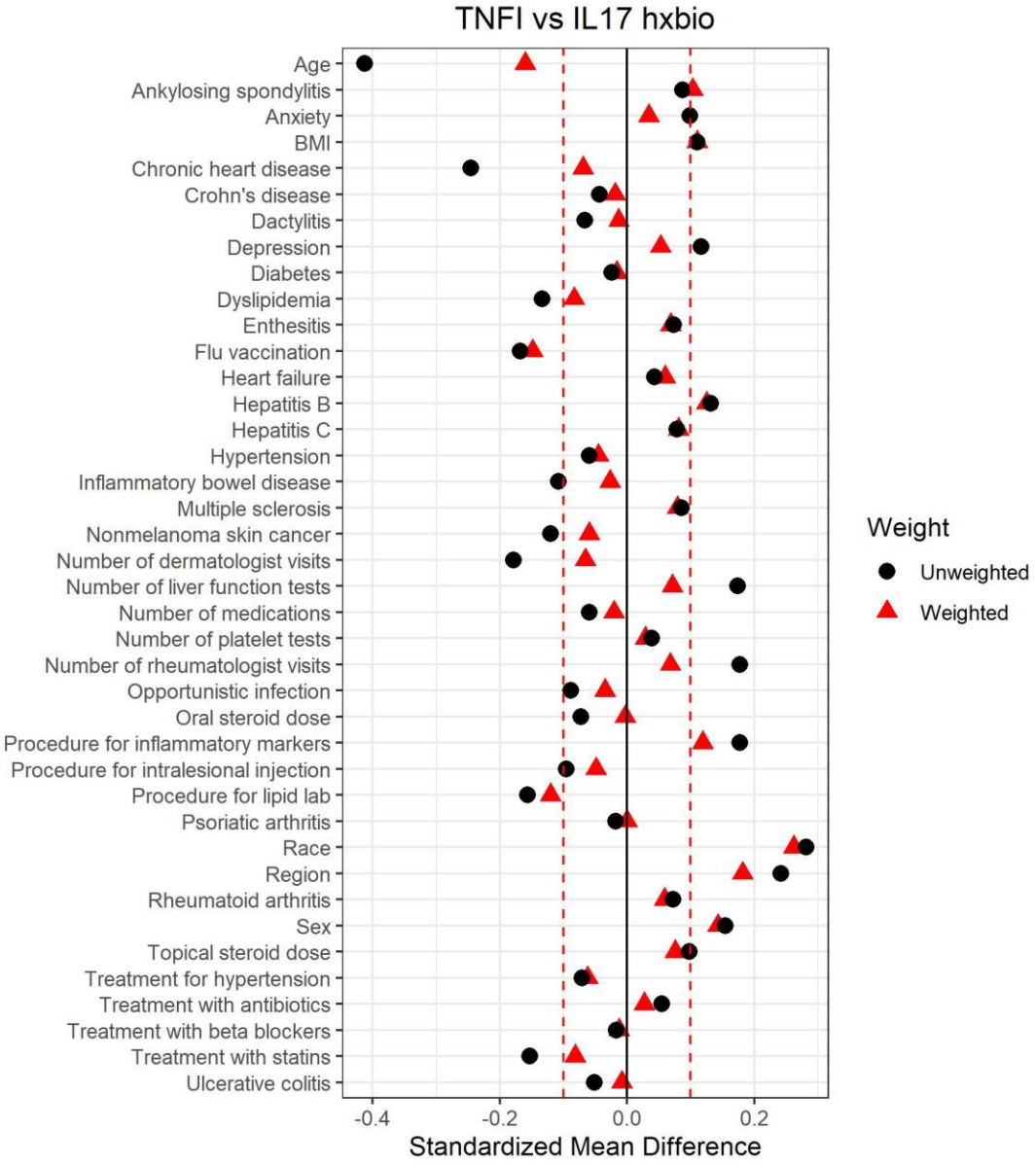


Figure A3.13. Propensity scores for psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.

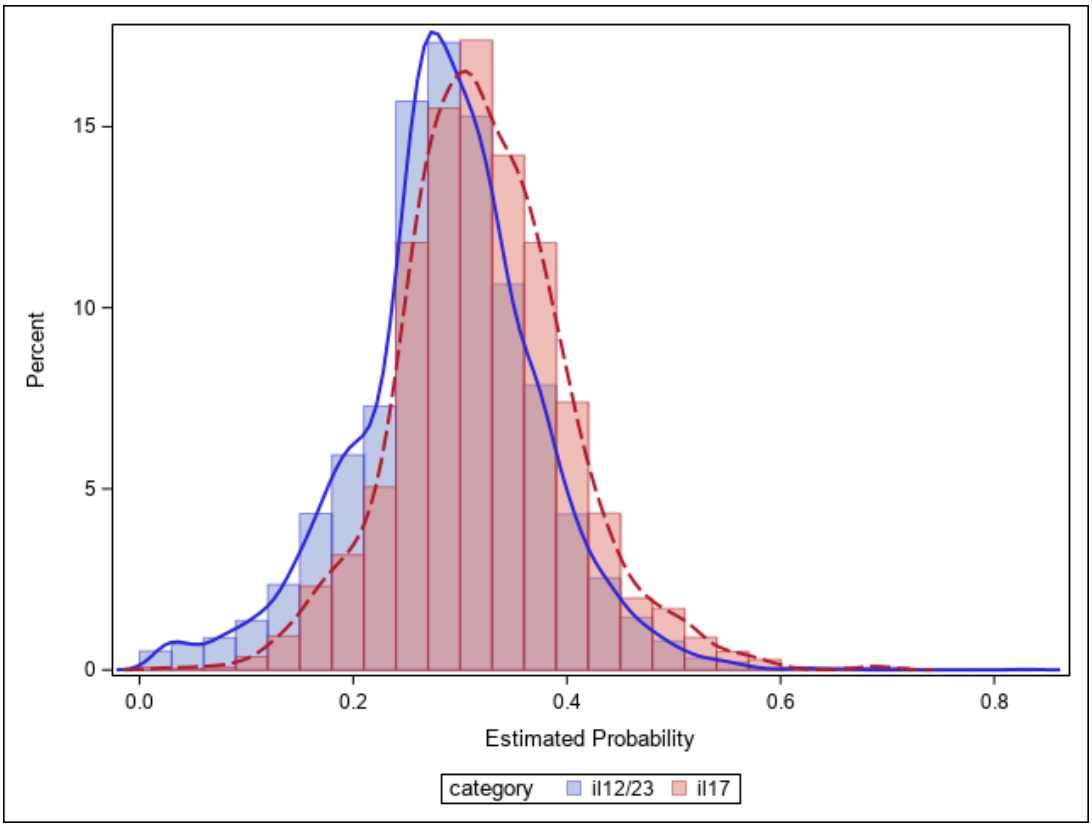


Figure A3.14. Weighted vs. unweighted standardized mean differences for psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.

Figure A3.15. Propensity scores for biologic-naïve psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.

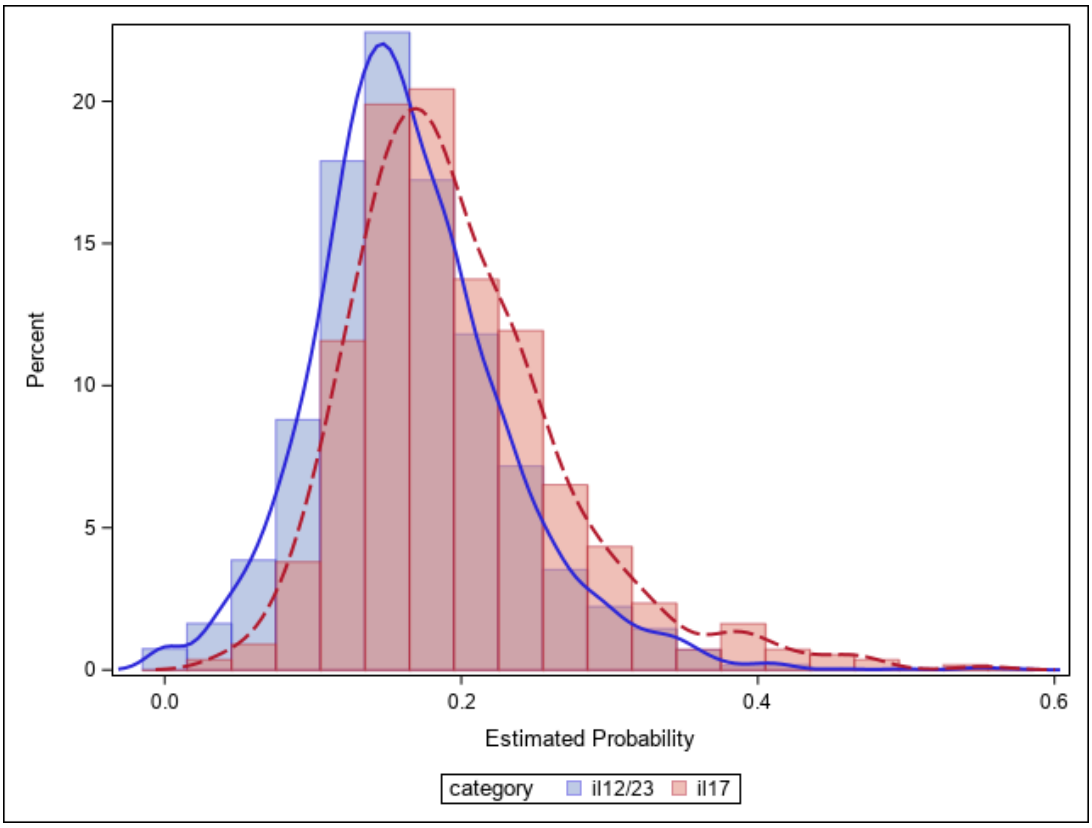


Figure A3.16. Weighted vs. unweighted standardized mean differences for biologic-naïve psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.

Figure A3.17. Propensity scores for biologic experienced psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.

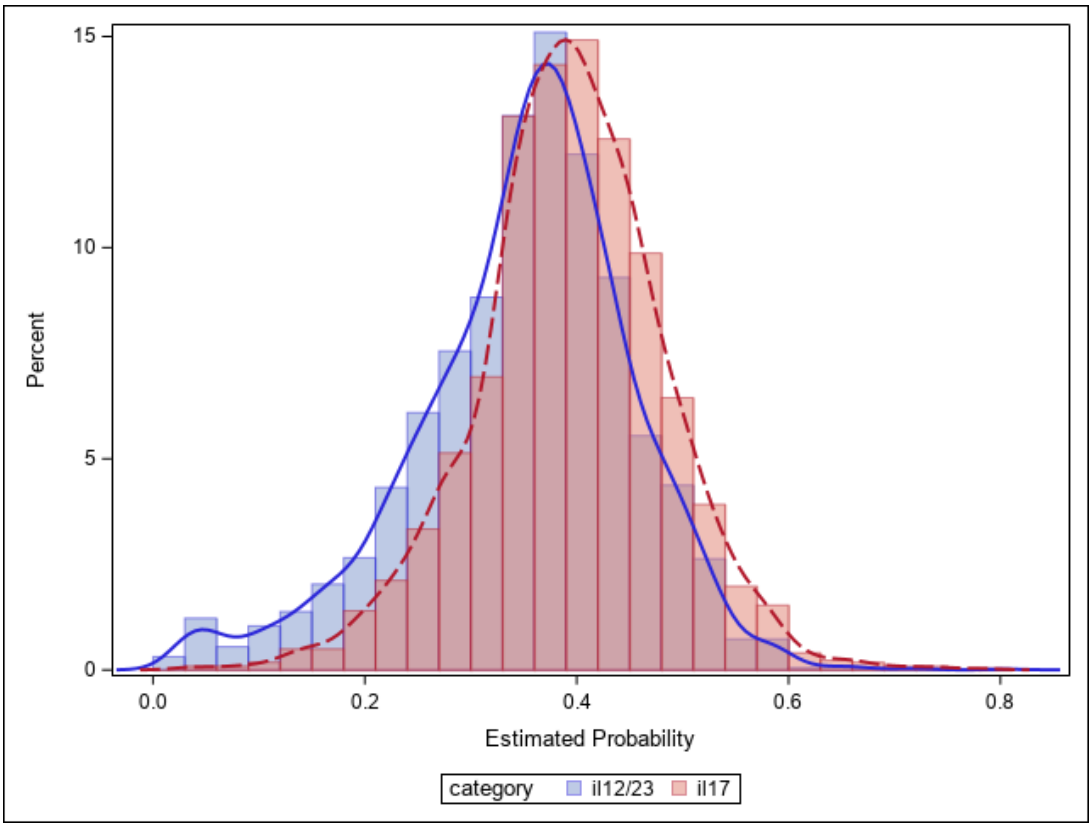
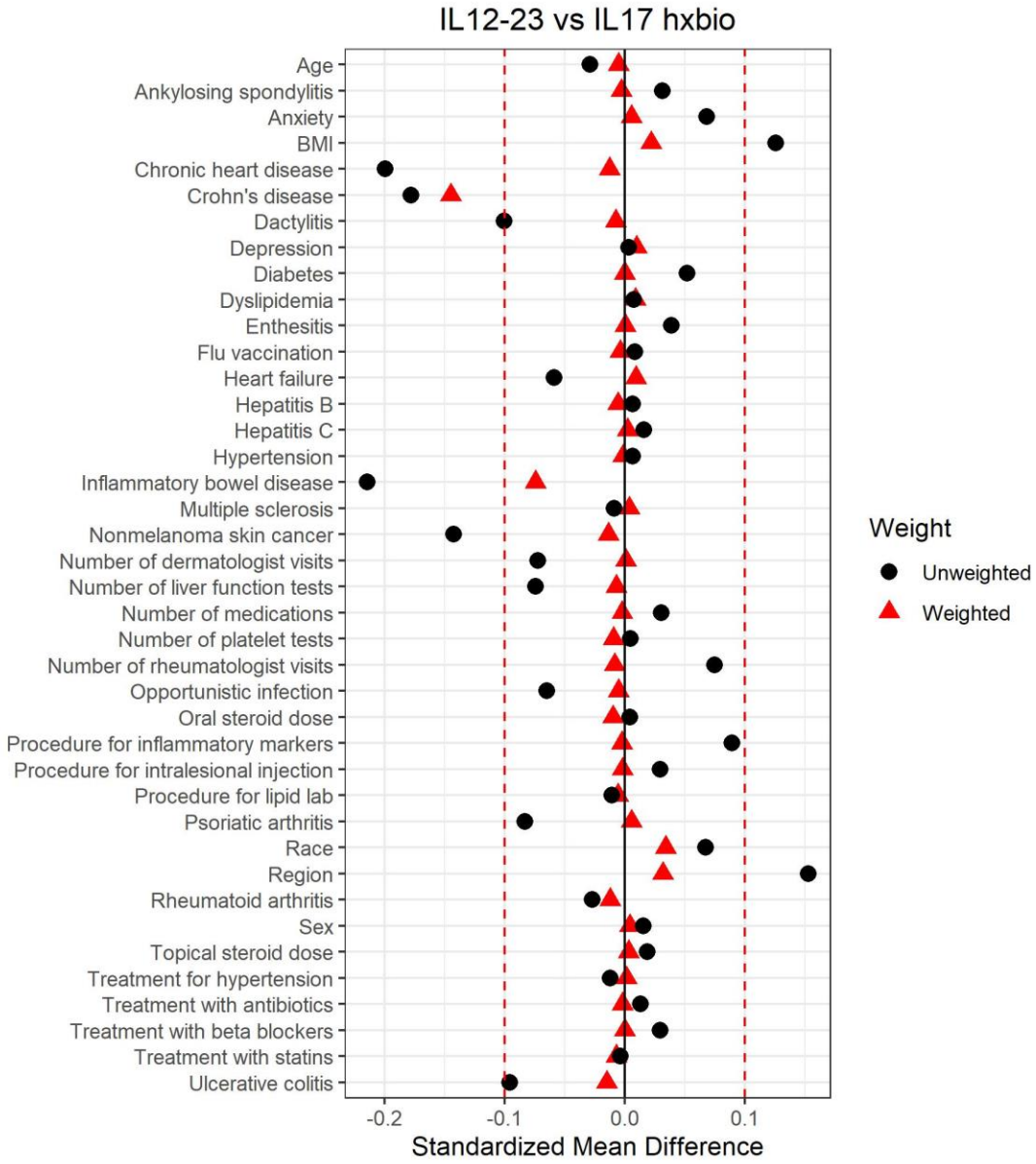


Figure A3.18. Weighted vs. unweighted standardized mean differences for biologic experienced psoriasis patients initiating either IL-12/23 or IL-17 inhibitors.



Appendix 4. Supplemental materials for "Comparative Risk of Infection-Specific Mortality by Therapy for Psoriasis in Medicare data linked to the National Death Index"

Appendix 4 Tables

Table A4.1. List of National Death Index codes for infection-specific mortality and the associated infections with ICD 10 codes.

Code	Description
00100	Certain infectious and parasitic diseases (A00-B99)
00200	Intestinal infectious diseases (A00-A09)
00300	Cholera (A00)
00400	Other intestinal infectious diseases (A01-A08)
00500	Typhoid fever (A01.0)
00600	Paratyphoid fevers and other salmonella infections (A01.1-A01.4, A02)
00700	Shigellosis (A03)
00800	Other bacterial food-borne intoxications (A05)
00900	Amebiasis (A06)
01000	Intestinal infections due to other specified organisms (A04, A07-A08)
01100	Diarrhea and gastroenteritis of infectious origin (A09)
01200	Tuberculosis (A16-A19)
01300	Respiratory tuberculosis (A16)
01400	Other tuberculosis (A17-A19)
01500	Zoonotic and other bacterial diseases (A20-A49)
01600	Plague (A20)
01700	Brucellosis (A23)
01800	Tetanus (A33-A35)
01900	Diphtheria (A36)
02000	Whooping cough (A37)
02100	Scarlet fever and erysipelas (A38, A46)
02200	Meningococcal infection (A39)
02300	Septicemia (A40-A41)
02400	Other zoonotic and bacterial diseases (A21-A22, A24-A32, A42-A44, A48-A49)
02500	Infections with a predominately sexual mode of transmission (A50-A64)
02600	Syphilis (A50-A53)
02700	Cardiovascular syphilis (A52.0)
02800	Neurosyphilis (A52.1-A52.3)
02900	Other and unspecified syphilis (A50-A51, A52.7-A52.9, A53)
03000	Gonococcal infection (A54)

03100	Other infections with a predominately sexual mode of transmission (A55-A64)
03200	Other infections caused by spirochetes, chlamydia or rickettsia (A65-A79)
03300	Lyme disease (A69.2)
03400	Typhus fever (A75)
03500	All other infections caused by spirochetes, chlamydia or rickettsia (A65-A68, A69.0-A69.1, A69.8-A69.9, A70-A74, A77-A79)
03600	Viral diseases (A80-B34)
03700	Acute poliomyelitis (A80)
03800	Rabies (A82)
03900	Arthropod-borne viral encepha1itis (A83-A84, A85.2)
04000	Yellow fever (A95)
04100	Other and unspecified arthropod-borne viral and hemorrhagic fevers (A90-A94, A96-A99)
04200	Herpes viral (herpes simplex) infections (B00)
04300	Zoster (herpes zoster) (B02)
04400	Smallpox (B03)
04500	Measles (B05)
04600	Rubella (German measles) (B06)
04700	Viral hepatitis (B15-B19)
04800	Human immunodeficiency virus (HIV) disease (B20-B24)
04900	Human immunodeficiency virus (HIV) disease resulting in infectious and parasitic diseases (B20)
05000	Human immunodeficiency virus (HIV) disease resulting in malignant neoplasms (B21)
05100	Human immunodeficiency virus (HIV) disease resulting in other specified diseases (B22)
05200	Human immunodeficiency virus (HIV) disease resulting in other conditions (B23)
05300	Unspecified human immunodeficiency virus (HIV) disease (B24)
05400	All other and unspecified viral diseases (A81, A85.0-A85.1, A85.8, A86-A89, B01, B04, B07-B09, B25-B34)
05500	Other and unspecified infectious and parasitic diseases and their sequelae (B35-B99)
05600	Mycoses (B35-B49)
05700	Protozoal diseases (B50-B64)
05800	Malaria (B50-B54)
05900	Leishmaniasis (B55)
06000	Trypanosomiasis (B56-B57)
06100	Pneumocystosis (B59)
06200	Other and unspecified protozoal diseases (B58, B60-B64)

06300	Helminthiases (B65-B83)
06400	Schistosomiasis (bilharziasis) (B65)
06500	Other and unspecified helminthiases (B66-B83)
06600	Sequelae of tuberculosis (B90)
06700	Sequelae of poliomyelitis (B9l)
06800	All other and unspecified infectious and parasitic diseases and their sequelae (B85-B89, B92-B99)
24700	Diseases of the respiratory system (J00-J98, U04)
24800	Acute upper respiratory infections (J00-J06)
24900	Acute pharyngitis and tonsillitis (J02-J03
25000	Acute laryngitis and tracheitis (J04)
25100	Other and unspecified acute upper respiratory infections (J00-J01, J05-J06)
25300	Influenza (J09-J11)
25400	Pneumonia (J12-J18)
25500	Viral pneumonia, not elsewhere classified (J12)
25600	Bacterial pneumonia (J13-J15)
25700	Pneumonia due to other or unspecified organisms (J16,J18)
25800	Other acute lower respiratory infections (J20-J22,U04)
25900	Acute bronchitis and bronchiolitis (J20-J21)
26000	Other and unspecified acute lower respiratory infections (J22,U04)
30800	Infections of skin subcutaneous tissue (L00-L08)
33000	Urinary tract infection, site not specified (N39.0)

Table A4.2. Propensity score variables for TNF-α and IL-12/23 blockers comparison and their unweighted and weighted standardized differences.

Variable name	Weighted standardized differences	Unweighted standardized differences
Age	-0.0171	-0.1134
Ankylosing spondylitis	-0.0250	-0.0795
Anxiety	0.0071	0.0224
BMI	0.0000	0.1219
Chronic heart disease	-0.0073	-0.0066
Crohn's disease	-0.0093	-0.0617
Dactylitis	0.0007	0.0282
Depression	0.0093	0.0321
Diabetes	0.0066	0.0542
Dyslipidemia	-0.0051	-0.0201
Enthesitis	0.0006	0.0209
Flu vaccination	-0.0113	-0.0332
Heart failure	0.0002	0.0607
Hepatitis B	-0.0020	0.0056
Hepatitis C	0.0013	-0.0267
Hypertension	-0.0061	-0.0022
Inflammatory bowel disease	-0.0155	-0.0997
Multiple sclerosis	0.0014	0.0759
Nonmelanoma skin cancer	-0.0003	0.0274
Number of dermatologist visits	0.0163	0.1780
Number of live function tests	-0.0041	-0.0462
Number of medications	-0.0003	0.0074
Number of platelet tests	-0.0062	-0.0554
Number of rheumatologist visits	-0.0156	-0.2021
Opportunisitic infections	-0.0021	0.0195
Oral steroid dose	-0.0098	-0.0995
Procedure for inflamaatory markers	-0.0178	-0.1620
Procedure for intralesional injection	-0.0047	-0.0398
Procedure for lipid lab	0.0013	-0.0103
Psoriatic arthritis	0.0037	-0.0716
Race	0.0361	0.0361
Region	0.0000	0.0702
Rheumatoid arthritis	-0.0338	-0.2332
Sex	0.0047	0.0220
Topical steroid dose	0.0063	0.0437
Treatment for hypertension	-0.0011	0.0107
Treatment with antibiotics	0.0018	-0.0151
Treatment with beta blockers	-0.0008	0.0038
Treatment with statins	-0.0012	-0.0153
Ulcerative colitis	-0.0185	-0.0742

Appendix 4 Figures

Figure A4.1. Propensity scores for biologic experienced psoriasis patients initiating either IL-12/23 or TNF-α inhibitors.

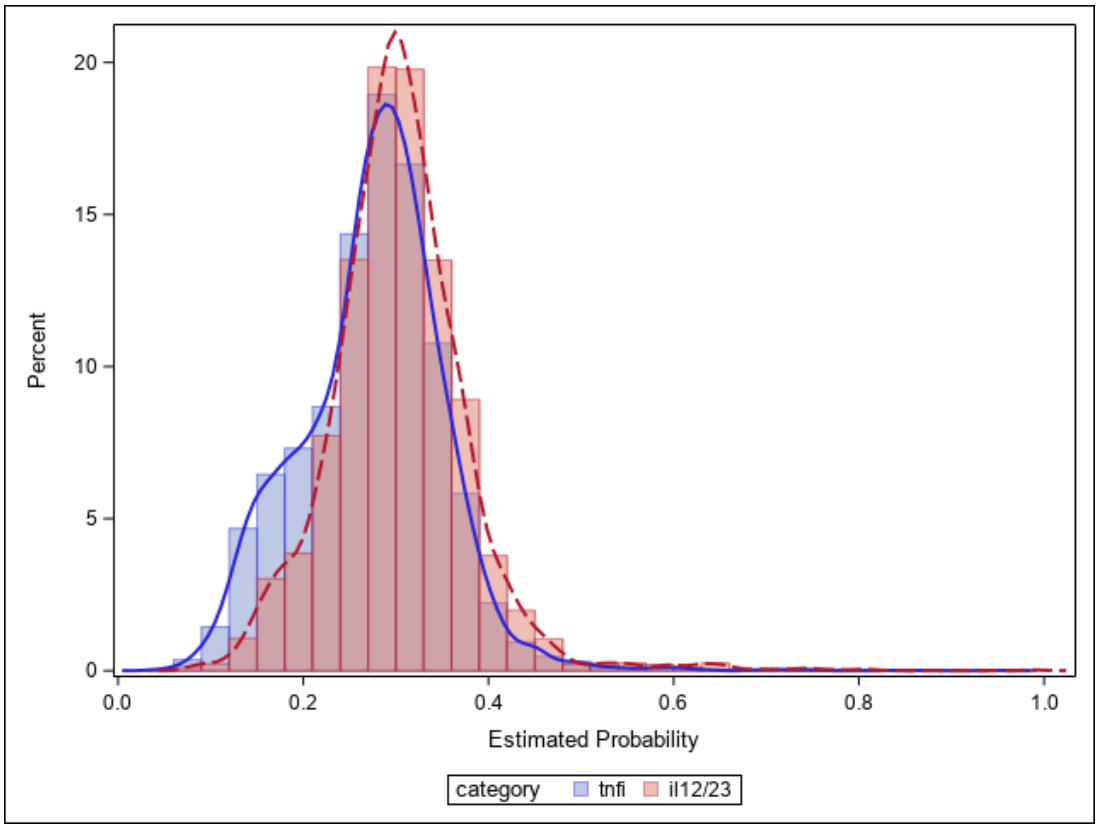


Figure A4.2. Weighted vs. unweighted standardized mean differences for psoriasis patients initiating either IL-12/23 or TNF-α inhibitors.