THE ROLE OF COMORBID DEPRESSION ON FREQUENCY OF PROVIDER VISITS AND STAGE OF DIAGNOSIS OF MELANOMA PATIENTS

By

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A Dissertation Submitted to the Department

of Health Informatics

Rutgers State University of New Jersey

School of Health Professions

in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August, 2019

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Abstract

The Role of Comorbid Depression on the Treatment and Survival Outcomes of Melanoma Patients

Depression has been cited by multiple sources to worsen outcomes of patients with melanoma. There have been exhaustive studies that have provided correlative and implicative evidence that comorbid depression leads to worse outcomes for melanoma patients. These reasons include poor adherence to follow-up care, initial diagnosis occurring at a later stage, among others. However, there have been few studies that have been able to quantify these relationships. This study quantified these observations via retrospective cohort data and found that melanoma patients with depression and higher PHQ4 scores presented to their healthcare providers with higher frequency and that melanoma patients with depression were more likely to be unmarried and white. However, no difference was found in regards to stage of malignancy at time of initial diagnosis among melanoma patients with and without depression. Therefore, this study identifies an inefficiency in healthcare provided to this subset of melanoma patients and advises healthcare providers to consider providing screening or referrals to specialists.

Acknowledgement

I would first and foremost like to express my most sincerest appreciation to my advisor, Dr. Frederick Coffman. Thank you for all of your support and guidance through every step of this process. You have been an incredible mentor who has helped me hone my skills and grow as a research scientist. I would also like to thank my committee members Dr. Shankar Srinivasan and Dr. Suril Gohel for serving as my committee members and providing me with invaluable feedback throughout this process. It is not without the advice and guidance of Dr. Coffman, Dr. Srinivasan, and Dr. Gohel that I would be able to make my dreams of this project come to fruition.

I would also like to thank Dr. Bijan Safai, Professor and Chairman of the Dermatology Department at New York Medical College, and Dr. Ashraf El-Shafei, Assistant Professor of the Psychiatry Department at New York Medical College, for encouraging me throughout this process and helping me fill in the gaps in my knowledge.

I would also like to dedicate this project to my beloved husband and children for their constant support and encouragement throughout this process. Their confidence in me is what made this work possible.

Finally, a special dedication to my parents for their endless love, faith and support.

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Chapter I

Introduction

1.1 Background and Significance of the Problem

Melanoma is not only one of the most prevalent cancers in the world but also has the most rapidly increasing incidence rates than any other cancer in the United States [Linos *et al.,* 2009; Jemal *et al.,* 2013; Gardener *et al.,* 2019]. In 2014, it was predicted that there would be over 76,000 cases diagnosed and would claim over 9,700 lives in the United States alone [Siegel *et al.,* 2014]. Statistics have also shown that caucasian men and women have an aggregate 1.91% risk of being diagnosed with this type of cancer [Geller *et al.,* 2002]. One landmark study, Geller *et al.,* 2002, has shown that between 1969 and 1999, melanoma incidence rates tripled among men between ages 45-64 and quintupled in men older than 65. The study also noted that incidence among men aged 20-44 years old experienced a near 2-fold increase of age and that women had shown an increase in incidence as well [Geller *et al.,* 2002]. Another study, Lens *et al.,* 2004, has supported the findings of this study by noting that melanoma incidence has also been increasing in females under the age of 40 since the 1960's and notes a specific increase in the incidence of localized tumors. This is phenomenon has also been edified by numerous other studies [Turner *et al.,* 2018; Tripp *et al.,* 2016; Garbe and Leiter, 2009; Leonardi *et al.,* 2018; Rastrelli *et al.,* 2011]

This trend of increasing incidence has not been isolated to the United States as it has been seen on a more global scale. There is a worldwide increase of about 3-7% of incidence rates each year, with rates doubling among fair-skinned Caucasians every 10-20 years [Lens *et al.,* 2004]. More specifically, Australia had an annual incidence rate of 55.8/100,000 among males and 42.9/100,000 among females, with a 1/25, and 1/34 chance of development in males and females [Lens *et al.,* 2004]. New Zealand in 1999 had the highest reported rates of Caucasians with 77.7/100,000 annual incidence [Lens *et al.,* 2004]. There is a combined 5.7% (5.4% for females and 5.9% for males) estimated risk of developing melanoma in New Zealand [Lens *et al.,* 2004].

1.2 U.S. Incidence Trends

While mortality rates have only recently stabilized in America, melanoma incidence rates are still increasing faster than other preventable cancers [Mayer *et al*., 2014]. This increase has been observed in very specific age groups and different populations and analyzing these observations together helps to illuminate characteristics about this malignancy [Mayer *et al*., 2014]. The sharpest increase in incidence is observed in older men greater than 60 years, with an even steeper increase being seen in areas of lower socioeconomic statuses where individuals are least likely to obtain screening [Mayer *et al*., 2014]. This Indicates that screening isn't the only attribution of rising incidence. Data from the Connecticut Tumor Registry from 1950-2007 reflected that incidence rates in men and women rose more than 17-fold (1.9 to 33.5 per 100,000) and 9-fold (2.6 to 25.3 per 100,000) [Mayer *et al*., 2014]. In 2014, it was predicted that

more than 76,000 cases of invasive melanomas were diagnosed and greater than 9,000 individuals lost their lives due to this disease [Mayer *et al*., 2014]. While the incidence rates in African Americans are lower than those of whites and the 5- year relative survival for African Americans and caucasians with melanoma are 74.1% and 92.9% respectively, melanomas in African Americans are more prominent in unexposed regions (hip, lower limbs, trunk, etc.) of the skin [Mayer *et al*., 2014]. Being that these melanomas are located in atypical regions can attribute to the decreased survival rate [Bradford, 2009; Mayer *et al*., 2014]. As per the California Cancer Registry from 1988-2001, Hispanic patients had a 1.8% annual increase in incidence of invasive melanoma with increasing tumor size in those thicker than 1.5mm [Mayer *et al*., 2014]. From the same registry in California in 1988-2007, Hispanic patients with lower socioeconomic status had a greater risk of having thick tumors (greater than 2 mm) and nodular melanoma subtype than those of higher socioeconomic statuses [Mayer *et al*., 2014].

Melanoma is most commonly found in the neck, trunk and head of men, while women tend to have it in their extremities [Mayer *et al*., 2014]. A study found that the average nevus count is about 25 in unexposed regions [Mayer *et al*., 2014]. Genetic variability, particularly in the skin and hair color are attributions to melanoma body sites [Mayer *et al.,* 2014]. Recent studies also show a left-sided dominance for skin cancers due to poor UVA-filtering of car windows [Mayer *et al*., 2014].

1.3 U.S. Mortality Trends

Mortality rates more than tripled (1.6 to 4.9 per 100,000) and doubled (1.3 to 2.6 per 100,000) in men and women as per Connecticut Tumor Registry data from 1950-2007. With more than 50% of melanoma deaths being in white men 50 years and older, lower education level and socioeconomic status, men have shown to have worse survival rates than women across all ages and stages [Mayer *et al*., 2014].

Melanoma mortality has been well researched and documented. As noted by Geller *at al.,* 2002, mortality increased in melanoma patients between the years of 1969 and 1999. Specifically, these studies indicated that male patients aged 45-64 years old saw an increase in mortality of 66% with females also showing increases in mortality [Geller *et al.,* 2002]. Furthermore, men older than 65 years old exhibited an increase in mortality by about 157% [Geller *et al.,* 2002]. Figures 1 and 2 illustrate the age-adjusted incidence and mortality rates by age diagnosis/death between the years 1975-2012 (SEER).

Age-Adjusted SEER Incidence Rates by Age of Diagnosis/Death of Melanoma (1975-2012)

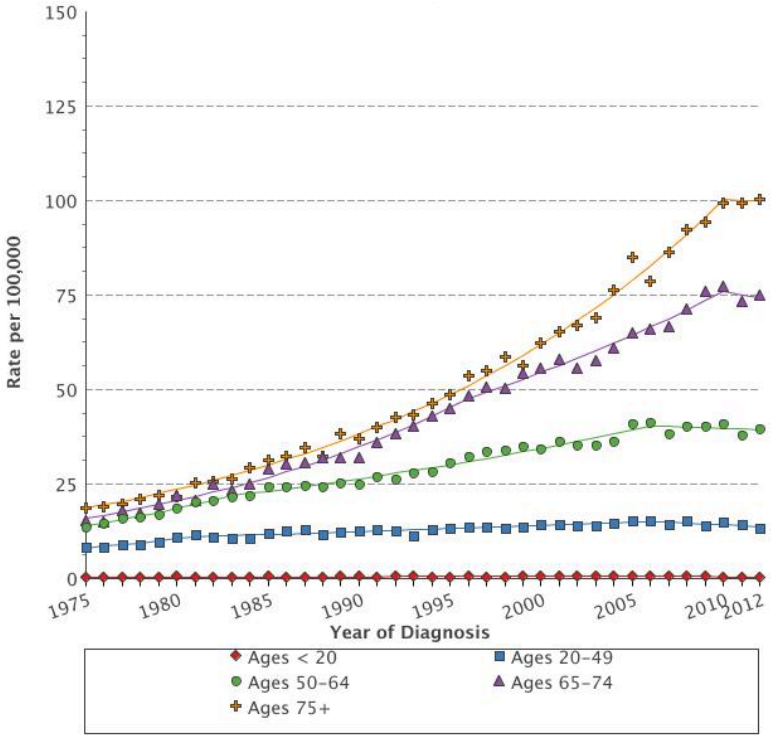

Figure 1 represents the trends for incidence rates of melanoma by age of diagnosis/death for all races and sexes from 1975-2012. All rates are per 100,000. The rates are also age-adjusted to the 2000 US Std Population. While the graph does reflect an increase in diagnosis and death in those of ages 50+, those younger than middle-aged maintained a consistent trend possibly due to increased screening and awareness [SEER].

Age-Adjusted U.S. Mortality Rates by Age of Diagnosis/Death of Melanoma (1975-2012)

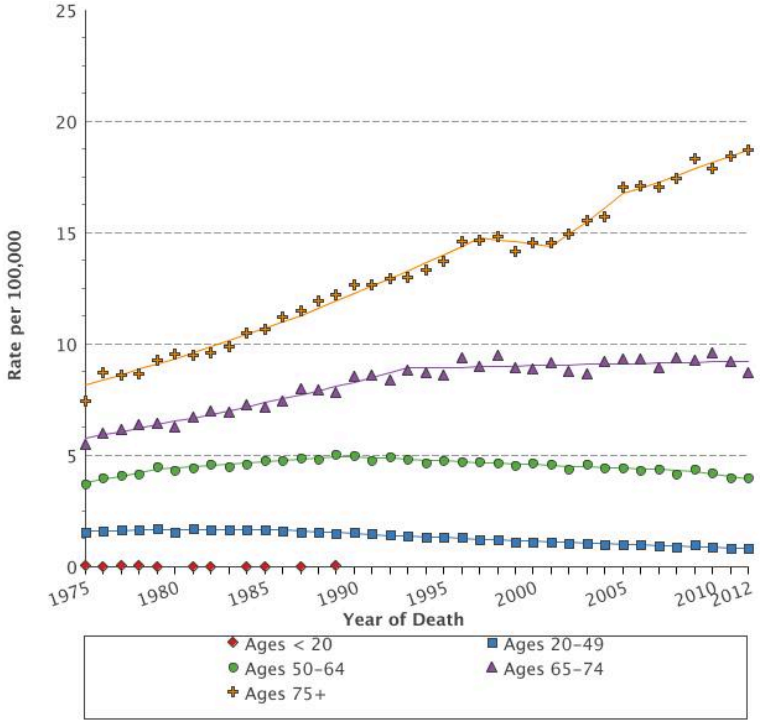

Figure 2 represents trends for mortality rates of melanoma by age of diagnosis/death for all races and sexes from 1975-2012. All rates are per 100,000. The rates are also age-adjusted to the 2000 US Std Population. While the graph reflects an increase in diagnosis/ death in those of ages 65+, those about 50 years of age and younger maintained a constant correlation possibly due to increased screening and awareness [SEER].

1.4 International Trends

With the greatest increase of melanoma being in those of European descent, Croatia has one of the highest incidence increase [Mayer *et al.,* 2014]. Mortality has been shown to have increased by a factor of 4 over the past 40 years [Mayer et al., 2014]. Despite melanoma deaths being very prominent in Europe, particularly Central and Eastern Europe holding about 35.5% of deaths in the 4 European regions, mortality is highest in New Zealand and Australia, with incidence being about 40-60 cases per

100,000 [Mayer et al., 2014]. Table 1 below summarizes incidence rates in 23 countries between the years 1980-1987 [Lens *et al.,* 2004].

	Male		Female	
Country	**Crude**	**ASR**	**Crude**	**ASR**
Australia	51.6	40.5	40.7	31.8
New Zealand	45.2	36.7	44.4	34.9
Sweden	19.8	12.6	19.9	13.3
U.S.A.	16.4	13.3	12.9	9.4
Denmark	14.8	10.6	17.6	13.0
Switzerland	12.5	9.3	15.0	11.1
The Netherlands	12.2	9.4	16.7	12.9
Austria	11.5	8.8	15.4	10.4
Canada	10.6	8.2	10.6	8.0
Hungary	10.3	7.6	10.3	6.8
Israel	9.7	9.4	11.0	9.8
Germany	9.3	6.5	11.4	7.1
France	8.6	6.8	11.1	7.9
U.K.	8.3	6.1	11.3	7.7
Poland	6.6	5.6	8.6	6.7
Italy	6.5	4.6	8.2	5.5
Russian Federation	6.3	5.4	6.4	4.7
Spain	4.0	2.8	6.8	4.5
South Africa	3.8	6.4	3.6	4.8
Brazil	2.9	3.5	2.0	2.2
Greece	2.5	1.9	3.2	2.0
Japan	0.63	0.40	0.49	0.29
China	0.21	0.22	0.17	0.17

Table 1 shows the incidence rates of malignant melanoma per 100,000 in 23 countries, with data from *GLOBOCAN 2000* [Lens *et al.,* 2004]. ASR: Age-standardized incidence rate.

1.5 Significance of the Problem

The increasing incidence and mortality in both the United States and Europe highlights the urgency of defining more refined modalities of screening and identification of at risk and current melanoma patients [Geller *et al.,* 2002]. Past efforts to reduce melanoma incidence and mortality have been centered upon public health campaigns to raise awareness of the cancer to little avail. As noted by Zoorob, 2001, melanoma was shown to increase by 200,000 cases and mortality by 46,000 cases within the observed time frame these initiatives were introduced. The United States Preventive Services Task Force (USPSTF), the governing body that recommends and approves screening protocols for the United States, currently recommends screening for high-risk patients and populations but maintains that low-risk patients should not be screened as there is insufficient evidence to determine if routine examinations by primary care physicians or by the individual can decrease mortality in low-risk patients [Zoorob, 2001].

However, one population of melanoma patients that remains under-screened are melanoma patients with depression. Current literature has exhaustively shown that melanoma patients with comorbid depression or depressive symptoms have worse outcome for several different reasons [Boz *et al.,* 2009; Pasquini and Biondi, 2007; Hartung *et al.,* 2017]. Unfortunately, exact incidence data, difference in stage of malignancy at time of diagnosis, and adherence to follow-up has not been established. There have however studies that provide correlative value that indicate psychiatric interventions lead to better patient outcomes [Fawzy *et al.,* 2003; Fawzy *et al.,* 1993]. Together, these indicate that there is a need for further observation of melanoma patients

with comorbid depression to determine if there is a role for altered screening practices for melanoma patients with comorbid depression. Furthermore, this study could counter the concerns of the USPSTF as the risks of leaving depressed patients unscreened would outweigh the risks of over-screening.

1.5.1 Cancer Registries Recommendations

The American Cancer Society (ACS), however, disagrees with the USPSTF and recommends alternative screening protocols. They advise physicians to give skin cancer examinations every 3 years for patients between 20-40 years old and yearly for those older than 40 years of age or for those with increased risk for skin cancer [Mayer *et al.,* 2014; Zoorob, 2001]. This is in addition to The American Academy of Dermatology which suggests that patients follow a comprehensive sun protection program, to perform regular self-skin examinations, and evaluate any unusual skin examinations [Mayer *et al.,* 2014; Zoorob, 2001]. This is in stark contrast to the current USPSTF recommendations.

1.5.2 Current Statistics on Early Stage Melanoma and SCREEN Project

Regardless of the differing opinions and methods of raising awareness and combating melanoma, current statistics indicate there are 1.3 million new cases of curable skin cancers each year and that patients who receive complete skin examinations are 6.4 times more likely to have a curable melanoma detected compared to those who receive partial skin examinations [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. With these principles in mind an experimental skin cancer screening program was carried out in

Schleswig-Holstein, Germany in 2008 [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. It was called the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) project [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. The SCREEN project involved training 1,700 physicians via an 8-hour examination training course prior to participation in the study [Katalinic *et al.,* 2012; Mayer *et al.,* 2014].

The sample population was defined between 1999 and 2003 and approximately 19% of Schleswig-Holstein's total population (all over 20 years of age) were included in the study [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. This population received full body examinations between 2003- 2004 and 585 of the total 360,288 participants were diagnosed with melanoma [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. All of the identified cases were placed into the Schleswig-Holstein Cancer Registry [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. Then in 2008, these same individuals were screened using the SCREEN protocols and 50% of those in the registry were identified by the SCREEN protocol [Katalinic *et al.,* 2012; Mayer *et al.,* 2014].

Mortality rates dropped after the implementation of the SCREEN protocol [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. The mortality rate for males and females were and 1.8-2.1/ 100,000 and 1.4/100,000 respectively between the years of 1990-2003 before the implementation of the SCREEN protocol [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. These numbers decreased by almost 50% in 2008-2009 for both males and females and an 7.4% annual decrease in melanoma mortality over a 10 year period [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. This was in contrast to the surrounding regions (Denmark, Hamburg, Lower Saxony, Mecklenburg-Vorpommern) that experienced no change in

melanoma mortality [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. Table 2 and Figure 3 represent a comparative analysis of mortality rates for malignant melanoma in Schleswig-Holstein SCREEN region with its surrounding regions [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. Figure 4 reflects the decrease in age specific mortality trends of men and women in Schleswig-Holstein from 1990-2008, representing the effects of implicating screening protocols [Katalinic *et al.,* 2012; Mayer *et al.,* 2014; Zoorob, 2001].

Population	Schleswig-Holstein: SCREEN Project Area	North: Denmark	East: Mecklenburg-Vorpommern	South: Hamburg	West: Lower Saxony	Germany Excluding Schleswig-Holstein
Men						
2009 Population	1.39 Million	2.74 Million	820,000	870,000	3.90 Million	38.8 Million
No. of MM deaths/y						
A: 1998-1999	42	117	15	19	112	1000
2003-2004	43	118	23	29	123	1229
B: 2008-2009	28	150	28	24	151	1382
A–B, %	−33	28	87	26	35	38
MM mortality: WASR (95% CI)						
A: 1998-1999	1.9 (1.5-2.4)	2.9 (2.4-3.3)	1.1 (0.7-1.5)	1.3 (0.9-1.8)	1.7 (1.5-1.9)	1.6 (1.6-1.7)
2003-2004	1.6 (1.2-1.9)	2.7 (2.4-3.1)	1.6 (1.1-2.2)	2.0 (1.5-2.5)	1.8 (1.5-2.0)	1.8 (1.7-1.9)
B: 2008-2009	1.0 (0.7-1.3)	3.2 (2.8-3.5)	1.6 (1.2-2.1)	1.4 (1.0-1.8)	2.0 (1.8-2.3)	1.8 (1.7-1.9)
A–B, %	−47	10	45	8	18	9
Women						
2009 Population	1.44 Million	2.79 Million	840,000	910,000	4.04 Million	40.3 Million
No. of MM deaths/y						
A: 1998-1999	45	86	17	22	112	940
2003-2004	39	103	20	23	116	984
B: 2008-2009	22	103	23	23	102	1148
A–B, %	−51	19	35	5	−9	22
MM mortality: WASR (95% CI)						
A: 1998-1999	1.4 (1.1-1.8)	1.8 (1.5-2.1)	0.8 (0.5-1.2)	1.2 (0.8-1.6)	1.3 (1.1-1.4)	1.1 (1.0-1.1)
2003-2004	1.3 (0.9-1.6)	1.8 (1.5-2.1)	1.0 (0.6-1.3)	1.1 (0.7-1.4)	1.2 (1.0-1.4)	1.1 (1.0-1.1)
B: 2008-2009	0.7 (0.5-1.0)	1.9 (1.6-2.1)	1.1 (0.7-1.5)	1.1 (0.7-1.5)	1.1 (0.9-1.3)	1.2 (1.1-1.2)
A–B, %	−49	5	29	−9	−13	10
Total 2009 population	2.83 Million	5.53 Million	1.66 Million	1.78 Million	7.94 Million	79.1 Million
No. of MM deaths/y						
A: 1998-1999	86	203	32	41	224	1940
2003-2004	82	221	43	52	239	2213
B: 2008-2009	50	252	50	46	253	2529
A–B, %	−42	24	56	12	13	30
MM mortality: WASR (95% CI)						
A: 1998-1999	1.7 (1.4-2.0)	2.3 (2.0-2.5)	1.0 (0.8-1.3)	1.2 (0.9-1.5)	1.4 (1.3-1.6)	1.3 (1.3-1.4)
2003-2004	1.4 (1.2-1.6)	2.3 (2.0-2.5)	1.3 (1.0-1.6)	1.5 (1.2-1.8)	1.5 (1.3-1.6)	1.4 (1.3-1.4)
B: 2008-2009	0.9 (0.7-1.1)	2.5 (2.2-2.7)	1.3 (1.0-1.6)	1.2 (1.0-1.5)	1.5 (1.4-1.7)	1.4 (1.4-1.5)
A–B, %	−48	4	32	2	7	10

Abbreviations CI, confidence interval; MM, malignant melanoma; SCREEN, Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany; WASR, world age-standardized rate per 100,000.

[a] Listed are the average numbers of deaths per year and the age-standardized mortality rate (WASR per 100,000) and 95% CI for 3 periods: A (1998/1999 [before the first screening activities]), 2003/2004 [during the SCREEN project], and B (2008/2009 [latest mortality data]).

Table 2: Mortality Comparison of Malignant Melanoma in Schleswig-Holstein with Adjacent Regions [Katalinic *et al.,* 2012]

Mortality Trends of Melanoma in Schleswig-Holstein, Germany (2000-2009)

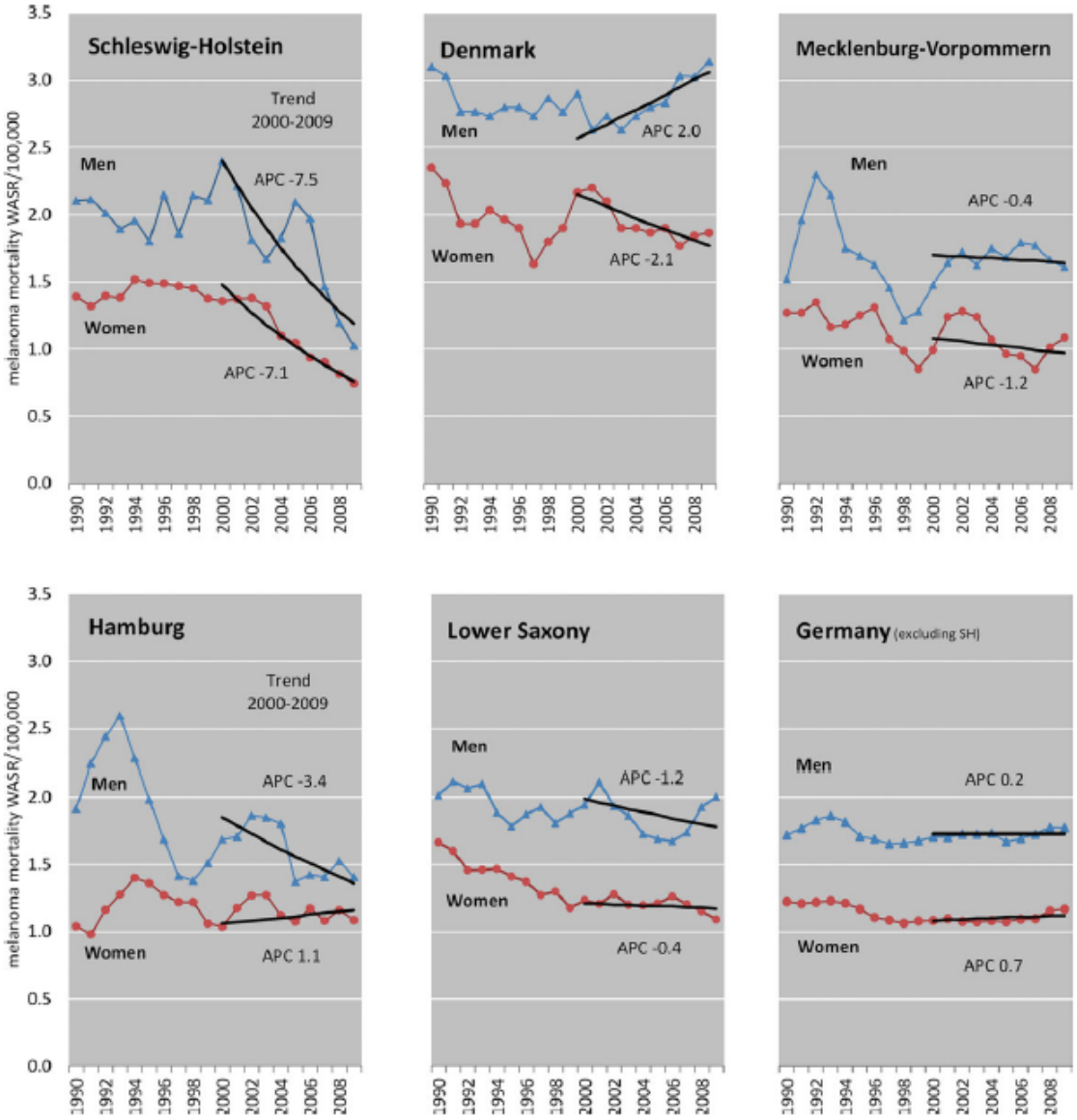

Figure 3 represents the mortality trends of melanoma using a 3-year moving average in Schleswig-Holstein's screened area and the adjoining regions from 2000-2009. WASR: World Population Age Standardized Rte per 100,000; APC: Annual Percentage Change [Katalinic *et al.,* 2012].

Age Standardized Trends of Mortality in Schleswig-Holstein, Germany

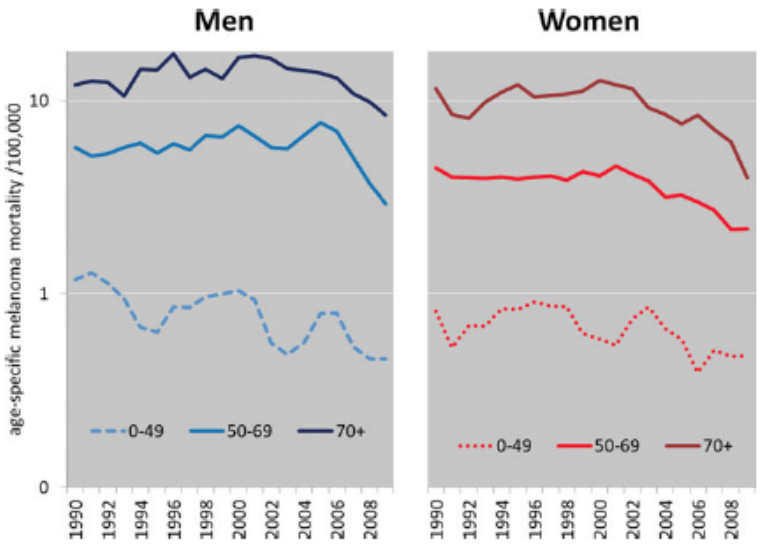

Figure 4 shows the age-standardized trends of mortality for the age groups birth to 49 years old, 50-69 years old, and 70+ years old per 100,000 on a logarithmic scale in the screening area of Schleswig-Holstein [Katalinic *et al.,* 2012].

1.5.3 SCREEN Conclusions and Implications for the U.S.

The results of the SCREEN study prove that screening protocols can be effective in diagnosing melanoma at earlier stages and proving subsequent patient outcomes [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. It also edifies how better, more refined, and more specific screening protocols can be invaluable in diagnosing melanoma and decreasing mortality [Katalinic *et al.,* 2012; Mayer *et al.,* 2014]. It is for these reasons that work must be done to develop a stronger and more unified screening protocol for the United States.

1.6 Relevance to Biomedical Informatics

The study relates to the biomedical informatics field in regards to how it uses biometrical and population data to analyze trends in disease incidence with the intention of influencing patient outcomes and healthcare delivery. Specifically, it will seek to determine if there is an existing population of melanoma patients with comorbid depression, assess their adherence to follow-up, and determine possible time-lag of initial diagnosis in comparison to a standard population. This study will influence future melanoma screening methods as it may decrease a threshold for screening among depressed patients and pave the way for future research on melanoma preventative care. On a broader scale, it will help policy makers in regulating future health policy decisions and budgeting for those of higher risk.

1.7 Goals and Objectives

The project is divided into three phases. The first phase of the project would be to analyze incidence data from the HINTS (Health Information National Trends Survey) to determine the proportion of melanoma patients with comorbid depression. The next phase would be to assess the inherent pitfalls in their care that their psychiatric condition predicates. The final phase will then use these associations to determine the role for preemptive screening in clinically depressed patients with implications that earlier identification will lead to better outcomes.

1.8 Hypothesis and Research Questions

I hypothesize that analysis of incidence of melanoma patients who suffer from depression concomitantly will allow us to determine the role of melanoma screening in patients with clinical depression to improve patient outcome. The variables that will be examined are as follows: concomitant of melanoma and depression, effect of depression on stage of melanoma at diagnosis, effect of depression on overall melanoma outcome, effect of depression on adherence to follow-up. Each of these variables are discussed in turn in chapter 2. This study will seek to answer the following research questions and associated statistical hypotheses:

Research Question 1 (RQ1). What proportion of the melanoma population has comorbid clinical depression?

Research Question 2 (RQ2). What are the effects of demographic variables on frequency of healthcare provider visits?

Research Question 3 (RQ3). At what stage of melanoma are patients with depression diagnosed versus population without depression?

Chapter II

Literature Review

2.1 Literature Review

Literature search involved reviewing multiple peer reviewed articles, books, and organization websites published on skin cancer, risk factors, prevalent populations at risk, healthcare methods and screening protocols. Electronic search engines were implemented in locating pertinent peer reviewed articles and analyses. Searched were NIH, JAMA, Nature, Google Scholar, amongst other search engines in order to ascertain the appropriate information. These articles (please see reference list) were carefully reviewed.

Search terms include:

"Skin Cancer" or "Melanoma Skin Cancer"

2A. Biology of Skin Cancer

Melanoma is a skin malignancy that is currently responsible for 80% of all skin cancer related deaths [Miller *et al.,* 2006]. Beginning from mutated melanocytes in the basal layer of the epidermis, the cancer will accrue further mutations that will allow them to grow and propagate vertically and burrow into deeper layers of the skin [Miller *et al.,* 2006]. Specifically, the mutations allow the now neoplastic cells to evade apoptosis, to

develop autonomous growth signaling, trigger angiogenesis, and metastasize to different regions of the body [Liu and Sheikh, 2014]. The transformation from melanocyte to malignant neoplasm has been dubbed by scholars to be known as the Clark model of progression.

There are multiple risk factors and carcinogenic insults that can both incite this transformation and make the transformation more likely. Those of Caucasian decent and light-skinned individuals have a much higher chance of developing melanoma. Furthermore, melanoma development has been linked in those who have had exposure to vinyl chloride, radiation, PCBs, frequent sunburns, and patients who have had melanocytic nevi [Liu and Sheikh, 2014]. But the most inexorable risk factor is UV exposure [Liu and Sheikh, 2014; MacKie *et al.,* 2009].

Increased time and severity of exposure to ultraviolet radiation will correlate with the risk of developing melanoma and will affect the type of melanoma that develops [MacKie *et al.,* 2009]. Also, individuals who experience chronic UV exposure tend to experience a more severe type of melanoma. One such subtype is lentigo maligna melanoma which is most commonly observed in the exposed areas of the body, and is most frequent in those who have under went chronic UV exposure [MacKie *et al.,* 2009]. This is in contrast banal naevi (type A melanoma) that occurs in people who have been exposed to short, acute periods of UV radiation at a relatively young age [MacKie *et al.,* 2009].

As such, the role of UV radiation in the pathogenesis of melanoma has been investigated extensively with many different papers coming to the common conclusion

that the UV radiation causes cancerous mutations in the melanocytes [Jhappan *et al.,* 2003]. UV radiation, specifically UVB, will cause damage to the physical DNA within melanocytes that will then lead to mutations in different genes [Jhappan *et al.,* 2003]. These physical damages are 6-4 photodimers and pyrimidine dimers and in many other cells, and p53 would be activated to cause apoptosis in the cells [Jhappan *et al.,* 2003]. However, melanocytes have a very high level of bcl2 and are therefore not as susceptible to p53 mediated apoptosis. Therefore the mutation persists in the further lineage of the cell, propagates, and accumulates further mutations which lead to melanoma [Jhappan *et al.,* 2003].

Therefore the more severe and more prolonged the exposure to UV radiation, the higher the probability that melanoma will develop [MacKie *et al.,* 2009; Jhappan *et al.,* 2003; Ali *et al.,* 2013; Dennis *et al.,* 2008; Leonardi *et al.,* 2018]. Studies have shown that the first decade of life is crucial, for children spending much time in high-UV environments increases the risk of developing melanoma later on in their lifetime [MacKie *et al.,* 2009; Jhappan *et al.,* 2003; Ali *et al.,* 2013]. One such high-UV environment is the use of tanning beds which have been shown to increase the chances of developing melanoma [Gardini *et al.,* 2018; Prado *et al.,* 2019]

Regardless of the carcinogenic insult, there are numerous genes and genetic signaling pathways that have been linked with melanomic tumorgenesis. Among them the most notable is the BRAF gene [Linos *et al.,* 2009; MacKie *et al.,* 2009; Jhappan *et al.,* 2003]. This gene has been implicated in over 66% of carcinomas [Jhappan *et al.,* 2003]. Other notable gene mutations that usher us on the path to melanoma are CDKN2A,

CDK4, and MC1R [MacKie *et al.,* 2009]. CDKN2A is involved in cell cycle regulation and progression and studies have shown that a germ-line mutation with this gene will lead to more further mutations that will progress to melanoma [MacKie *et al.,* 2009]. CDK4 has also been shown to play a role in pathogenesis in a small subset of families with melanoma but more research is needed before a more definitive role can be established [MacKie *et al.,* 2009]. MC1R has functionality in the production of freckles and red hair, however studies have shown that there is an interaction between this gene and CDKN2A that is conducive to the development of melanoma [MacKie *et al.,* 2009]. These studies have shown that the degree of prevalence and penetrance of MC1R in families is relevant to the development of the cancer in familial gene lines that also harbor the MC1R mutation [MacKie *et al.,* 2009].

2B. Risk factors

The results of these studies and other similar ones triggered investigation and research into the pathogenesis and causation of the malignancy and the rapid increase in the incidence of the disease. Results indicated that there was a very complicated interplay between many factors that determined the presence of melanoma in patients. These factors were identified to include sun exposure, genetics, and age [Linos *et al.,* 2009; MacKie *et al.,* 2009; Ward-Peterson *et al.,* 2016]. These factors, however, have been long known to have causative roles in melanoma pathophysiology and have been well researched. But literature review has noted several behavioral factors that have been shown to be associated with melanoma incidence. These factors include socioeconomic

status, prior history of malignancy, and marital status among others. Being married has long been beloved to have a protective effect against melanoma as patients whom are married tend to present earlier in their disease course [McLaughlin *et al.,* 2011; Mintzi *et al.,* 1978; Sharon *et al.,* 2018; Ortiz *et al.,* 2007; Levita, 2018; Sharon, 2018].

Depression, interestingly, has long been associated with worsening outcomes in melanoma patients. There has been a great deal of studies done have shown this using correlative and implicating reasoning but, upon extensive review, have not been able to identify quantitative associations. That is what this study seeks to ascertain.

2C. Population of Melanoma Patients With Depression

Current studies have found it difficult to ascertain the exact population of patients with melanoma and comorbid depression but most sources agree that there is a relationship [Gogas *et al.,* 2017; Kasparian *et al.,* 2009; Kasparian, 2013]. Many studies have shown that depression may develop in patients after they have been diagnosed however it is often difficult to determine the onset of the depression in relation to whether the symptoms were present before or after the diagnosis of the malignancy [Erim *et al.,* 2013; Guzzetta *et al.,* 2018; Krajewski *et al.,* 2017]. Most literature sources however note that between 6-28% of the total population with melanoma suffer from depression and psychological distress [Kasparian *et al.,* 2009; Kasparian, 2013].This is a wide range and further work must be carried out to determine the exact proportion of patients with melanoma and comorbid depression.

2D. Treatment Implications of Depression

The link between depression and cancer in general has been well studied and documented (Boz *et al.,* 2009; Pasquini and Biondi, 2007; Hartung *et al.,* 2017). These studies often cite the obvious physical and emotional strain that having an malignancy places on a person. One watershed study carried out in in 1979 by Rogentine *et al.,* noted that psychological factors, specifically a level of psychological distress, was noted to correlate with overall prognosis of the malignancy (Rogentine *et al*., 1979). However, many more contemporary studies have gone farther by seeking to extrapolate the effects on survival and longevity of the patients (Pasquini and Biondi, 2007). Pasquini and Biondi, 2007 carried out an 8 year follow up study with 10,000 oncology patients that demonstrated a positive correlation between depression and cancer mortality, pointing to the conclusion that the coexistence of the two does indeed lead to an increased risk of death in patients.

Spiegel and Giese-Davis, 2003, similarly, demonstrated a link between depression and cancer progression. They were able to note that patients with untreated depressive disorders may experience faster progression of the cancer. The interpretation of these results are subject to ongoing debate with numerous different points of view, some say that depression may have a direct neuro-immunomodulatory effect, or depressed patients may have poorer adherence to cancer treatments, or depression related behaviors affect several other aspects of patient's lives such as health status, parental role, and working role. Therefore, current literature notes a precedent that concomitant depression will lead to a worsening outcome for the patient.

Melanoma is not exempt from these principles of oncologic care. The deleterious effects that concomitant depression has on melanoma treatment is multifactorial. Each will be discussed in turn below however, the central motif of the patient experience is the depression that the lesions cause and the predicated avoidance of care that the depression causes.

One study carried out by Boz *et al.,* 2009 sought to discover the effect that depression had on melanoma care. The study notes that clinical depression may have a delay in identification and treatment of melanoma. The study notes that the psychiatric disorder may lead the patient to have an apathy and ambivalence towards seeking care for self-identified lesions.

Brown *et al.,* 2000 sought to better understand this phenomenon. They observed that patients who used less avoidant coping mechanisms and more concerned about their disease experienced improved survival durations and relapse times (Brown *et al.,* 2000). These are directly in contrast with known symptoms of depression. Therefore it is reasonable to assume that many of the maladaptive trends seen in melanoma patients with depression stem from deviation from this baseline attitude.

Lehto *et al.,* 2007 was noted to have similar observations. The goal of that study was to establish a baseline psychological profile that could be predictive of survival and recurrence of the disease. According to the study, patients who were noted to have anger non-expression and hopelessness, both which are very much consistent with typical presentations of depression, were noted to have reduced survival and increased propensity to recurrence (Lehto *et al.,* 2007).

There is also indirect evidence to support the negative role depression has patients with melanoma. Fawzy *et al.,* 2003 noted that patients who were able to improve their 5-6 year survival and morbidity with psychiatric intervention. Beutel *et al.,* 2015 showed that psychotherapy had a positive effect on treatment course of the malignancy. These studies aggregately evidence the role that depression plays on the overall prognosis and treatment of melanoma.

Understanding these basic principles of the effect that depression has on melanoma outcomes.

2E. Immunomodulatory Therapy and Depression

Recent years has seen the rise of immunomodulatory therapy for melanoma. By targeting specific mediators that have been shown to be crucial to the malignant transformation of melanocytes, these therapies have been shown to be effective in treatment of the malignancy [Navines et al., 2009; Lugowska et al., 2018; Alexandrescu et al., 2010]. However, the treatments have thus far been shown to have many side-effects, including depression [Navines et al., 2009; Hanna et al., 2017; Kovacs et al., 2016]. And, mimicking other predicted barriers that depression presents to melanoma treatment, development of depression within patients receiving immunomodulatory therapy has been shown to limit the efficacy of the treatment [Navines et al., 2009; Kovacs et al., 2015]. Fortunately, studies have shown that emotional support and targeted interventions can stymie this phenomenon which allows the treatment to continue [Kovacs et al., 2015]. This edifies yet another link between depression and melanoma and

demonstrates that proper care of a patient entails tending to both the physiological component of the malignancy as well as the psychiatric.

2F. Effect of Depression on Time of Diagnosis/ Stage Identified

There is an exhaustive amount of studies that link delayed diagnosis or diagnosis at a later stage of melanoma with worsened outcome [Erikkson *et al.,* 2014; Tripp *et al.,* 2016; Robinson *et al.,* 2016; Prado *et al.,* 2019]. This is talked about extensively above from a biological and medical perspective; however, this principle is of grave importance when considering patients with melanoma. There have been multiple studies that correlate depressive mood and psychological distress in melanoma patient led to poor follow-up and decreased willingness to receive care [Baughan *et al.,* 1993; Kasparian *et al.,* 2009; Livingstone *et al.,* 2015; Rogiers *et al.,* 2018; Schuermeyer *et al.,* 2015].

However there is a lack of literature that quantifies the effect that depression has on initial diagnosis of melanoma and at what stage that the malignancy is noted. This will be an active research question for the proposed project and will be examined in-depth.

2G. Effect of Depression on Follow-up

Many studies have also shown that concomitant depression in melanoma patients has an effect on the rates of follow-up treatment and adherence to treatment regimens. As noted by Kasparian *et al.,* 2009, SEER data between 1995-2001 noted that 83% of melanoma cases in the US were diagnosed while they were still in their primary site but these diagnoses still caused the affected patient to experience significant immediate

stress, experience underlying fear of disfigurement, threatens the self-esteem and self-confidence of the patient, and, most importantly, have their emotional needs and distress underappreciated by their social circle and healthcare providers (Kasparian *et al.,* 2009).

The study then notes that these factors led to poor adherence by melanoma patients for follow-up (Kasparian *et al.,* 2009). According to another study, Baughan *et al.,* 1993, 54% of melanoma patients with pigmented lesions reported a significant degree of psychological distress before their follow-up appointments and consultations and that a smaller sect of these patients endorsed physical symptoms of anxiety such as diarrhea, nausea, and insomnia (Baughan *et al.,* 1993). One study carried out in Germany was targeted at ascertaining the percentage of melanoma patient who were able to follow-up with their healthcare providers as recommended (Livingstone *et al.,* 2015). The study noted that of those who were unable to do so, patients with concomitant depression and anxiety were of the worst offenders (Livingstone *et al.,* 2015). These studies are amble support that depression is a significant hindrance on a melanoma patient's likelihood of obtaining appropriate follow-up.

This was also evidenced by Blum *et al.,* 2003. This study examined psychological burden being diagnosed with melanoma placed on the patient and quantified it using the Hospital Anxiety and Depression Scale (HAD). They noted that the diagnosis of melanoma caused a pronounced increases the level of psychological distress for the patient which could have impacted delivery of care (Blum *et al.,* 2003).

2.2 Introduction to Current Recognition and Screening Protocols

This section seeks to review and surmise current screening and diagnostic modalities available for melanoma. Understanding the state of current science is necessary for determining how capable these modalities are for identifying and treating patients with melanoma and furthermore to understand the need for more behavioral based screening modalities and predictors.

2.3 Recognition Patterns

The ABCDE (asymmetry, border, color, diameter, and evolution) classification system was designed to help clinicians determine the malignant potential of melanoma lesions [Mayer *et al.,* 2014; Wills, 2002]. The most recent modality to the system was consideration of evolution of the lesion which has been noted to increase the sensitivity of the system's ability to determine especially cancerous subtypes such as the nodular subtype [Mayer *et al.,* 2014; Wills, 2002]. The utility of this modality is evident when considering the rapidly growing nature of nodular melanomas. Nodular melanomas are detectable within 5 months as opposed to the 9 month with the superficial spreading subtype [Mayer *et al.,* 2014]. Furthermore, diameter measurements have been shown to be a less reliable determinant due to the fact that about 1/3rd of melanomas have an initial diameter of less than or equal to 6 mm [Mayer *et al.,* 2014]. Also benign lesions such as atypical nevi and seborrheic keratoses, may be asymmetric, exceed 6 mm in diameter, or vary in color [Mayer *et al.,* 2014]. These highlight many of the flaws inherent in the ABCDE system and are testaments to the need for better categorization modalities.

One such modality is the “ugly duckling” classification system. The purpose of this system is to identify an individual’s nevus phenotype paying special attention to what seem to be atypical lesions and can be taught to healthcare providers [Mayer *et al.,* 2014]. Studies have shown that dermatologists, dermatology nurses, and non clinicians have 89%, 88%, and 85% sensitivities respectively of identifying suspicious nevi using pattern recognition [Mayer *et al.,* 2014].

2.4 Risk-Assessment Aids

Evidence-based assessment tools are imperative for identifying those at high risk for melanoma and potential candidates for screening [Mayer *et al.,* 2014]. And while there haven’t been definitive models that target those most susceptible, it has been known that white middle aged and senior men, particularly those without significant others or partners, who could aid in early diagnosis via skin inspection, are likely candidates [Mayer *et al.,* 2014; Aitken *et al.,* 2009]. However, many, particularly the majority of high risk patients have limited proficiency in internet usage or may have limited access, and are therefore unable to learn the most up-to-date screening techniques [Mayer *et al.,* 2014]. Hence, clinicians and providers who are aware of the most recent advances in melanoma screening and detection provide routine skin examination of the high-risk areas such as the back and scalp [Mayer *et al.,* 2014; Aitken *et al.,* 2009]. There have been multiple risk assessment tools contrived in order to help diagnose and assess the severity of the patients’ melanomas [Mayer *et al.,* 2014].

The National Cancer Institute designed the Melanoma Risk Assessment Tool to calculate the individual's 5-year prospect of developing melanoma for patients up to 70 years of age [Mayer *et al.,* 2014]. The assessment tool is used by examining the back of the patient for any suspicious moles while taking into account a patient's history of sun exposure and complexion [Mayer *et al.,* 2014]. Another similar tool was developed in Australia takes in account location of the lesion, hair color, freckles, common and atypical nevi, family and personal history of melanoma and nonmelanoma skin cancer, in addition to a patient's sun exposure history [Mayer *et al.,* 2014]. However, a third study examining white patients between the ages of 35-74 years, determined that the most common risk factors were the male sex, old age, a greater number of severe sunburns between the ages of 2-18 years old, freckles on the arms before the age of 20 years, raised moles on both arms, lighter hair color at age 15 years, and a history of nonmelanoma skin cancer [Mayer *et al.,* 2014]. And with the area being 0.70 under the receiver operating curve for these common risk factors indicates that the experiment predicts melanoma very well [Mayer *et al.,* 2014]. Also, screening in the higher 15% risk category captures about 50% of melanomas, a relatively high proportion of cases [Mayer *et al.,* 2014].

2.4.1 New Technologies

Recent advances in imaging could potentially better melanoma diagnoses. Recent studies have focused have sought to analyze and describe the utility of these emergent modalities which include dermoscopy, total body photography (TBP), confocal

microscopy, and other diagnostic aids [Mayer *et al.,* 2014]. Each modality is discussed below.

2.4.2 Total Body Photography

Total Body Photography (TBP) implementation is becoming more prevalent in dermatological practice [Mayer *et al.,* 2014]. However, clinical evidence for the technology is lacking with limited criteria for defining suspicious lesions [Mayer *et al.,* 2014].

A recent study compared TBP and serial dermatoscopy and showed that TBP had lower biopsy rates than serial dermatoscopy and furthermore concluded that TBP had a better rate of detecting denovo melanomas than dermatoscopy did [Mayer *et al.,* 2014]. Another study however provides evidence of greater efficacy by using the two modalities in conjunction [Mayer *et al.,* 2014]. It shows that melanomas found by screening with TBP and sequential dermatoscopy were thinner than those found with traditional screening methods [Mayer *et al.,* 2014]. Further studies of 2-step methods in high-risk patients noticed that after 10-years of regular follow-up with dermatoscopy and photography, about 40% of melanomas diagnosed were associated with lesions not under initial dermatoscopic surveillance, concluding that combining methods increased melanoma detection [Mayer *et al.,* 2014]. Despite TBP being hindered by cost, access, and insurance reimbursement policies, implementation will likely continue to increase [Mayer *et al.,* 2014].

2.4.3 Confocal Scanning Laser Microscopy (CSLM)

CSLM is another recent technological innovation that uses a low power laser that reflects off structures in the epidermis and creates a 3-D image, with comparable resolution to standard histology [Mayer *et al.,* 2014]. It has a specificity and sensitivity of about 86% and 90% in regards to its ability to detect lesions [Mayer et al; 2014]. Despite CSLM being limited by cost and training specialization needed and the fact that histological examination remains the standard for lesion diagnosis, there is much promise for CSLM [Mayer *et al.,* 2014]. A study comparing margin differences for identifying lento maligna melanoma by CSLM and dermatoscopy was that CSLM was able to detect the subclinical disease less than 5mm beyond the dermatoscopy margin, exceeding baseline excision margin for these lesions [Mayer *et al.,* 2014]. As technology betters and more clinical research becomes available, CSLM may reduce the number of benign biopsy specimens and provide additional information on margins of a particular lesion that could change management [Mayer *et al.,* 2014].

2.4.4 Novel Diagnostic Aids

There have also recently been the development of novel diagnostic aids that can provide ancillary functionality in the efforts of diagnosing the given melanomas. Novel diagnostic aids, including multispectral devices, substitute higher sensitivity for lower specificity [Mayer *et al.,* 2014]. Multispectral devices, such as SIAscopes, measure blood, collagen, and melanin in the papillary dermis and epidermis [Mayer *et al.,* 2014]. Studies show that the sensitivity and specificity are similar to those experienced by

dermatoscopy by clinically trained dermatologists. MELAFind implements automated software for image analysis and recommends whether to obtain a biopsy specimen of a lesion. Studies note that the sensitivity and specificity for MELAFind lesions to be 98.4% and 9.9%, better than those of expert clinicians using dermatoscopic imaging [Mayer *et al.,* 2014]. However, with the low specificity trade-off and the $150/image fee usage will likely decrease [Mayer *et al.,* 2014]. Electrical impedance spectroscopy, like the SciBase II device, measures tissue impedance to current flow with small electrodes, have high sensitivity values, but specificity varies from 25% to 49%. However, while newer novel technologies better the outcome, certain challenges such as usage efficiency, cost, time needed for training, and lack of insurance coverage, can lead to decreased usage [Mayer *et al.,* 2014].

The most revolutionized technology includes smartphone applications that sends images to Board-certified dermatologists, and although can have very high sensitivity and specificity of 98.1% and 93.7%, the ranges are vast, and can be as low as 6.8% and 30.4% [Mayer *et al.,* 2014]. Hence, authors believe that due to this great range, results can be unreliable [Mayer *et al.,* 2014].

With the incessant increase of incidence and mortality rates, melanoma is a paramount concern in developed countries. Due to these increasing rates, new aids and diagnostic technologies have been developed to increase early detection with decreasing the number of unnecessary procedures [Mayer *et al.,* 2014]. And while these advancements better early detection, these methods are better implemented as compliments to full body skin examinations by trained clinicians [Mayer *et al.,* 2014].

2.4.5 Criteria for Early Dermoscopy

The ABCD rule helps clinicians to determine if a skin lesion's probability of needing further biopsy [Mayer *et al.,* 2014; Argenziano *et al.,* 2012; Carli *et al.,* 2001; Mayer *et al.,* 2014]. This rules mandates observation of a lesion's asymmetry, border irregularly, color variation, and diameter/depth [Argenziano *et al.,* 2012; Carli *et al.,* 2001; Mayer *et al.,* 2014]. While this rules clinical relevance is hard to be overstated, they are not sensitive enough to identify a skin lesion in the pre-cancerous stage as it most often centered on observation of the size of the skin lesion [Argenziano *et al.,* 2012; Carli *et al.,* 2001; Mayer *et al.,* 2014]. By the time the skin lesion has grown to be larger than 6 mm, the lesion has already progressed to malignancy [Argenziano *et al.,* 2012; Carli *et al.,* 2001; Mayer *et al.,* 2014]. For this reason, clinician need other screening tools and modalities to bypass this limitation of the standing decision protocols and allow them to investigate smaller and banal-looking melanomas [Argenziano *et al.,* 2012; Carli *et al.,* 2001; Mayer *et al.,* 2014].

Dermoscopy is one such tool. The main benefits of this tool present themselves in regards to its economy, efficacy, sensitivity and specificity, and low-invasiveness [Carli *et al.,* 2001]. Dermoscopy is a low-cost diagnostic modality that allows providers to screen patients patient's for melanoma very rapidly [Carli *et al.,* 2001]. In a recent study examining 1,328 patients with at least one melanocytic or non-melanocytic lesion who have been randomly examined with or without dermoscopy found that the complete skin examination without dermoscopy was 70 seconds and 142 seconds with dermoscopy, a difference of 72 seconds ($p<0.001$) [Argenziano *et al.,* 2012; Mayer *et al.,* 2014]. A more

thorough examination with dermoscopy, adding less than 3 minutes, is a justifiable amount of time to possibly avoid skin cancer and melanoma [Argenziano *et al.,* 2012; Mayer *et al.,* 2014].

Dermoscopy has also been shown to be a very accurate testing modality as it boasts high sensitivity and specificity [Carli *et al.,* 2001]. A retrospective study was carried out to determine how well the study was able to determine true-positive (TP), false-positive (FP), true-negative (TN), false-negative (FN) diagnoses [Carli *et al.,* 2001; Valachis *et al.,* 2009]. The engineers of the study analyzed photographs of dermatological lesions and observed the diagnosis assigned via visual observation and then compared the accuracy of these diagnosis' with ones that used dermoscopy [Carli *et al.,* 2001; Valachis *et al.,* 2009]. Results of the study indicated that diagnosis' that were assigned using dermoscopy were revealed to be more sensitive, specific, and accurate than visual examination [Carli *et al.,* 2001; Valachis *et al.,* 2009]. Dermoscopy showed sensitivity values of 90-95% while the average values for clinical examination were between 70-80% [Carli *et al.,* 2001; Valachis *et al.,* 2009]. This highlights an ability of dermoscopy to augment the sensitivity and specificity of melanoma diagnoses [Carli *et al.,* 2001; Valachis *et al.,* 2009].

In a similar vein, dermoscopy helps to reduce the need for unnecessary procedures [Carli *et al.,* 2001]. Many providers will opt to excise clinically equivocal lesion to ensure that unrecognized melanomas aren't treated [Carli *et al.,* 2001]. This is done with the intention of avoiding poor patient outcome and is due to the lack of clear clinical criteria to guide physicians whom observe equivocal lesions [Carli *et al.,* 2001].

Dermoscopy could help to ameliorate these unnecessary procedures by reducing the number of false-positives [Carli *et al.,* 2001].

2.4.6 Dermoscopy and the Number Needed to Extract

The number needed to extract (NNE) is a measure used to determine the accuracy of diagnosing melanoma and experiments have shown those implementing dermoscopy improved the NNE by reducing the number of unnecessary excisions of benign lesions [Argenziano *et al.,* 2012].

Meta-analyses show that dermoscopy utilized in clinical and experimental settings reflects a vast improvement in diagnosing melanoma [Argenziano *et al.,* 2012; Mayer *et al.,* 2014]. Experiments have shown that those implementing dermoscopy improved the NNE by reducing the number of unnecessary excisions of benign lesions [Argenziano *et al.,* 2012]. A survey was conducted to compare NNE values in specialized clinical settings (SCS) that used dermoscopy against those at non-specialized clinical settings (NSCS) that did not use dermoscopy over a ten-year period (1998-2007) [Argenziano *et al.,* 2012]. Results yielded that NNE increased in NSCS over the ten-year period and decreased in SCS indicating that unnecessary procedures decreased by a significant degree [Argenziano *et al.,* 2012].

There are other factors that influence the NNE. Age is one such factor as aside from the physician's knowledge on the subject, other factors influence the NNE, such as the lesion and the patient [Argenziano *et al.,* 2012]. For instance, the probability of contracting melanoma increases with age and those with multiple nevi and the "ugly

mole" syndrome are between the ages of 20-50 [Argenziano *et al.,* 2012]. Also, to rule out melanoma, the lesion must be excised, and the burden of excising a benign lesion, could be costly [Argenziano *et al.,* 2012]. Hence, in order to minimize the number of lesions excised, particularly in those with multiple nevi, clinicians may implement a comparative method in order to evaluate a single nevus in respect to the individual's entire nevus profile [Argenziano *et al.,* 2012]. Most have groups of nevi with similar dermoscopic or clinical appearances, known as the signature nevus, hence, a lesion uncommon to the pattern, referred to as the ugly duckling, should raise a red flag irrelevant to if it coincides with the ABCD method of the melanoma-specific dermoscopic criteria [Argenziano *et al.,* 2012].

2.4.7 Mortality of Melanoma

Altering and preventing mortality from melanoma is possible through several different interventions [Argenziano *et al.,* 2012]. We can first use medical interventions to attack and alter the tumor itself [Argenziano *et al.,* 2012]. We can then change the behavior and lifestyle of the patient which can have indirect effects on the malignant potential of the melanoma [Argenziano *et al.,* 2012]. And lastly we can have physician and care provider centered efforts that involve improving their ability to identify melanomas [Argenziano *et al.,* 2012]. Medical science is currently unable to alter the behavior of melanoma and it is currently very difficult to educate and implement lifestyle interventions in a wide patient population [Argenziano *et al.,* 2012]. Therefore, it is most feasible to educate physicians on how to better their examination techniques to better

identify melanomas [Argenziano *et al.,* 2012]. One report indicates that giving general physicians and practitioners a 2-hour training session on using dermoscopy had a 25% better chance of detecting suspicious skin tumors opposed to those who only used naked-eye skin examinations [Argenziano *et al.,* 2012]. This is further evidence that validates dermoscopy as a worthwhile diagnostic tool that physicians can utilize.

Another study was carried out to determine the efficacy of total body skin examinations (TBSE) in reducing the development of melanoma in patients [Argenziano *et al.,* 2012]. This was done by observing the risk of developing melanoma in patients who do not receive TBSE in order to determine risks of not detecting skin cancer without TBSE and the number of examined patients with at least one type of skin cancer [Argenziano *et al.,* 2012]. Results show that more skin malignancies are found in those with localized dermatologic problems through that would otherwise be missed if TBSE was not implemented [Argenziano *et al.,* 2012]. It was found that 47 patients in a group of individuals needed to undergo TBSE to find at least one skin malignancy (including melanoma and nonmelanoma skin cancer (NMSC)) and 400 patients had at least one melanoma [Argenziano *et al.,* 2012]. Older patients, particularly those with a passed medical history of NMSC or of fairer skin, those inquiring about a skin lesion, particularly those presenting with a lesion on frequently uncovered areas, had a higher susceptibility of identifying a skin cancer via TBSE [Argenziano *et al.,* 2012]. Hence, TBSE should continuously be implemented in clinical settings in order to diagnose melanoma or NMSC [Argenziano *et al.,* 2012]. The procedure is useful in determining

skin cancer, and the risk of harm from unnecessary biopsies, false-positive results, are reasonably low [Argenziano *et al.,* 2012].

While physician centered education and improvement and TBSE have been shown to be effective in detecting melanoma, dermoscopy is still considered to have the best ability to detect melanaoma [Argenziano *et al.,* 2012; Valachis *et al.,* 2009]. Most studies agree that dermoscopy reflects sensitivity values of about 90-95% while the average value being 70-80% [Carli *et al.,* 2001; Valachis *et al.,* 2009]. Hence, it is believed that dermoscopy provides better sensitivity and specificity in melanoma diagnosis [Valachis *et al.,* 2009].

2.5 Time-trend of Melanoma Screening Practice by PCP

Melanoma incidence rates have progressed enough over the past 2 decades to have reached magnitude of an epidemic disease [Valachis *et al.,* 2009]. Mortality is also increasing in older men concurrently [Valachis *et al.,* 2009]. Mortality, however, is dependent on a lesion's thickness at diagnosis, with thicker tumors leading to worse outcomes [Dickson et al., 2012; Black et al., 2001; Valachis *et al.,* 2009]. Therefore early-stage diagnosis before progression of the lesion is key to decreasing mortality rates in patients [Valachis *et al.,* 2009]. Over 80% of melanomas can be treated with simple excision and other localized treatment modalities but they first must be identified [Valachis *et al.,* 2009]. Full body skin examinations (FBSE) is capable of carrying out this identification [Valachis *et al.,* 2009].

FBSE is quick, painless, and easily performed without requiring any technological modalities and proficiency [Valachis *et al.,* 2009]. The exam can detect non-melanoma skin cancers, basal cell carcinomas (BCC), and squamous cell carcinomas which can lead to improvement of a better quality of life with a decreased financial burden for the patient [Valachis *et al.,* 2009]. Many regular visits with their primary medical doctors, implementing FBSE within the primary care setting can better early diagnosis rate [Valachis *et al.,* 2009]. Studies have shown however that many physicians do not carry out full skin cancer exams [Valachis *et al.,* 2009]. Skin cancers are screened for less than other diseases in which screening protocols are in place [Valachis *et al.,* 2009]. It was noted in a study that as time passed, less primary medical physicians performed FBSE [Valachis *et al.,* 2009]. It can be determined that the increase in incidence of melanoma with the reduction of melanoma screening results from the lack of data about skin cancer screening and effects of screening procedures [Valachis *et al.,* 2009].

2.6 Current Screening Guidelines

Current screening guidelines are perplexing and confusing to not only the public, but physicians as well [Mayer *et al.,* 2014]. There are different recommendations from different governing bodies [Mayer *et al.,* 2014]. The American Cancer Society (ACS) suggests that primary care physicians (PCPs) should examine the patient for skin lesions "on the occasion of a periodic health examination" for men and women greater than 20 years old [Mayer *et al.,* 2014]. The American Academy of Dermatology however states patients should perform skin self-examinations (SSEs), but doesn't specify who and how

often screening should be done by physician skin examinations (PSEs) [Mayer *et al.,* 2014].

The USPSTF however recommends no screening [Mayer *et al.,* 2014; Swetter *et al.,* 2014]. As per their statement in 2009, the organization deems inconclusive evidence to recommend routine skin cancer screening by PCPs or SSEs [Mayer *et al.,* 2014; Swetter *et al.,* 2014]. Therefore has yet to provide specific guidelines for screening, but it suggests that practitioners stay "alert" during the physical exam for possibly malignant lesions, for many global studies have concluded that provider detection of melanoma correlates with thinner tumors at diagnosis [Mayer *et al.,* 2014]. Ultimately, as per the Affordable Care Act, all suggestions by the USPSTF with a grade B and above must be endorsed within one year of the ruling [Mayer *et al.,* 2014, Swetter *et al.,* 2014].

2.6.1 Physician Screening Rates

The prevalence of yearly provider skin examinations range from 8-21% [Mayer *et al.,* 2014]. Physicians are less likely to perform routine screening than physician assistants or nurse practitioners due to their main concerns being acute and chronic complaints and illnesses opposed to the often lengthy routine screenings [Mayer *et al.,* 2014]. This has been shown in many different studies. A 2005 survey of a random sample size of 10,486 individuals (50+ years old) from The National Health Interview Survey (NHIS) illustrated that only 16% and 13% of men and women had PSE in the previous year [Mayer *et al.,* 2014]. A Multivariate analyses carried out in another study shows that lower rates of skin examination are exhibited in those within the ages of 50 and 64,

without a prior history of skin cancer, lower level of education, and lack of other types of routine screenings [Mayer *et al.,* 2014]. As per the 2010 NHIS study, approximately 51%, 105 million, adults in the U.S. are susceptible to developing melanoma according to the USPSTF's criteria (age, sunburns, family history, and race), with 24% having had at least one PSE [Mayer *et al.,* 2014]. In a 1600 physician survey, it was deduced that the main reasons for not performing full body skin examinations are due to competing comorbidities, patient embarrassment, and time constraints [Mayer *et al.,* 2014]. However, patients with a high prevalence of development, influence of medical training, and patient insistence, resulted in skin examinations [Mayer *et al.,* 2014]. A meta analysis of 9 US studies noted that the proportion of PMDs who perform full body skin screenings have decreased from 1987-2004 [Mayer *et al.,* 2014].

2.6.2 Professional and Public Education

Programs that train PMDs to carry out full body skin examinations (FBSE) have proven to decrease incidence and mortality through increasing diagnosis and management protocols [Mayer *et al.,* 2014]. Clinical studies in France reported the benefits of training general practitioners about melanoma which show that trained providers were more than twice as likely to diagnose melanoma than those without training [Mayer *et al.,* 2014].

An American study evaluated the effects of certain web-based interactive training for providers [Mayer *et al.,* 2014]. The study evaluated INFORMED (Internet-based program for Melanoma Early Detection) and 54 PMDs from 2 related health care delivery systems on practice patterns and graded them based on the number referral/visits

to a dermatologist, and obtained biopsy specimen over a 6 month period after training [Mayer *et al.,* 2014]. Results show that the appropriate diagnosis and management increased from 36% pre-training to 47% post-training, with the greatest increases observed in diagnosis of benign lesions and decreasing dermatology rates [Mayer *et al.,* 2014].

Surveys also show that medical students feel uncomfortable and that their skin cancer examination training is limited [Mayer *et al.,* 2014]. One study concluded that 22.6% of fourth-year medical students were able to notice a melanoma lesion on a patient's finger [Mayer *et al.,* 2014]. Studies show that the inclusion of educational programs focused on melanoma detection and found that after viewing an educational film, students had better knowledge and understanding of melanoma and were able to identify high-risk patients and sex-specific anatomic sites of increased risk [Mayer *et al.,* 2014]. And students were ultimately more comfortable in skin cancer examinations [Mayer *et al.,* 2014]. Similar results were also experienced after a sample group of 74 third-year medical students after viewing a one-hour melanoma simulation and skills training [Mayer *et al.,* 2014].

Nurses can also have vital roles in melanoma prevention [Mayer *et al.,* 2014]. While also limited by time, nurses are limited by their inability to differentiate suspicious and benign lesions [Mayer *et al.,* 2014]. However, their skills have bettered after training showed in a study of 104 nursing students learning about examining and early detection principles of simulated lesions on standardized patients [Mayer *et al.,* 2014] .These

simulations bettered knowledge of identifying high/at-risk individuals [Mayer *et al.,* 2014].

2.6.3 Problems with Screening + Need for Protocols

While there are no significant risks from these examinations, they could be embarrassing to patients and a misdiagnosis can have serious emotional and financial impacts on the patient due to unnecessary treatment [Mayer *et al.,* 2014]. Full-body screening examinations edifies this trend seen across many screening modalities.

FBSE can result in the detection of many benign skin conditions procedures [Mayer *et al.,* 2014]. As noted in Mayer *et al.,* 2014, FBSE in New Zealand and Australia, regions were FBSE is more commonly used, has led to decreased mortality rates. The study notes that the use of FBSE has led to earlier detections of malignancies which leads to better patient outcomes [Mayer *et al.,* 2014]. However, the study also notes that there are currently no guiding screening protocols to determine which patients receive the examination and that over sensitive diagnosis and subsequent investigations, such as unnecessary biopsies, may lead to avoidable economic burdens [Mayer *et al.,* 2014]. Therefore, it is imperative to arrange educational programs about skin cancer screening procedures for physicians and the general population in order to achieve maximum participation in melanoma screening [Mayer *et al.,* 2014; Valachis *et al.,* 2009].

This unfortunate trend is seen across all the modalities discussed. Each modality has shown to be effective in diagnosing melanoma but are without guiding protocols and

recommendations on when to carry out the screen. These, therefore, demonstrate the need for more clearly defined screening protocols that are capable of guiding healthcare provider decisions on which patients to screen.

Chapter III

Methodology

Chapter 3 presents an overview of the methodology used for this study. This overview will include the following: study design, population, sampling method, sample size, instrumentation, and data analysis methods.

3.1 Research Overview

Melanoma is rapidly becoming a public health concern. It currently is one of the most prevalent cancers in the world and its presence in the world is only continuing to rise. In light of these trends, many studies have been carried out to determine and define the pathophysiological mechanisms behind the malignancy and to determine the corresponding risk factors that are associated with the disease. One risk factor that warrants further investigation is the role of comorbid depression on patient outcome. Literature thus far has been able to identify correlative evidence that suggests implicates comorbid depression in melanoma patients as a factor that will worsen prognosis, but there is a severe deficit in quantitative analysis of these trends. Therefore, this project seeks to firmly establish the role that depression plays in hindering melanoma patients from receiving appropriate follow-up care, the effect on the overall outcome of patients with melanoma and comorbid depression, and to determine if there is a difference in

stage of melanoma at the time of diagnosis. An identified association between several or all of these variables will help to determine if patients with known depression should have a lower threshold for preventative melanoma screening.

3.2 Research Design

This is a retrospective correlational study. Retrospective studies were examined and analyzed to quantify and qualify the effect of a given exposure has on a predicted subset of outcomes that have already occurred. This study examined data from 2011, 2012, 2013, 2014, and 2017.

Associations found within the data were subject to correlational analysis. The goal of a correlational study is to determine if a given dependent variable varies in the context of an independent variable. The researcher, in this setting, was not able to manipulate either the independent or dependent variables as the outcome of this interplay has occurred before the study began. The study was able to determine the relationship between the variables but was unable unable to define the cause of the relationship. In other words, relationships between the variables can be identified but not causation.

3.3 Research Questions and Associated Hypothesis

This study was driven by the following three research questions and associated statistical hypotheses:

Research Question 1 (RQ1). What proportion of the melanoma population has comorbid clinical depression?

Null Hypothesis 1 (H01): There is not a statistically significant population of melanoma patients that also have depression.

Alternative Hypothesis 1 (HA1): There is a statistically significant population of melanoma patients that also have depression.

Research Question 2 (RQ2). What are the effects of comorbid depression and demographic variables on frequency on healthcare provider visits?

Null Hypothesis 2 (H02): There is not a statistically significant relationship between comorbid depression and demographic variables on frequency of healthcare provider visits.

Alternative Hypothesis 2 (HA2): There is a statistically significant relationship between comorbid depression and demographic variables on frequency of healthcare provider visits.

Research Question 3 (RQ3). At what stage of melanoma are patients with depression diagnosed versus population without depression?

Null Hypothesis 3 (H03): There is not a statistically significant difference in the stage of melanoma at the time of diagnosis in patients with and without depression.

Alternative Hypothesis 3 (HA3): There is a statistically significant difference in the stage of melanoma at the time of diagnosis in patients with and without depression.

3.4 Population and Sample Criteria

The present study includes population data taken from the Health Information National Trends Survey (HINTS). HINTS is an organization that takes biennial, cross-sectional surveys to assess and quantify the impact of the health information environment. Specifically, HINTS aims to measure how people access and use health information and the degree in which people partake in healthy behaviors. Finally, HINTS also seeks to determine the focus on cancer prevention and control.

As we are primarily focused on Melanoma patients within the HINTS database, we observed and combined data from previous years to ensure a large enough sample size and power to properly run univariate and multivariate analysis, these data sets include: HINTS 5 cycle 1(2017), HINTS 4 cycle 4 (2014), HINTS 4 cycle 3 (2013), HINTS 4 cycle 2 (2012), HINTS 4 cycle 1 (2011). A sample size of one-hundred and ninety participants was taken from all of these data sets. Surveys queried comorbid incidence of melanoma and depression, stage of melanoma at the time of initial diagnosis in patients with melanoma versus patients with melanoma and comorbid depression, overall survival of patients with melanoma versus patients with melanoma and comorbid depression, and the difference in adherence to follow-up care in patients with melanoma in contrast to patients with melanoma and comorbid depression. The data was then weighted using jackknife replication JK1, the number of jackknife replicates is 50. Replicate weights are done to provide more information on the standard error, while retaining information about the sample design, so that the standard errors can help us find more precise significance tests as well as more precise confidence intervals.

This present study includes responses from 33,354 people. Of the one-hundred and ninety participants (99 males, 86 females, and 5 non-gender conforming), categorical variables of interest, including age, race, gender, frequency of visitation of health care professional, emotional support, stage of melanoma diagnosis, occupational status, income, marital status, self-reported depression, and PHQ4, more information can be found in table 3. The mean age of the participants was 63.6 years (SD=1.73) and the racial distribution was separated into 96% Non-Hispanic White, 4% Non-White. Some participants failed to answer some questions or abstained from answering questions for personal reasons. As such failure to properly answer or abstinence from answering was considered as a null response and not taken into consideration for data analysis.

3.4.1 Categorical Representation of Data

In order to properly ensure the quality of our analysis, responses to some of the HINTS survey questions that allow for multiple levels of response were considered in their regard to the average. For example, the responses for open-ended question such as, "How often have you visited your healthcare physician?" were grouped in regards to the average. For this case, the average was 3 visits to the healthcare physician, as such responses were categorized responses as "greater than or equal to 3" or "less than 3."

Furthermore, this grouping also occurred in regard to categories of household income, age, race, and PHQ4 score. The incomes of participants were given using self-report measures on a scale of 1-5, with varying levels of income for each response, we grouped responses 1-3, and 4-5 to be less than $50,000 dollars and greater than or equal

to $50,000 dollars respectively. The age range was also measured on a 1-5 scale, with ages 18-64 being represented by numbers 1-3, and 4-5 being ages 65+, we grouped this variable of 18-64 being coded as 1, and 65+ being coded as 2 in the analysis. As numerous races were reported, but the majority being predominantly Non-Hispanic White, we coded race as Non-Hispanic White and Non-White. The PHQ4 score was weighted and the mean was found to be 1.7, we categorized the data for PHQ4 as being above this mean, or equal/below this mean.

Two more variables that were investigated were stage of diagnosis and total score of health professional support. Stage of diagnosis was categorized into early stage or advanced stage which was found based on the strength of treatment recommended to the patient. Early stage was assigned to a patient who has only received surgery to excise the tumor and no further treatment is necessary, while advanced stage was assigned to treatment regimens that included chemotherapy in addition to tumor excision. Likewise, total score of health professional support was categorized into below average, or average and above, with the average being 11.1 on a scale of 7-25. Higher scores meant that the patient felt more professional support from the healthcare professional. The decision about whether total score of health professional support is above or below average is derived from a questionnaire that asked patients to rate their level of uncertainty during care, the degree to which their feelings were addressed, the health care professionals availability to being asked questions, the amount their health care professional involved them in decision making, if the health care professional explained adequately the patient's condition, and if the healthcare professional spent enough time with the patient.

3.4.2 Instrumentation

No measurement instruments or tools were used for this study. Data was taken from HINTS. As noted above, HINTS is a national surveillance services that seeks to monitor the impact and changes in cancer communication as well as other key processes in health among American adults.

The current iteration of HINTS is HINTS 5, Cycle 1 (2017); HINTS 4, Cycle 4 (2014); HINTS 4, Cycle 3 (2013); HINTS 4, Cycle 2 (2012); HINTS 4, Cycle 1 (2011). Surveys were collected via self-administered mail questionnaires. Items in the HINTS surveys were borrowed from existing national-level surveys and other smaller, health related, survey organizations. However, all items are carefully tested via cognitive interviewing before the survey is fielded to ensure that they are psychometrically sound.

3.4.3 Data Collection Procedures

Prior to the use of the data, the researcher must agree to a data use agreement for HINTS data use. This allows HINTS to register the use of their data.

3.5 Measures

The measures that were analyzed in this were the behavioral variables that were discussed above. They are: comorbid incidence of melanoma and depression, stage of melanoma at the time of initial diagnosis in patients with melanoma versus patients with melanoma and comorbid depression, and the difference in adherence to healthcare provider visits in patients with melanoma in contrast to patients with melanoma and

comorbid depression. Due to a large number of variables potentially being used in the study, the operationalization of variables as well as the location of the original data can be found in Appendix A.

3.6 Data Analysis

R software was used to carry out statistical analysis and any inferential tests were two-sided tests and utilize a 95% significance level. Descriptive statistics are included for any independent and dependent variables in the study and frequencies and percentages will be included for all categorical variables. The list of these variables, which includes the scale of each variable, can be found in Appendix A.

All inferential tests were performed using survey data analysis which took into account the variable PERSON_FINWT0 from the hints datasets. This variable is a weight variable designed in the original survey which is used to make the sample more representative of national estimate.

Proportions of categorical variables are detailed above and chi-squared tests were used to determine relationships between these categorical variables. Specifically, the chi-squared tests were able to determine relationships between participants with melanoma and participants with melanoma and comorbid depression. Statistical assumptions such as absence of outliers, normality, linearity, and homoscedasticity were checked prior to hypothesis testing. Hypothesis testing will be done using multivariate analysis to survey and analyze the relationships between the independent and dependent variables.

Hypothesis testing for the first research question, RQ1, "What proportion of the melanoma population has comorbid clinical depression?" was performed using frequency distribution and the results are displayed in a distribution table of all categorical variables of interest.

Univariate analysis was used to address the second research question, RQ2, "What are the effects of comorbid depression and demographic variables on frequency of healthcare provider visits?"

Multivariate analysis was performed to address the third research question, RQ3, "At what stage of melanoma are patients with depression diagnosed versus populations without depression?"

An association table was created containing all of the variables, association (chi-square tests), between all life factors, comorbidities, demographics, stage of diagnosis and frequent provider visits. Multivariate analyses were carried out. Variables with high missing proportions were removed from the multivariate analysis. A stepwise independent variable selection method was utilized when selecting the appropriate variable from the list of independent variables. These variables must have a P-value of at least 0.03 to enter the model, and a P-value of 0.05 to stay in the model.

The multivariate analysis used Stage of Diagnosis as the dependent variable, and Depression, Gender, Race, HHInc, Emotional Support, Total Score of Health Support, and Occupation Status as the independent variables.

3.7 Summary

Chapter 3 details the methods that were used in this retrospective, correlational study. Data from HINTS was used for this study and the population of the study included American adults aged 18 and older between the years of 2011, 2012, 2013, 2014 and 2017. Hypothesis testing was carried out via multivariate analysis to survey and analyze the relationships between the independent and dependent variables. Univariate analysis and bivariate- chi square. The detailed description of these variables can be found in appendix A.

Chapter IV

Results

4.1 Sample and Model Specification

A population of N=33,354 responses were obtained for analysis containing a sample size of 190 patients with melanoma. Appendix A lists the names, descriptions and levels of measurement for variables of this study.

Chi-squared analysis was carried out in a univariate perspective to determine relationships regarding the variables that alter care for melanoma. Odd-ratios were then calculated to determine if co-morbid depression had an effect the frequency a melanoma patient with depression visited healthcare providers and the stage of malignancy at the time of diagnosis. Each relationship is discussed in turn below.

R- Software was utilized to conduct descriptive statistics of the variables as well as univariate and multivariate analyses. The inferential tests were two-sided and a 95% significance level was set for determining statistical significance. All inferential tests were performed using survey data analysis which incorporated the variable PERSON_FINWT0 from the HINTS datasets. This is a weighted variable designed in the original survey and is used to make the sample more representative of national estimates. Frequency distribution was used to address the first research question. Univariate analysis

analyses were used to address research question 2, multivariate analysis was used to address research questions 3.

4.2 Descriptive Statistics

Table 3: Measures of Central Tendency for Continuous Variables of Study

Variable	Unweighted Sample Size	Weighted Sample Size	Weighted Mean	Weighted Standard Deviation	Weighted Median
Age	185	7196360	63.6	1.73	64.4
PHQ4	155	5622628	1.7	0.22	0
TotalScoreOfHealthSupport	172	6741943	11.1	0.43	9

Table 3 shows the measures of central tendency (mean, median, standard deviation) for the continuous variables in the study. The mean age of the participants was 63.6 years with 1.73 standard deviation as for PHQ4 the mean was 1.7 and 0.22 standard deviation. The total score of health support for the mean was 11.1 with 0.43 standard deviation.

Table 4: Frequencies and Percentages of the Categorical Variables of Interest

Variable	Unweighted Sample Size	Unweighted Percent	Weighted Sample Size	Weighted Percent
FreqGoProvider_cat				
greater or equal to 3	122	65.9	4440719	61.3
less than 3	63	34.1	2801678	38.7
StageOfDiag				
Advance Stage	27	25.7	982891	24.5
Early Stage	78	74.3	3036823	75.5
MedConditions_Depression				
1	29	25.9	733623	17.3
2	83	74.1	3511425	82.7
Emotional Support				
1	96	85.7	3833840	90.3
2	16	14.3	411208	9.7
GenderC				
1	99	53.5	3774723	51.9
2	86	46.5	3495122	48.1
Married2				
Married/Living as Married	122	64.2	5202983	70.2
Not married	68	35.8	2204368	29.8
AgeGrpB				
1	6	3.2	399000	5.5
2	14	7.6	902385	12.5
3	57	30.8	2278210	31.7
4	56	30.3	1614156	22.4
5	52	28.1	2002609	27.8
Race2				
Non-Hispanic White	158	92.9	6250875	96
Non-white	12	7.1	263647	4
HHInc				

less than $50,000	63	37.7	2157858	33.2
greater or equal to $50,000	104	62.3	4338390	66.8
PHQ4_cat				
above average	66	42.6	2040951	36.3
average or lower	89	57.4	3581677	63.7
TotalScoreOfHealthSupport.new				
above average	68	39.5	2522964	37.4
average or lower	104	60.5	4218979	62.6

Table 4 presents the frequencies and percentages of the comorbidities and demographic variables used in the study.

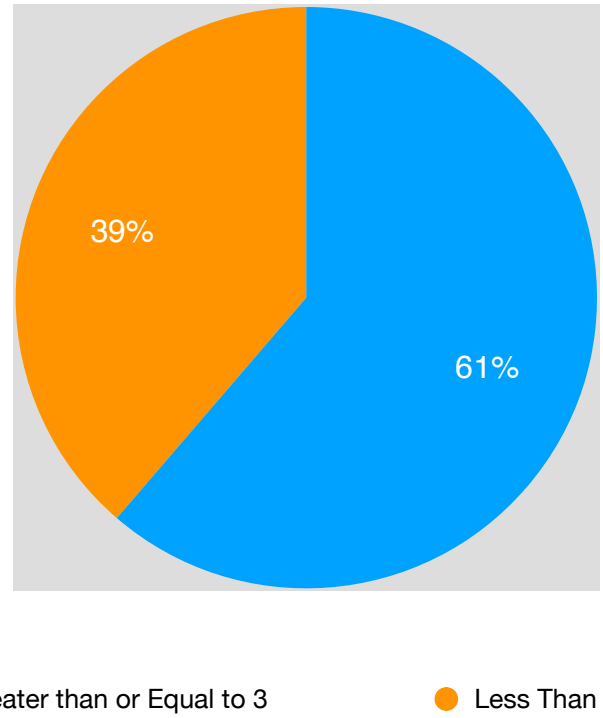

Chart 1: Frequency of Provider Visits for Melanoma Patients

Results show that around 61% of melanoma patients go to their doctor more than 3 times/ year.

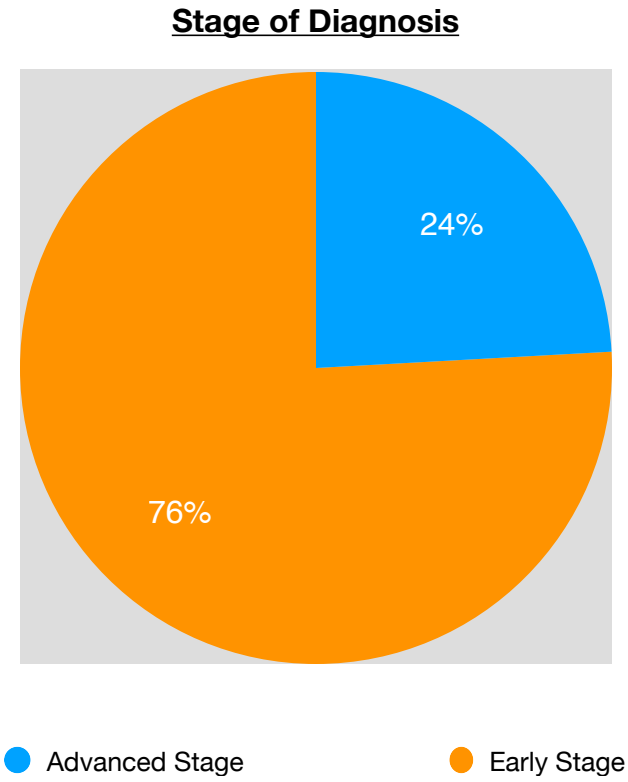

Chart 2: Stage of Diagnosis of Melanoma Patients

Analyses reveal that about 76% of melanoma patients were diagnosed with melanoma at an earlier stage.

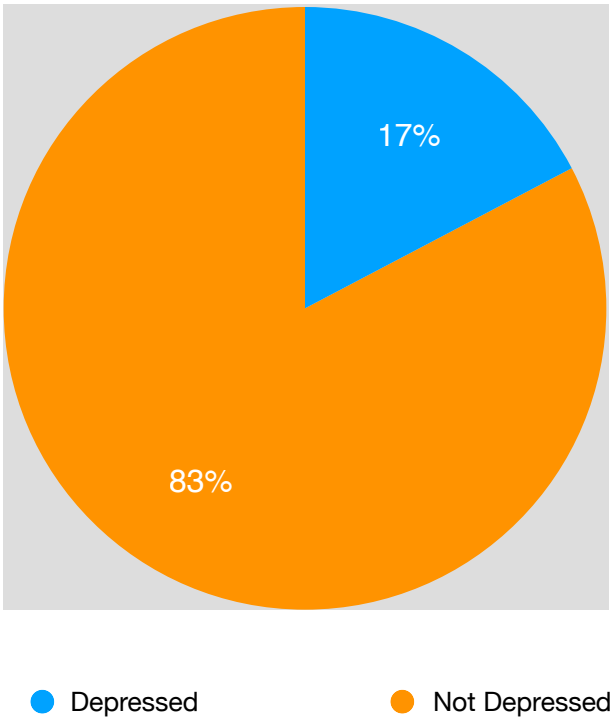

Chart 3: Population of Melanoma Patients with Depression

Results show that about 17% of melanoma patients are also diagnosed with clinical depression.

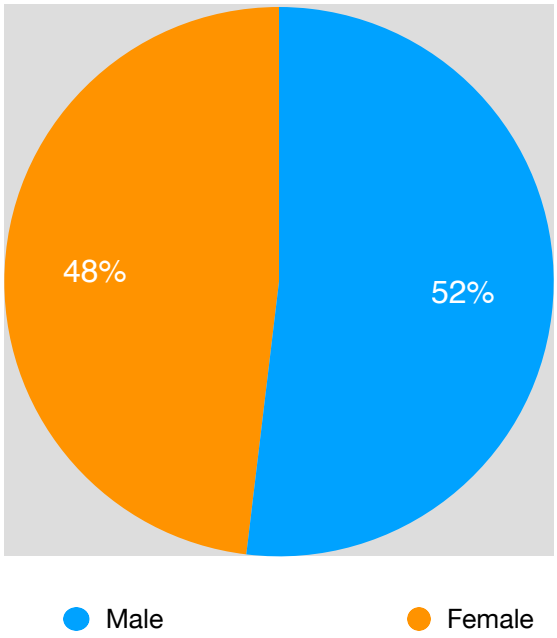

Chart 4: Gender of General Population with Melanoma

Chart 4 illustrates that about 52% of melanoma patients are males.

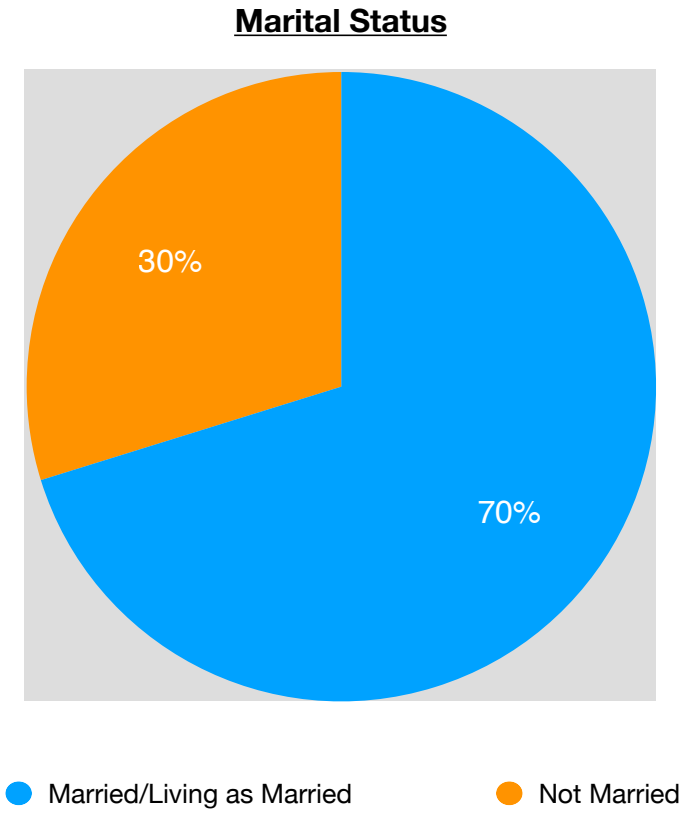

Chart 5: Marital Status of Melanoma Patients

Analyses reveal that about 30% of the melanoma population are not married.

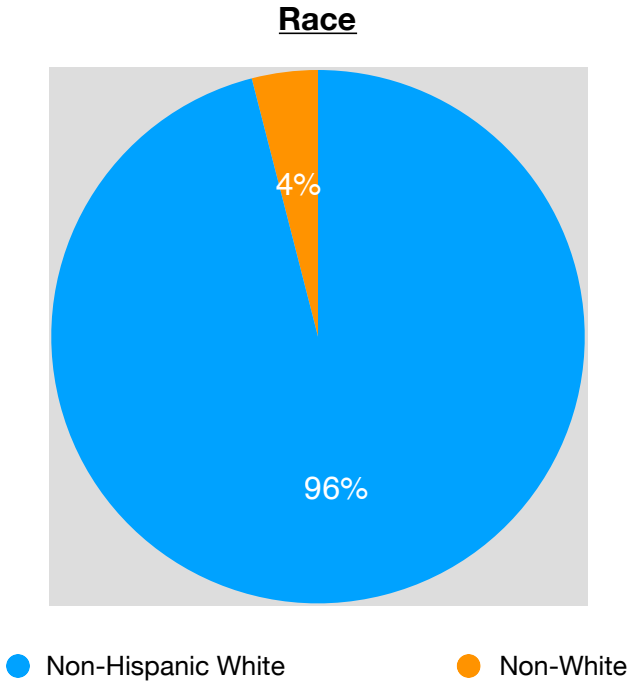

Chart 6: Race of Melanoma Patients

With only 4% of melanoma patients being Non-White, Non-Hispanic Whites are the most likely to be diagnosed with melanoma.

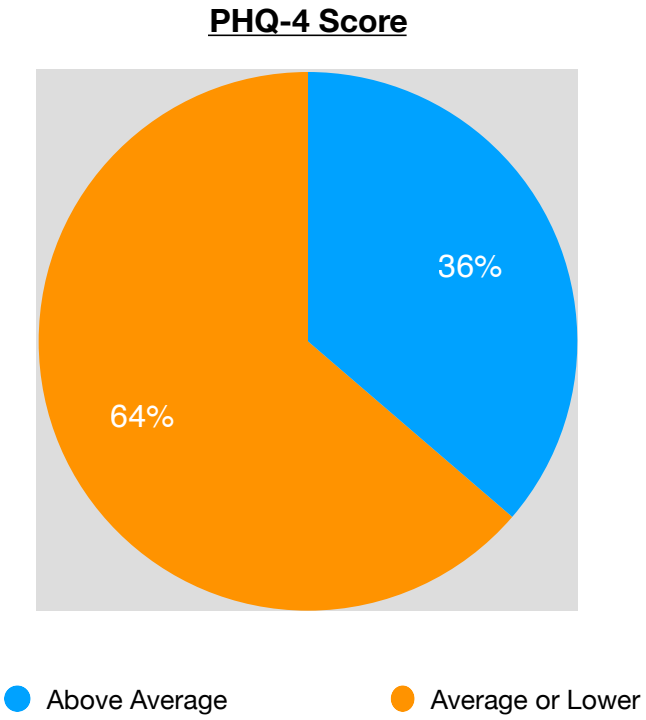

Chart 7: PHQ-4 Score for Melanoma Patients

Results show that around 36% of melanoma patients have an above average PHQ4 score (1.7), meaning there is a correlation between melanoma and depression.

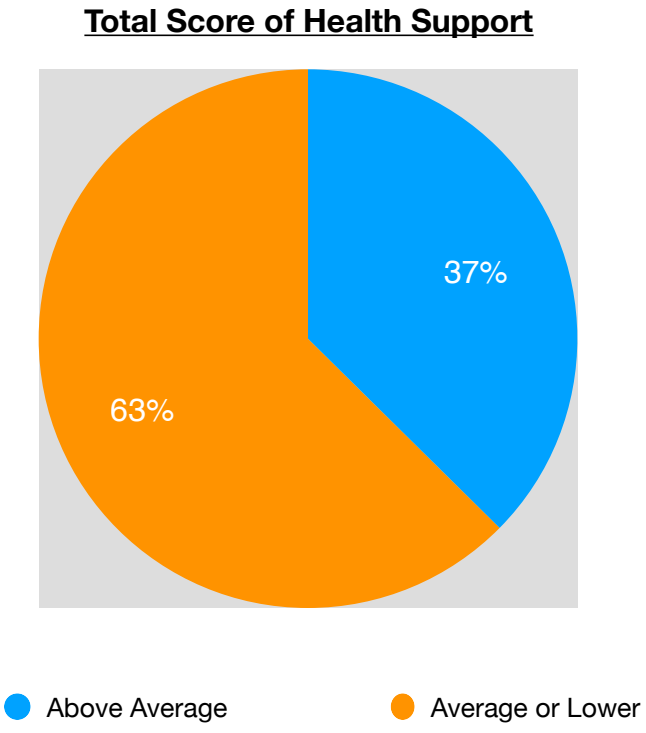

Chart 8: Total Score of Health Support of Melanoma Patients

Analysis shows the majority of melanoma patients are within the average or lower of total score of health support, while less than half of the melanoma patients are above the average (11.1).

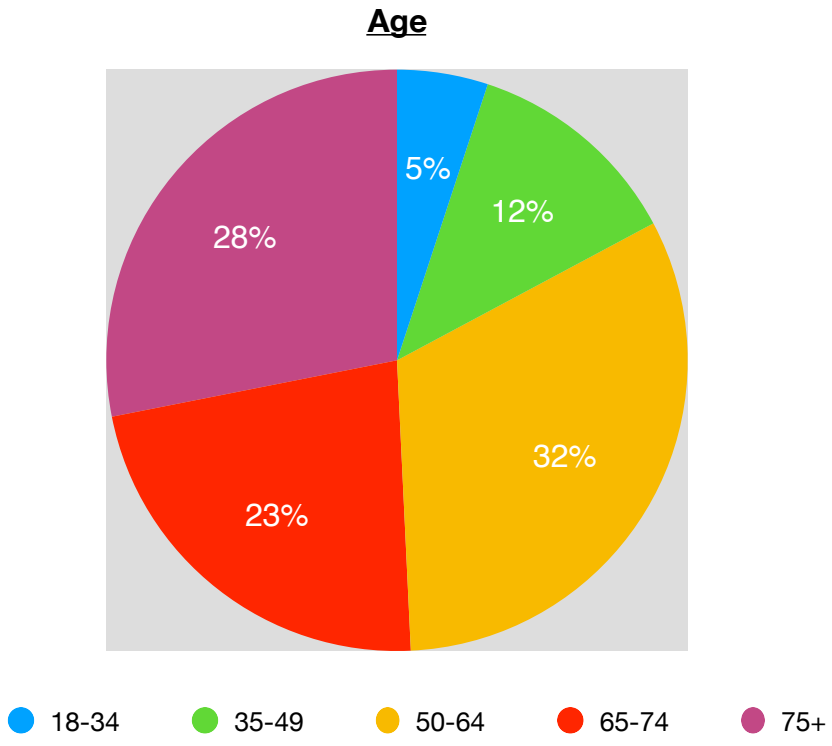

Chart 9: Age of Melanoma Patients

Results reveal that the majority of patients with melanoma are above the age of 50.

4.3 Assumptions

The data set was investigated to make sure that it satisfied the assumption of the multivariate analysis and association analysis of this study. Absence of missing data was considered as a null response and was not taken into consideration for data analysis. Variables with high missing proportion was not included in the multivariate analysis. The population data revealed relationships but further examination was done to determine true, statistically significant relationships. The results of these studies determined which variables was to be included in the multivariate analyses.

4.4 Descriptive Statistics (Frequency Distribution) and Bivariate Analysis (Chi-square) for Melanoma Patients with Comorbid Clinical Depression

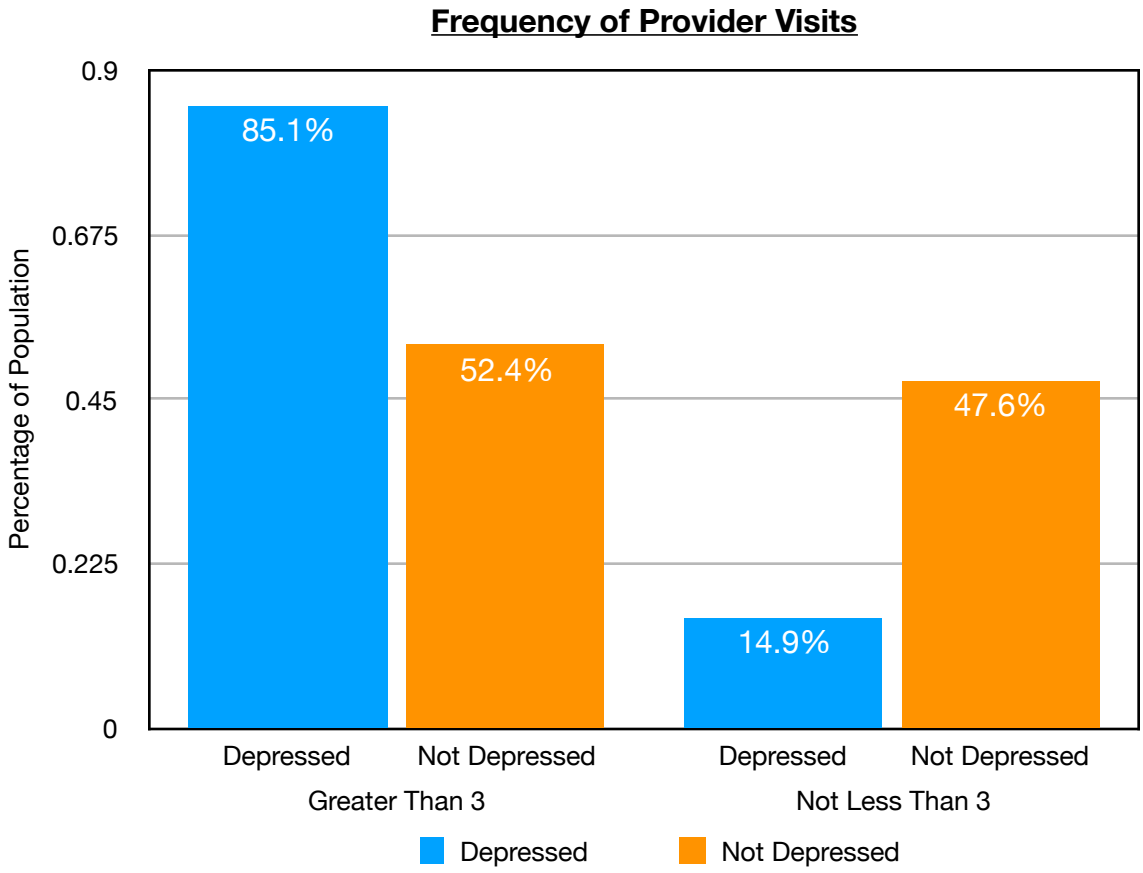

Chart 10: Comparison of Melanoma Patients with and without Depression Based on Frequency of Provider Visits

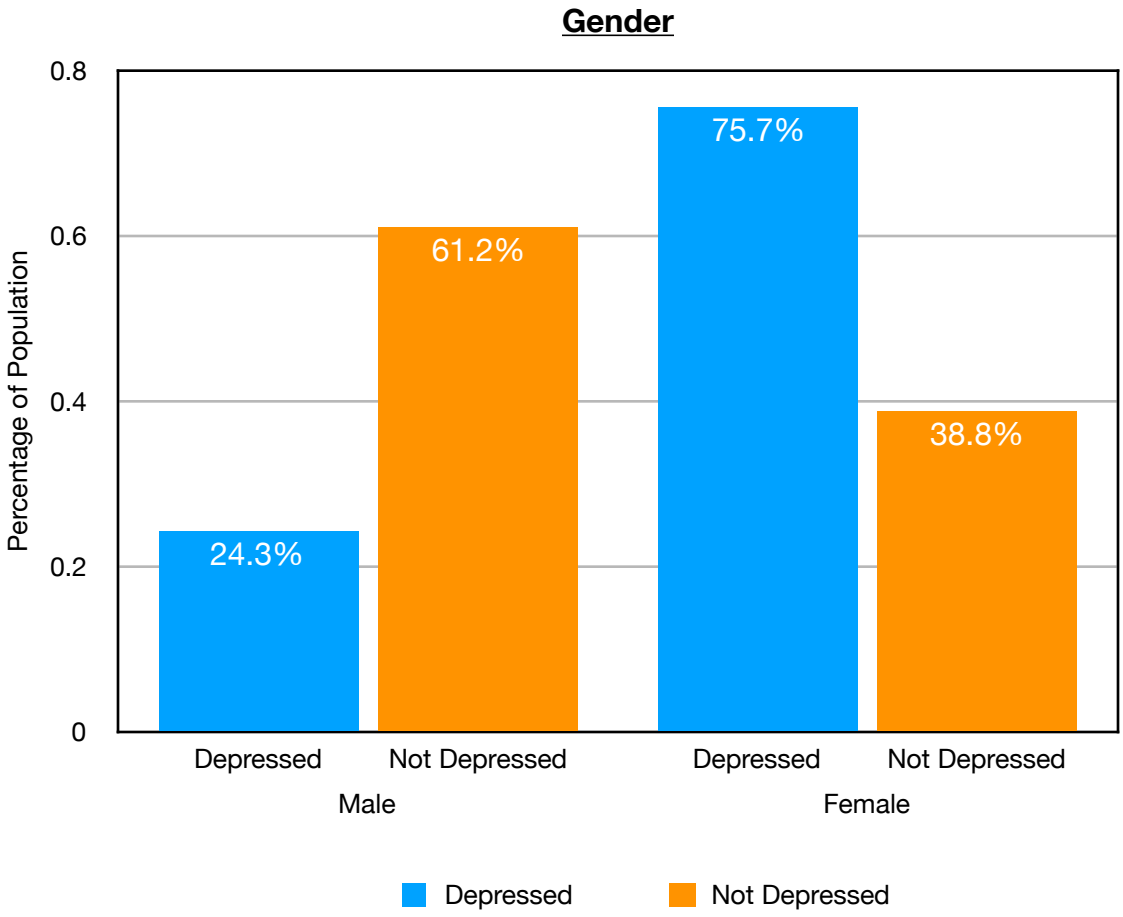

Chart 11: Comparison of Melanoma Patients with and without Depression Based on Gender

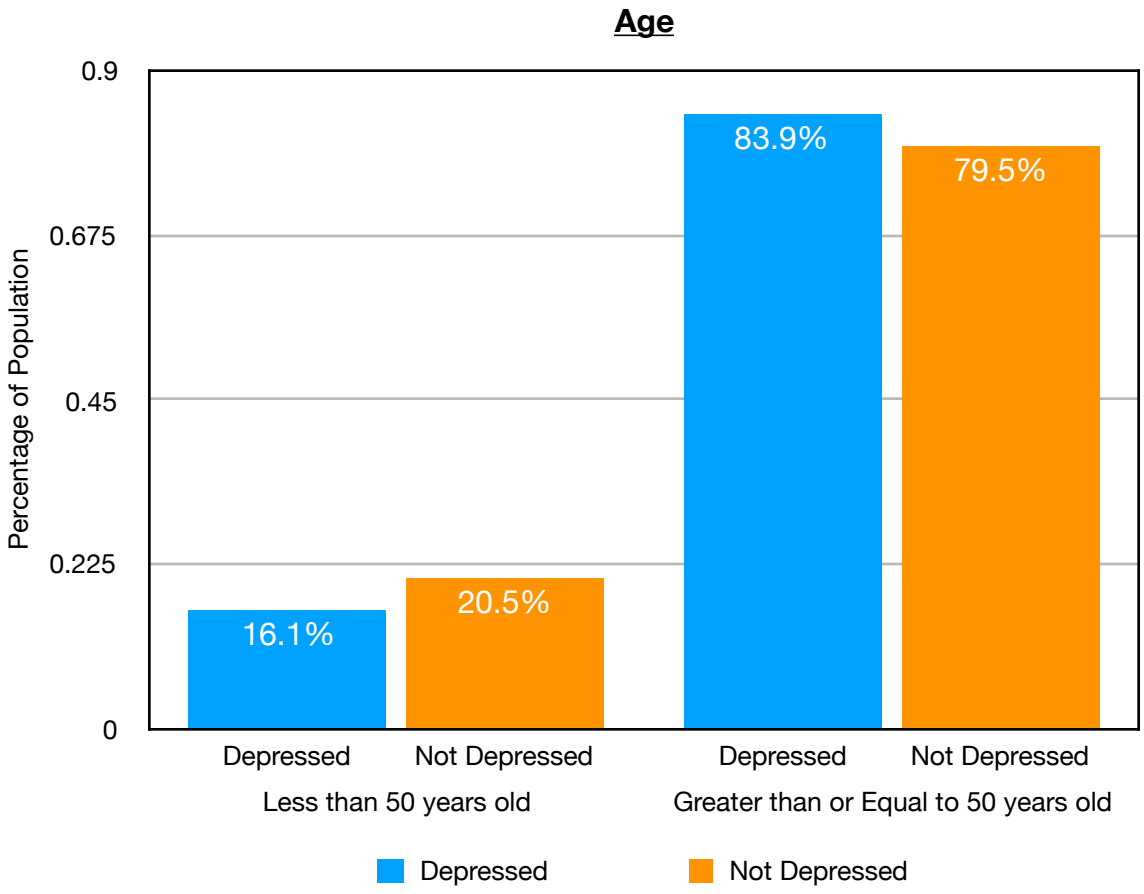

Chart 12: Comparison of Melanoma Patients with and without Depression Based on Age

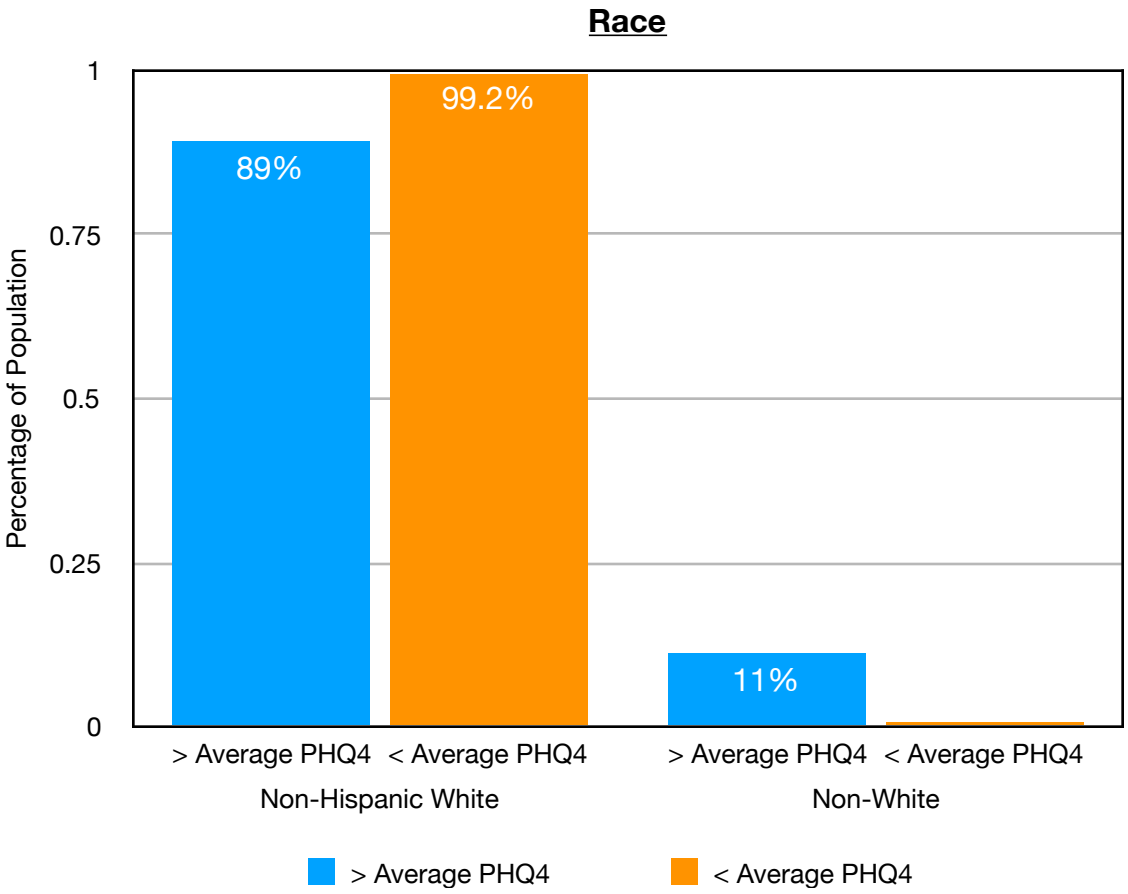

Chart 13: Comparison of Melanoma Patients with and without Depression Based on Race

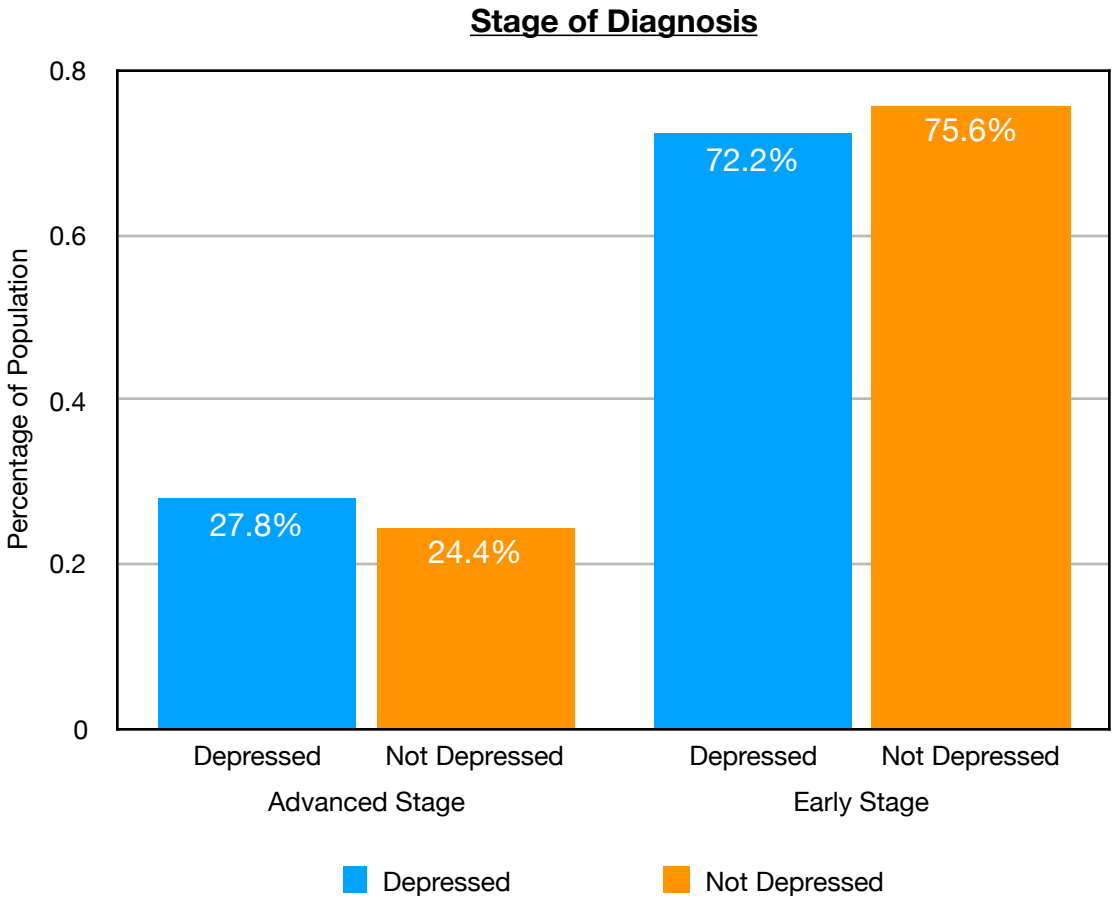

Chart 14: Comparison of Melanoma Patients with and without Depression Based on Stage of Diagnosis

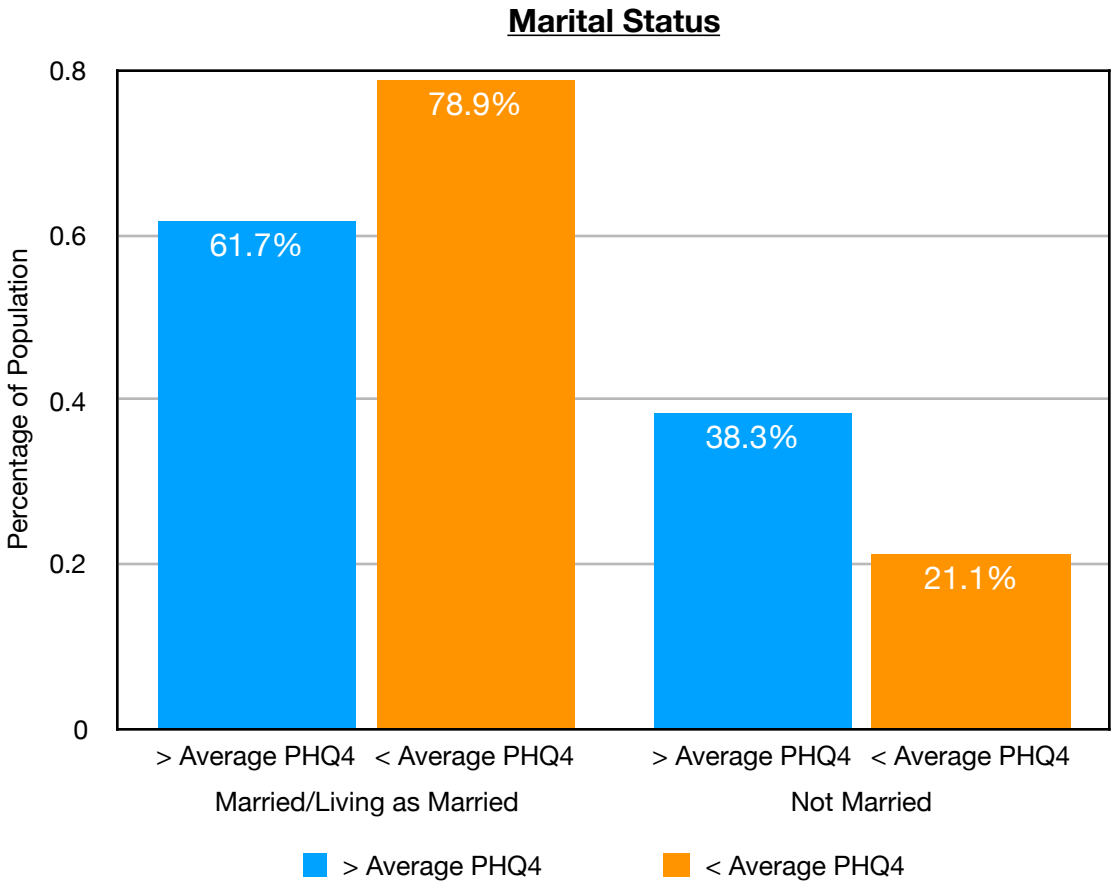

Chart 15: Comparison of Melanoma Patients with and without Depression Based on Marital Status

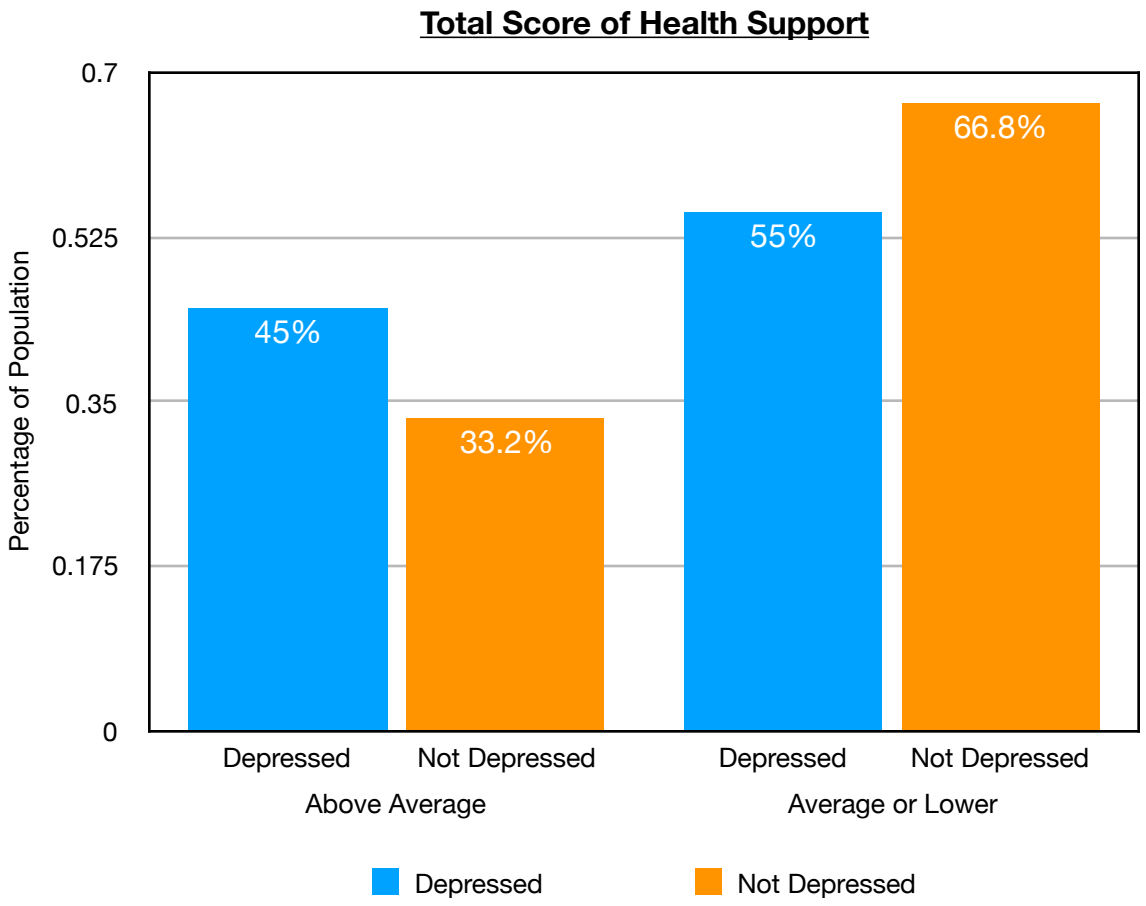

Chart 16: Comparison of Melanoma Patients with and without Depression Based on Total Score of Health Support

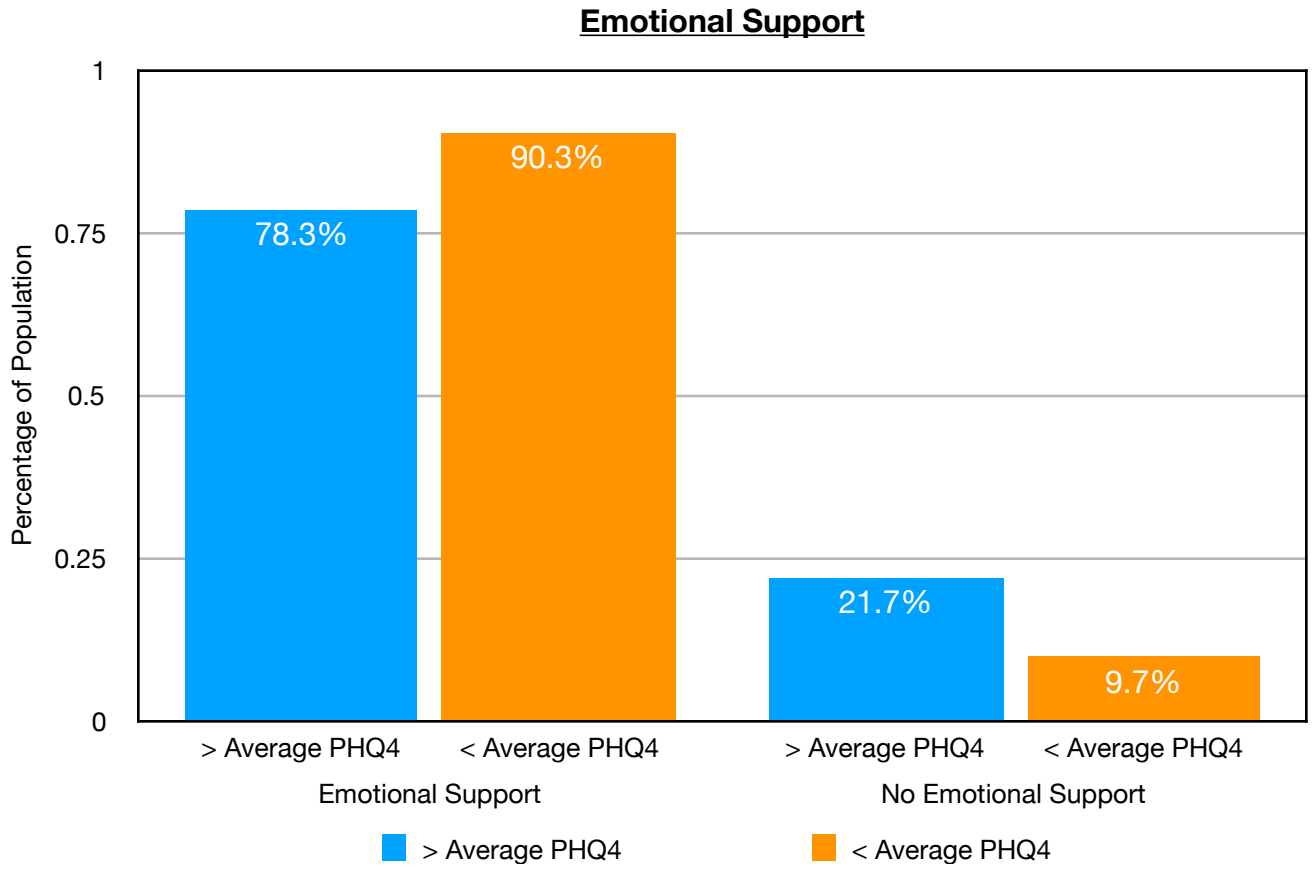

Chart 17: Comparison of Melanoma Patients with and without Depression Based on Total Score of Emotional Support

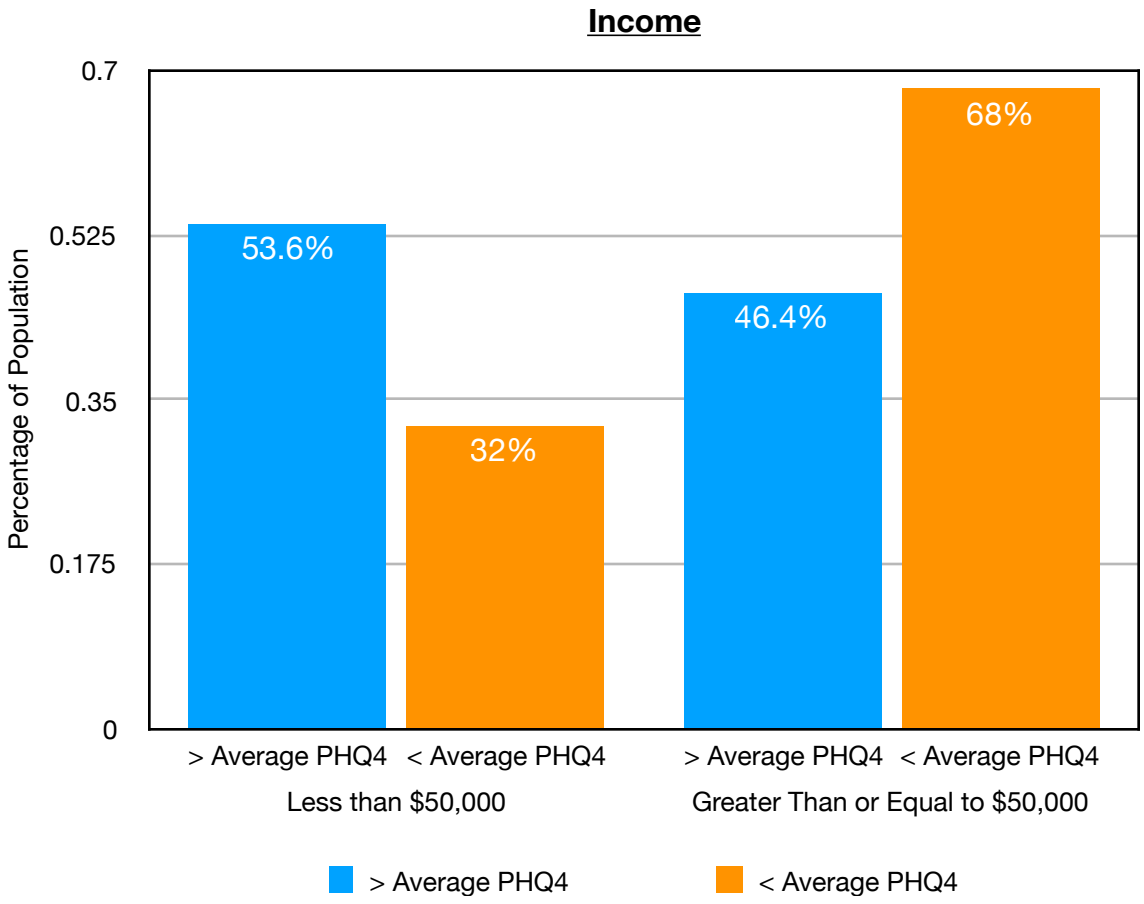

Chart 18: Comparison of Melanoma Patients with and without Depression Based on Income

The fulcrum of this project rests on the effect of depression on the diagnosis of melanoma. As such, it was imperative to first establish the presence of depression among the studied melanoma population and, furthermore, the effect depression has on observed demographic factors.

Depression was predicted to correlate with a decreased frequency of provider visits, however, revealed the contrary. As discussed further below, melanoma patients with depression were more likely to visit their healthcare providers as those without depression ($p = 0.0023$). Furthermore, it was found that gender and age (Charts 12 and 13) led to variation among the melanoma patient population regarding depression. As shown in Table 5, it was found that 28.9% of female melanoma patients suffered from concomitant depression in comparison to 71.1% that of female patients that did not ($p = 0.0037$) and that 13.0% of melanoma patients under the age of 50 suffered from depression ($p = 0.0127$).

PHQ4 Scores

The patient health questionnaire 4 is a survey used by clinicians to screen patients for anxiety and depression. Like all screening tests, it is a starting point for treatment for these psychiatric maladies, and as such, it was essential to analyze the scores of melanoma patients in relation to other demographic variables.

As revealed in Table 6, over half of all patients with above average PHQ4 scores were found to have high frequency of provider visits ($p = 0.0001$) which is consistent with what was evidenced in the frequency of visits analysis discussed below. Above the

average PHQ4 scores also showed to have a relationship with race ($p = 0.0033$), as the majority of patients with above average PHQ4 score were Non-Hispanic whites. However, despite this high frequency of visits, patients with above average PHQ4 score had no difference in stage of melanoma at the time of diagnosis than the general population. Above average PHQ4 score similarly did not have a relationship between gender, occupational status, or ages. However, above average PHQ4 scores were found to have a significant relationship with marital status ($p = 0.0002$) and emotional support (0.0033) as shown in table 6.

Table 5: Association Between Depression and Demographic and Life Factors

Variable	Yes (Weighted)	No (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	598674 (85.1%)	1815669 (52.4%)	0.0023
less than 3	105012 (14.9%)	1650839 (47.6%)	
GenderC			
1	176094 (24.3%)	2115170 (61.2%)	0.0037
2	547587 (75.7%)	1341053 (38.8%)	
AgeGrpB			
Less than 50	107217 (16.1%)	716516 (20.5%)	0.0127
Greater or equal to 50	561237 (83.9%)	2765565 (79.5%)	
TotalScoreOfHealthSupport.new			
Above Average	318108 (45%)	1060638 (33.2%)	0.0711
Average or Lower	386613 (55%)	2134881 (66.8%)	
StageOfDiag			
Advance Stage	199367 (27.8%)	783524 (24.4%)	0.7787
Early Stage	516535 (72.2%)	2431383 (75.6%)	

Table 6: Association with PHQ-4 Total Score

Variable	Above Average (Weighted)	Average or Lower (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	1730248 (85.4%)	1500989 (42.4%)	0.0001
less than 3	295130 (14.6%)	2042516 (57.6%)	
Race2			
Non-Hispanic White	1714318 (89%)	3248998 (99.2%)	0.0033
Non-white	211617 (11%)	27573 (0.8%)	
MaritalStatus			
1	1223778 (61.7%)	2745943 (78.9%)	0.0002
2	758799 (38.3%)	734009 (21.1%)	
HHInc			
1	430136 (23.1%)	163286 (5%)	0.0574
2	247392 (13.3%)	452384 (13.9%)	
3	246147 (13.2%)	291670 (9%)	
4	369265 (19.8%)	836651 (25.8%)	
5	571513 (30.7%)	1498918 (46.2%)	
EmotionalSupport			
1	1123663 (78.3%)	2680240 (96.4%)	0.0033
2	312200 (21.7%)	99008 (3.6%)	
StageOfDiag			
Advance Stage	311563 (24.2%)	671328 (25.7%)	0.8939
Early Stage	974058 (75.8%)	1943923 (74.3%)	
GenderC			
1	948458 (48%)	2119732 (59.2%)	0.2717
2	1027350 (52%)	1461945 (40.8%)	
AgeGrpB			
1	117815 (5.9%)	36088 (1%)	0.1350
2	171130 (8.5%)	570694 (16.2%)	

3	735247 (36.7%)	1145768 (32.5%)	
4	595968 (29.7%)	621025 (17.6%)	
5	385560 (19.2%)	1151184 (32.7%)	

Research Question 1 (RQ1). What proportion of the melanoma population has comorbid clinical depression?

Null Hypothesis 1 (H01): There is not a statistically significant population of melanoma patients that also have depression.

***Alternative Hypothesis 1 (HA1)*:** There is a statistically significant population of melanoma patients that also have depression

Table 7 shows a descriptive statistic frequency distribution was performed to investigate RQ1. As seen in Table 7, 17.3% of melanoma patients suffer with depression.

Table 7: Descriptive Statistics/Frequency Distribution for Depression

Variable	Unweighted Sample Size	Unweighted Percent	Weighted Sample Size	Weighted Percent
MedConditions_Depression				
1	29	25.9	733623	17.3
2	83	74.1	3511425	82.7

In conclusion as it relates to the Null Hypothesis: Reject the Null Hypothesis 1. There is a statistically significant population of melanoma patients who also have depression.

4.5 Univariate Analysis for Frequent Go Provider

Research Question 2 (RQ2). What are the effects of comorbid depression and demographic variables on frequency of healthcare provider visits?

Null Hypothesis 2 (H02): There is not a statistically significant relationship between comorbid depression and demographic variables on frequency of healthcare provider visits.

Alternative Hypothesis 2 (HA2): There is a statistically significant relationship between comorbid depression and demographic variables on frequency of healthcare provider visits.

Frequency of provider visit is widely believed to be an important factor in leading melanoma patients to a good outcome. Therefore all population variables were analyzed to determine if they had positive or negative effects on the patient's ability to see their healthcare providers. Analysis, specifically, was cruxed upon a patient's ability to see their healthcare provider more than or less than three times.

Results in Table 5 show that patients with depression were found to be visit their doctor more than three times in a given interval in comparison to patients without depression ($p= 0.0023$) and that only 14.9% of the depressed patient population visited their doctor less than three times ($p= 0.0023$). More so, univariate analysis in Table 9 show that patients with depression were 5 times more likely to go to their healthcare providers ($p = 0.0051$). These findings also coincided with the results that indicated that 85.4% of patients with above average patient health questionnaire 4 (PHQ4) ratings went

to their providers more than three times (p = 0.0001). This was further validated by univariate analysis which showed that patients with above PHQ4 scores were 7 times more likely to go to their healthcare provider more than 3 times (p = 0.0001). These findings indicate that patients with depression were more likely to go to their healthcare providers.

Income, in contrast, was found to be a limiting factor in follow-up care. Analysis in Table 8 indicates that only 39.5% of patients in that population with an income of less than $50,000 saw their provider more than three times (p = 0.0163). 46.7% of men were found to go to their providers more than three times and 53.3% of women were found to go their providers more than three times. Interestingly, age, degree of emotional support, and total health support were not found to have any effect on the patient's rate of seeing their providers.

Table 9 below shows a univariate analysis was performed to test the null hypothesis of RQ2. The dependent variable was Frequency of Provider visits. Independent variables included: Depression, PHQ4, Gender, Stage of Diagnosis, Age, Race, Income, Emotional Support, Total Score of Health Support.

Conclusion as it Relates to the Null Hypothesis 2: Reject the Null Hypothesis 2. Results show that there is a statistically significant relationship between Depression and Frequent-go Provider.

Table 8: Association with Frequent-Go Provider

Variable	greater or equal to 3 (Weighted)	less than 3 (Weighted)	P value
MedConditions_Depression			
1	598674 (24.8%)	105012 (6%)	0.0023
2	1815669 (75.2%)	1650839 (94%)	
PHQ4_cat			
above average	1730248 (53.5%)	295130 (12.6%)	0.0001
average or lower	1500989 (46.5%)	2042516 (87.4%)	
HHInc			
Less than $50,000	1528602 (39.5%)	545574 (22.2%)	0.0163
Greater than or equal to $50,000	2338912 (60.5%)	1918206 (77.8%)	
GenderC			
1	2055133 (46.7%)	1681417 (62.2%)	0.1132
2	2346815 (53.3%)	1021525 (37.8%)	
AgeGrpB			
1	317713 (7.4%)	81287 (2.9%)	0.1540
2	305484 (7.1%)	596901 (21.3%)	
3	1539135 (35.9%)	739075 (26.4%)	
4	1073689 (25%)	524894 (18.7%)	
5	1052988 (24.6%)	859520 (30.7%)	
Race2			
Non-Hispanic White	3680438 (94.7%)	2546036 (97.8%)	0.2729
Non-white	206994 (5.3%)	56653 (2.2%)	
TotalScoreOfHealthSupport.new			
above average	1579761 (36%)	943202 (40.7%)	0.6573
average or lower	2804643 (64%)	1375571 (59.3%)	
EmotionalSupport			
1	2151321 (89.1%)	1607665 (91.6%)	0.7010
2	263022 (10.9%)	148186 (8.4%)	

StageOfDiag			
Advance Stage	479607 (20.3%)	487711 (30.9%)	0.3548
Early Stage	1886636 (79.7%)	1090906 (69.1%)	

Table 9: Univariate Analysis: FreqGoProvider

				Univariate		
Name	**Levels**	**Ref**	**OR**	**low95**	**up95**	**pVal**
MedConditions_Depression	2	1	**5.18**	**1.68**	**15.99**	**0.0051**
PHQ4_cat	average or lower	above average	**7.98**	**3.33**	**19.12**	**0.0001**
HHInc	2	1	**9.61**	**1.86**	**49.60**	**0.0076**
	3	1	**1.43**	**0.24**	**8.61**	**0.6944**
	4	1	**9.03**	**1.95**	**41.79**	**0.0055**
	5	1	**6.05**	**1.45**	**25.30**	**0.0148**
GenderC	2	1	**0.53**	**0.24**	**1.16**	**0.1151**
AgeGrpB	2	1	**7.64**	**0.75**	**77.58**	**0.0874**
	3	1	**1.88**	**0.25**	**14.37**	**0.5452**
	4	1	**1.91**	**0.25**	**14.72**	**0.5350**
	5	1	**3.19**	**0.42**	**24.26**	**0.2639**
Race2	Non-white	Non-Hispanic White	**0.40**	**0.07**	**2.18**	**0.2887**
EmotionalSupport	2	1	**0.75**	**0.18**	**3.19**	**0.7020**
TotalScoreOfHealthSupport	average or lower	above average	**1.03**	**0.94**	**1.14**	**0.4945**
StageOfDiag	Early Stage	Advance Stage	**0.57**	**0.17**	**1.89**	**0.3587**

4.6 Multivariate Analysis Comparing Stage of Diagnosis of Melanoma Patients with and Without Depression

Research Question 3 (RQ3): At what stage of melanoma are patients with depression diagnosed versus population without depression?

Null Hypothesis 3 (H03): There is not a statistically significant difference in the stage of melanoma at the time of diagnosis in patients with and without depression

Alternative Hypothesis 3 (HA3): There is a statistically significant difference in the stage of melanoma at the time of diagnosis in patients with and without depression

Table 10 shows that race does not have an effect on the stage of melanoma at the time of diagnosis. 5.61% of non-white patients were found to have an advanced stage of the malignancy at the time of diagnosis and 27.4% of white patients were found to have an advanced stage of the malignancy at the time of diagnosis ($p = 0.0861$). Furthermore, multivariate analysis, as seen in Table 11, yielded that non-white patients compared to non-Hispanic white patients were more than 65 times more likely to be diagnosed at an early stage of the malignancy ($p = 0.0703$). This is likely secondary to the known biological tenants of melanoma that dictate that white patients are more susceptible to the malady, as described above.

Also, as per multivariate analysis in Table 11, it was also found that patients with average or lower scores of health support were 31% less likely to be diagnosed at an early stage ($p = 0.0350$).

Conclusion as relates to Null Hypothesis 3: Accept the Null Hypothesis 3. There is no statistically significance difference in the stage of melanoma at the time of diagnosis in patients with and without depression.

However, it is imperative to note that melanoma patients with depression were not found to be diagnosed at a later stage when compared to a normal population of melanoma patients. Neither was there an appreciable difference in stages of diagnosis for gender, emotional support, employment, marital status, nor PHQ4 scores.

Table 10: Association with Stage of Diagnosis

Variable	Advance Stage (Weighted)	Early Stage (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	479607 (49.6%)	1886636 (63.4%)	0.3548
less than 3	487711 (50.4%)	1090906 (36.6%)	
GenderC			
1	512386 (52.1%)	1638829 (54.7%)	0.8631
2	470505 (47.9%)	1358963 (45.3%)	
MaritalStatus			
1	758360 (77.2%)	1890920 (68%)	0.6668
2	8119 (0.8%)	122121 (4.4%)	
3	26897 (2.7%)	218062 (7.8%)	
4	151401 (15.4%)	350332 (12.6%)	
5	0 (0%)	47945 (1.7%)	
6	38114 (3.9%)	151643 (5.5%)	
AgeGrpB			
1	36088 (3.7%)	72616 (2.5%)	0.2942
2	186840 (19%)	459316 (16.1%)	
3	48463 (4.9%)	859674 (30.1%)	
4	397487 (40.4%)	599209 (21%)	
5	314013 (31.9%)	862590 (30.2%)	
Race2			
Non-Hispanic White	931219 (98.8%)	2467019 (93.1%)	0.0861
Non-white	10884 (1.2%)	183076 (6.9%)	
HHInc			
1	50939 (6.1%)	194233 (6.9%)	0.3479
2	95292 (11.4%)	432989 (15.4%)	

3	127574 (15.2%)	329639 (11.7%)	
4	82568 (9.9%)	872065 (31%)	
5	481141 (57.4%)	982310 (34.9%)	
MedConditions_Depression			
1	199367 (20.3%)	516535 (17.5%)	0.7787
2	783524 (79.7%)	2431383 (82.5%)	
EmotionalSupport			
1	825242 (84%)	2713297 (92%)	0.3001
2	157649 (16%)	234621 (8%)	
SkinCancerSelfCheck			
1	278829 (74.8%)	182882 (18.8%)	0.0056
2	0 (0%)	11770 (1.2%)	
3	93742 (25.2%)	778951 (80%)	
PHQ4_cat			
above average	311563 (31.7%)	974058 (33.4%)	0.8939
average or lower	671328 (68.3%)	1943923 (66.6%)	
TotalScoreOfHealthSupport.new			
above average	407523 (43.8%)	950483 (33.7%)	0.5125
average or lower	523707 (56.2%)	1873139 (66.3%)	

Table 11: Multivariate Analysis: Stage of Diagnosis

				Multivariate		
Name	**Levels**	**Ref**	**OR**	**low95**	**up95**	**pVal**
GenderC	2	1	**0.25**	**0.04**	**1.49**	**0.1330**
OccupationStatus	2	1	**0.00**	**0.00**	**0.03**	**0.0014**
	3	1	**0.07**	**0.00**	**1.83**	**0.1166**
	5	1	**0.07**	**0.01**	**0.70**	**0.0275**
	6	1	**0.00**	**0.00**	**0.00**	**0.0000**
Race2	Non-white	Non-Hispanic White	**65.37**	**0.77**	**5564.34**	**0.0703**
HHInc	2	1	**0.15**	**0.00**	**15.18**	**0.4237**
	3	1	**0.01**	**0.00**	**1.37**	**0.0727**
	4	1	**3.51**	**0.01**	**2414.02**	**0.7074**
	5	1	**0.01**	**0.00**	**1.10**	**0.0597**
MedConditions_Depression	2	1	**0.53**	**0.05**	**5.31**	**0.5896**
EmotionalSupport	2	1	**0.24**	**0.00**	**16.64**	**0.5149**
TotalScoreOfHealthSupport	average or lower	above average	**0.69**	**0.50**	**0.97**	**0.0350**

Chapter V

Discussion

It has been widely reported that melanoma patients with co-morbid depression would experience worse outcomes. However, this reported relationship has been poorly qualified and quantified. Therefore, this study sought to examine possible barriers to care among the population of melanoma patients with co-morbid depression.

Depression

This study, first, determined the population of melanoma patient suffered from depression. As per our analysis, it was found that 28.9% of female melanoma patients suffered from depression ($p = 0.0037$). Furthermore, it was found that of the total population with melanoma, 16.8% of melanoma patients above the age of 50 experienced co-morbid depression whereas only 13.0% of these patients were under the age of 50. Aggregately, these findings illustrate that co-morbid depression was present within the examined population.

Frequency of Healthcare Provider Visits

Once this was established, the population was examined to determine their quantitative rates of follow-up. It has been well reported that patients with depression

were less likely to follow-up with their chosen healthcare providers however, the findings of this present study was to the contrary [Baughan et al, 1993, Kasparian et al., 2009; Livingstone et al, 2015]. Analysis revealed that melanoma patients with depression were five times more likely to present to their healthcare providers for care more than three times in a given interval in comparison to melanoma patients without depression. It was postulated that patients with depression exhibited poor follow-up behaviors as a result of the negative symptoms of their malady however, melanoma patients with depression may rebuke this trend as these types of patients may be visiting their healthcare providers to not only create regiments to combat melanoma but also to follow-up with providers to obtain care for their depression.

This trend was also observed in melanoma patients with high PHQ4 scores. The PHQ4, again, is a screening test for depression and anxiety and in regards to this study can be considered a surrogate marker for the presence of depression in melanoma patients [Kroenke *et al.,* 2009]. As per this present analysis, it was shown that 85.4% of melanoma patients with high PHQ4 scores visited their healthcare providers more than three times in a given interval. This trend may also be explained as melanoma patients with depression seeking care for their dual hardships.

Furthermore, it was found that less male patients with melanoma and depression saw their providers more than three times when compared to women. It was predicted that men would see their providers more than women as the incidence of melanoma in men is higher than it is in women [Mayer *et al.,* 2014; Albert, 2015]. However, this trend may be explained by social culture as women are more inclined to take better care of

themselves, while men are less likely to do so or less likely to even notice as they may not be as focused on appearance as females would be.

The final variable that was found to have an effect on provider visits was income. It was found that patients with an annual income of less than $50,000 being less likely to see their healthcare provider more than three times. This is consistent with predictions as it has been reported that patients with lower socioeconomic status are less likely to adhere to follow up protocol or attain initial screening [Mayer *et al.,* 2014]. This may be due to the financial strain of regularly seeing one's healthcare provider, not only in the actual cost of the visit but also in the potential loss of money from having to miss work to do so.

Interestingly, we were unable to find any significant effect of age, race, degree of emotional support, or total health support rating on the patient's rate of seeing their provider. This implies that of the factors investigated presence of depression, PHQ4 scores, and income were the most important correlative factors for number of visits to primary care physicians.

Stage of Melanoma at Time of Diagnosis

Stage of melanoma at the time of diagnosis is well-reported and significant prognostic indicator as patients who are diagnosed at later stages tend to have worse outcomes [Krige *et al.,* 1991]. As such, all demographic variables of patients with melanoma were analyzed to probe for this relationship.

Race was shown to have no effect on stage of malignancy at the time of initial diagnosis. Analysis revealed that only 5.6% of non-white patients were diagnosed at

advanced stages 27.4% of white patients were diagnosed at advanced stages. This is consistent with known principles of melanoma as white patients are more susceptible to the malignancy [Mayer *et al.,* 2014].

Melanoma patients suffering from depression, curiously, were found to not have a difference in stage of their malignancies at the time of their respective diagnosis' in comparison to melanoma patients without depression. This, again, was in direct contradiction to predictions as it was widely held that patients with depression would be diagnosed at a more advanced stage due to the apathy characterized by the affliction [Boz *et al.,* 2009]. Our findings, however, were unable to support this claim. Similarly, PHQ4 scores and emotional support did not have a relationship with a patient's stage at diagnosis. Emotional support was also found to have no effect on a patient stage of malignancy at the time of diagnosis. It was predicated that strong support systems would lead to preemptive screening habits from patients but that this was not the case as per analysis [Rogentine *et al.,* 1979].

Similarly, there was no relationship between stage of melanoma at the time of diagnosis and frequency of visiting healthcare providers. A positive association was predicated as, again, worse outcomes are predicted for patients who are diagnosed at later stages. Therefore, it was predicted that patients who are diagnosed later would be prompted to adhere to stricter follow-up regiments but analysis revealed that this was not the case [Krige *et al.,* 1991].

This was predicted to be due to the fact that low income may bar patients from obtaining potentially expensive treatments however this was also deemed to not have a

significant effect on stage of diagnosis. Gender and marital status also were found to have no effect on the patient's stage of diagnosis.

PHQ4 Scores

The patient health questionnaire 4, again, is a clinical screening tool used to screen patients for depression and anxiety. Therefore, it can be used as a surrogate marker within populations for the presence of depression and demographic variables were analyzed in relation to it with this in mind.

Unsurprisingly, there is a relationship between high PHQ4 scores and higher frequencies of visiting healthcare providers. While unexpected, this is in direct correlation with population of melanoma patients with depression also being found to visit their providers with higher frequency. Furthermore, analysis revealed further consistencies with results found regarding depression. Specifically, PHQ4 scores were found to have a relationship with race as patients with high PHQ4 scores were white but PHQ4 scores were found to have no relation with stage of malignancy at the time of diagnosis, age, or occupational status.

However, higher PHQ4 scores were found to have significant relationships with several depression adjacent demographic variables. It was found that only 30.8% of patients with above average PHQ4 scores were married. Marriage has a known protective effect from the negative symptoms of depression [Rogentine *et al.,* 1979]. This is consistent with findings regarding emotional support as patients with 75.9% of patients

with high PHQ4 scores were found to have low degrees of emotional support in their lives.

Final Conclusion

Aggregately, these findings illustrate inefficiencies within care provided to melanoma patients with co-morbid depression. Melanoma patients with depression were noted to have more frequent visits with their healthcare providers, however, analyses also showed that these more frequent visits did not positively or negatively affect the stage of a patient's malignancy at time of initial diagnosis. Again, stage of diagnosis is a key prognostic indicator of melanoma outcomes and these findings demonstrate that more must be done during those visits to treat a patient's melanoma more appropriately.

As such, one limitation of this study that requires further inquiry is delineation of the types of care that melanoma patients with depression seek. Within the study, a high frequency of healthcare provider visits was defined as "greater than 3" however, these types of visits were never delineated. Therefore it is reasonable to suspect that the providers that these patients sought were not tasked with or responsible for providing care for the patient's co-morbid melanoma. For example, visits with psychiatrists were likely counted within that statistic but psychiatrists do not provide care to a patient's melanoma nor do they actively screen or treat their patients for melanoma. They, typically, attend to organic maladies from the context of the effect it has on the patient's psychiatric help and, appropriately so, do not prescribe treatment regiments for these organic maladies, which melanoma unequivocally falls into.

Another limitation to this study is that it does not include considerations of genetic predispositions and profiles of patients which may play an important role in the etiology and progression of Melanoma prevalence. This study was, however, able to quantify associated demographic factors regarding depression in that melanoma patients with high PHQ4 scores were found less likely to be married and had low degrees of emotional support in their lives. Both of these facets are crucial for high quality of life within melanoma patients and their absence has been shown to worsen patient experience. This study, as discussed above, quantifies these relationships and as such, may empower healthcare providers to consider adapting their melanoma screening practices in accordance with these findings.

Therefore, this study recommends to appropriate healthcare providers to consider stricter melanoma screening practices or to consider referrals to appropriate healthcare providers for depressed patients whom are unmarried and white. As discussed above, this population of patients was noted to visit healthcare providers frequently however, these visits did not result in early detection of their malignancies. Therefore, this represents inefficiency in the care of these patients as appropriate providers can provide screening or referrals to other providers who can provide them with care for melanoma.

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APPENDIX A

Operationalizations of variables of study

Variable Name	Description	Original categories	Recoded categories	Hints variable derived from
Age	What's your age?	continuous	Above average Average or lower	Age
Race	what's your race?	1 Non-Hispanic White 2 Non Hispanic Black or African American 3 Hispanic 4 Non-Hispanic Asian 5 Non-Hispanic Other -9 Missing	1 White 2 Non White	RaceEthn5
Gender	Are you male or female?	1 Male 2 Female -9 Missing	1 Male 2 Female	GenderC
Marital Status	What is your Marital Status?	1 Married 2 Living as married 3 Divorced 4 Widowed 5 Separated 6 Single, never married -9 Missing	1 Married 2 Single	MaritalStatus

Occupational Status	What's your current occupational status?	1 Employed 2 Unemployed 3 Home maker 4 Student 5 Retired 6 Disabled -9 missing	No change	OccupationStatus
Income	What's your combined annual household income?	1 Less than $20,000 2 $20,000 to < $35,000 3 $35,000 to < $50,000 4 $50,000 to < $75,000 5 $75,000 or more -9 Missing	Less than $50,000 Greater or equal to $50,000	HHInc
Depression	Has a doctor/other health pro ever told you that you had depression/anxiety disorder?	1 Yes 2 No -9 Missng	no change	MedConditions_Depression
Health Provider Visits	Past 12 months, how many times did you go to a doctor/nurse/ health pro to get care...?	Continuous	Less than 3 Greater than or equal to 3	FreqGoProvider
Stage of Diagnosis	Which of the following cancer treatments have you ever received?	1 Chemotherapy 2 Radiation 3 Surgery 4 Other	Advance Stage Early Stage	StageOfDiag

PHQ4	PHQ-4 total score Derived composite from LittleInterest, Hopeless, Nervous and worrying	continuous	Average or lower Above average	PHQ4
Emotional Support	Is there anyone you can count on to provide you with emotional support when you need it?	1 Yes 2 No -9 Missng	No change	EmotionalSupport
Total Score Of Health Support	Derived from chance to ask questions, feelings addressed, involved with decisions, understood next steps, explained clearly, spent enough time, help with uncertainty	Average or lower Above average	no change	TptalScoreOfHealthSupport
Age group B	5 Level Age Categories Version B	1 18-34 2 35-49 3 50-64 4 65-74 5 75+ -9 Missing	Less than 50 Greater than or equal to 50	AgeGroupB

Appendix B

Tables and Charts for Preliminary Results

Distribution of Continuous Variables of Interest

Variable	Unweighted Sample Size	Weighted Sample Size	Weighted Mean	Weighted Standard Deviation	Weighted Median
Age	185	7196360	63.1	1.73	64.4
PHQ4	155	5622628	1.7	0.22	0
TotalScoreOfHealthSupport	172	6741943	11.1	0.43	9

Distribution of the Categorical Variables of Interest

Variable	Unweighted Sample Size	Unweighted Percent	Weighted Sample Size	Weighted Percent
FreqGoProvider_cat				
greater or equal to 3	122	65.9	4440719	61.3
less than 3	63	34.1	2801678	38.7
StageOfDiag				
Advance Stage	27	25.7	982891	24.5
Early Stage	78	74.3	3036823	75.5
MedConditions_Depression				
1	29	25.9	733623	17.3
2	83	74.1	3511425	82.7
Emotional Support				
1	96	85.7	3833840	90.3
2	16	14.3	411208	9.7
SkinCancerHPExam				
1	5	13.2	129471	8.9
2	3	7.9	72091	5

3	30	78.9	1247462	86.1
SkinCancerSelfCheck				
1	11	28.9	469577	32.4
2	1	2.6	11770	0.8
3	26	68.4	967677	66.8
CaMelanoma				
1	190	100	7407351	100
GenderC				
1	99	53.5	3774723	51.9
2	86	46.5	3495122	48.1
OccupationStatus				
1	59	32.2	2654604	37.1
2	7	3.8	413164	5.8
3	11	6	591672	8.3
5	100	54.6	3333225	46.5
6	6	3.3	171082	2.4
MaritalStatus				
1	116	63.4	4965360	69.7
2	6	3.3	237623	3.3
3	18	9.8	418546	5.9
4	30	16.4	870295	12.2
5	2	1.1	47945	0.7
6	11	6	588640	8.3
Married2				
Married/Living as Married	122	64.2	5202983	70.2
Not married	68	35.8	2204368	29.8
SpeakEnglish				
1	95	92.2	3973804	93.4
2	7	6.8	272958	6.4
3	1	1	9855	0.2
AgeGrpB				
1	6	3.2	399000	5.5
2	14	7.6	902385	12.5

3	57	30.8	2278210	31.7
4	56	30.3	1614156	22.4
5	52	28.1	2002609	27.8
EducA				
1	9	4.9	530854	7.4
2	34	18.5	1232129	17.3
3	62	33.7	2583666	36.2
4	79	42.9	2789627	39.1
RaceEthn				
1	7	4.1	210754	3.2
2	158	92.9	6250875	96
3	1	0.6	10884	0.2
4	1	0.6	7802	0.1
7	3	1.8	34207	0.5
Race2				
Non-Hispanic White	158	92.9	6250875	96
Non-white	12	7.1	263647	4
HHInc				
1	20	12	689817	10.6
2	21	12.6	740276	11.4
3	22	13.2	727765	11.2
4	38	22.8	1508369	23.2
5	66	39.5	2830021	43.6
PHQ4_cat				
above average	66	42.6	2040951	36.3
average or lower	89	57.4	3581677	63.7
TotalScoreOfHealthSupport.new				
above average	68	39.5	2522964	37.4
average or lower	104	60.5	4218979	62.6
Age.new above average	114	61.6	3881665	53.9
average or lower	71	38.4	3314694	46.1

Descriptive Statistics/Frequency Distribution for Depression

Variable	Unweighted Sample Size	Unweighted Percent	Weighted Sample Size	Weighted Percent
MedConditions_Depression				
1	29	25.9	733623	17.3
2	83	74.1	3511425	82.7

Association with Medical Conditions Depression

Variable	Yes (Weighted)	No (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	598674 (85.1%)	1815669 (52.4%)	0.0023
less than 3	105012 (14.9%)	1650839 (47.6%)	
GenderC			
1	176094 (24.3%)	2115170 (61.2%)	0.0037
2	547587 (75.7%)	1341053 (38.8%)	
AgeGrpB			
1	72616 (10.9%)	36088 (1%)	0.0127
2	34601 (5.2%)	680428 (19.5%)	
3	137784 (20.6%)	974051 (28%)	
4	312442 (46.7%)	692120 (19.9%)	
5	111011 (16.6%)	1099394 (31.6%)	
StageOfDiag			
Advance Stage	199367 (27.8%)	783524 (24.4%)	0.7787
Early Stage	516535 (72.2%)	2431383 (75.6%)	
OccupationStatus			
1	191137 (28.9%)	1335399 (38.8%)	0.0689
2	0 (0%)	70588 (2%)	
3	134689 (20.4%)	398657 (11.6%)	
5	268292 (40.6%)	1639323 (47.6%)	

6	66469 (10.1%)	0 (0%)	
EducA			
1	29330 (4.4%)	247519 (7.3%)	0.8672
2	143556 (21.5%)	517543 (15.2%)	
3	189650 (28.4%)	1213749 (35.6%)	
4	305917 (45.8%)	1430889 (42%)	
Race2			
Non-Hispanic White	585393 (89.7%)	3040490 (95.7%)	0.3553
Non-white	67076 (10.3%)	136739 (4.3%)	
HHInc			
1	142157 (20.1%)	245391 (7.8%)	0.4235
2	160206 (22.6%)	368075 (11.7%)	
3	76816 (10.9%)	393273 (12.5%)	
4	102920 (14.5%)	770673 (24.4%)	
5	225725 (31.9%)	1377777 (43.7%)	
EmotionalSupport			
1	637684 (86.9%)	3196156 (91%)	0.5800
2	95939 (13.1%)	315269 (9%)	
TotalScoreOfHealthSupport			
7	105545 (15%)	1150835 (36%)	0.0711
8	84286 (12%)	445205 (13.9%)	
9	75797 (10.8%)	124270 (3.9%)	
10	35826 (5.1%)	340616 (10.7%)	
11	85159 (12.1%)	73955 (2.3%)	
12	0 (0%)	75801 (2.4%)	
13	9941 (1.4%)	110401 (3.5%)	
14	144938 (20.6%)	209008 (6.5%)	
15	15640 (2.2%)	178542 (5.6%)	

16	16276 (2.3%)	218784 (6.8%)	
17	10884 (1.5%)	61817 (1.9%)	
18	62066 (8.8%)	0 (0%)	
19	0 (0%)	162175 (5.1%)	
20	11061 (1.6%)	0 (0%)	
21	39436 (5.6%)	11324 (0.4%)	
23	0 (0%)	32786 (1%)	
24	7866 (1.1%)	0 (0%)	

Association with PHQ-4 Total Score

Variable	Above Average (Weighted)	Average or Lower (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	1730248 (85.4%)	1500989 (42.4%)	0.0001
less than 3	295130 (14.6%)	2042516 (57.6%)	
EmotionalSupport			
1	1123663 (78.3%)	2680240 (96.4%)	0.0033
2	312200 (21.7%)	99008 (3.6%)	
Race2			
Non-Hispanic White	1714318 (89%)	3248998 (99.2%)	0.0033
Non-white	211617 (11%)	27573 (0.8%)	
MaritalStatus			
1	1223778 (61.7%)	2745943 (78.9%)	0.0002
2	758799 (38.3%)	734009 (21.1%)	
HHInc			
1	430136 (23.1%)	163286 (5%)	0.0574
2	247392 (13.3%)	452384 (13.9%)	
3	246147 (13.2%)	291670 (9%)	

4	369265 (19.8%)	836651 (25.8%)	
5	571513 (30.7%)	1498918 (46.2%)	
StageOfDiag			
Advance Stage	311563 (24.2%)	671328 (25.7%)	0.8939
Early Stage	974058 (75.8%)	1943923 (74.3%)	
GenderC			
1	948458 (48%)	2119732 (59.2%)	0.2717
2	1027350 (52%)	1461945 (40.8%)	
OccupationStatus			
1	766771 (39.4%)	1337794 (37.7%)	0.5731
2	61898 (3.2%)	121398 (3.4%)	
3	238643 (12.3%)	294703 (8.3%)	
5	765542 (39.3%)	1756867 (49.5%)	
6	112679 (5.8%)	41571 (1.2%)	
AgeGrpB			
1	117815 (5.9%)	36088 (1%)	0.1350
2	171130 (8.5%)	570694 (16.2%)	
3	735247 (36.7%)	1145768 (32.5%)	
4	595968 (29.7%)	621025 (17.6%)	
5	385560 (19.2%)	1151184 (32.7%)	
EducA			
1	250992 (12.6%)	168681 (4.8%)	0.4870
2	303395 (15.2%)	614777 (17.7%)	
3	528335 (26.5%)	1226077 (35.2%)	
4	907721 (45.6%)	1470417 (42.3%)	
SpeakEnglish			
1	731323 (79.3%)	1810982 (100%)	0.0106
2	181124 (19.6%)	0 (0%)	
3	9855 (1.1%)	0 (0%)	

Association with FreqGoProvider

Variable	greater or equal to 3 (Weighted)	less than 3 (Weighted)	P value
MedConditions_Depression			
1	598674 (24.8%)	105012 (6%)	0.0023
2	1815669 (75.2%)	1650839 (94%)	
PHQ4_cat			
above average	1730248 (53.5%)	295130 (12.6%)	0.0001
average or lower	1500989 (46.5%)	2042516 (87.4%)	
HHInc			
1	616774 (15.9%)	73043 (3%)	0.0163
2	328076 (8.5%)	373435 (15.2%)	
3	583752 (15.1%)	99096 (4%)	
4	689764 (17.8%)	737333 (29.9%)	
5	1649148 (42.6%)	1180873 (47.9%)	
GenderC			
1	2055133 (46.7%)	1681417 (62.2%)	0.1132
2	2346815 (53.3%)	1021525 (37.8%)	
OccupationStatus			
1	1451220 (33.7%)	1203384 (43.8%)	0.5712
2	314133 (7.3%)	99031 (3.6%)	
3	408828 (9.5%)	182844 (6.7%)	
5	1977452 (45.9%)	1250101 (45.5%)	
6	157084 (3.6%)	13998 (0.5%)	
MaritalStatus			
1	2807678 (65.4%)	2157682 (79.1%)	0.3646
2	77254 (1.8%)	79097 (2.9%)	
3	299345 (7%)	103628 (3.8%)	
4	582372 (13.6%)	279096 (10.2%)	

5	47945 (1.1%)	0 (0%)	
6	478846 (11.2%)	109795 (4%)	
SpeakEnglish			
1	2496454 (93.3%)	1461777 (98.6%)	0.1452
2	170240 (6.4%)	21447 (1.4%)	
3	9855 (0.4%)	0 (0%)	
AgeGrpB			
1	317713 (7.4%)	81287 (2.9%)	0.1540
2	305484 (7.1%)	596901 (21.3%)	
3	1539135 (35.9%)	739075 (26.4%)	
4	1073689 (25%)	524894 (18.7%)	
5	1052988 (24.6%)	859520 (30.7%)	
EducA			
1	419674 (9.8%)	111180 (4.1%)	0.5147
2	872564 (20.3%)	359565 (13.2%)	
3	1421580 (33%)	1146513 (42%)	
4	1587488 (36.9%)	1112038 (40.7%)	
Race2			
Non-Hispanic White	3680438 (94.7%)	2546036 (97.8%)	0.2729
Non-white	206994 (5.3%)	56653 (2.2%)	
TotalScoreOfHealthSupport.new			
above average	1579761 (36%)	943202 (40.7%)	0.6573
average or lower	2804643 (64%)	1375571 (59.3%)	
EmotionalSupport			
1	2151321 (89.1%)	1607665 (91.6%)	0.7010
2	263022 (10.9%)	148186 (8.4%)	
SkinCancerHPExam			
1	63402 (12.2%)	66070 (7.7%)	0.5096
2	7866 (1.5%)	64225 (7.5%)	

3	449615 (86.3%)	722992 (84.7%)	
SkinCancerSelfCheck			
1	126418 (24.3%)	343159 (40.2%)	0.4381
2	11770 (2.3%)	0 (0%)	
3	382695 (73.5%)	510128 (59.8%)	
StageOfDiag			
Advance Stage	479607 (20.3%)	487711 (30.9%)	0.3548
Early Stage	1886636 (79.7%)	1090906 (69.1%)	

Univariate Analysis-FreqGoProvider

				Univariate		
Name	**Levels**	**Ref**	**OR**	**low95**	**up95**	**pVal**
MedConditions_Depression	2	1	**5.18**	**1.68**	**15.99**	**0.0051**
PHQ4_cat	average or lower	above average	**7.98**	**3.33**	**19.12**	**0.000**
HHInc	2	1	**9.61**	**1.86**	**49.60**	**0.0076**
	3	1	**1.43**	**0.24**	**8.61**	**0.6944**
	4	1	**9.03**	**1.95**	**41.79**	**0.0055**
	5	1	**6.05**	**1.45**	**25.30**	**0.0148**
GenderC	2	1	**0.53**	**0.24**	**1.16**	**0.1151**
OccupationStatus	2	1	**0.38**	**0.05**	**2.82**	**0.3458**
	3	1	**0.54**	**0.09**	**3.40**	**0.5120**
	5	1	**0.76**	**0.33**	**1.75**	**0.5222**
	6	1	**0.11**	**0.01**	**1.03**	**0.0545**
AgeGrpB	2	1	**7.64**	**0.75**	**77.58**	**0.0874**
	3	1	**1.88**	**0.25**	**14.37**	**0.5452**
	4	1	**1.91**	**0.25**	**14.72**	**0.5350**
	5	1	**3.19**	**0.42**	**24.26**	**0.2639**
EducA	2	1	**1.56**	**0.16**	**15.22**	**0.7046**

	3	1	**3.04**	**0.33**	**28.34**	**0.3294**
	4	1	**2.64**	**0.30**	**23.46**	**0.3839**
Race2	Non-white	Non-Hispanic White	**0.40**	**0.07**	**2.18**	**0.2887**
EmotionalSupport	2	1	**0.75**	**0.18**	**3.19**	**0.7020**
TotalScoreOfHealthSupport	average or lower	above average	**1.03**	**0.94**	**1.14**	**0.4945**

Association with Stage of Diagnosis

Variable	Advance Stage (Weighted)	Early Stage (Weighted)	P value
FreqGoProvider_cat			
greater or equal to 3	479607 (49.6%)	1886636 (63.4%)	0.3548
less than 3	487711 (50.4%)	1090906 (36.6%)	
Race2			
Non-Hispanic White	931219 (98.8%)	2467019 (93.1%)	0.0861
Non-white	10884 (1.2%)	183076 (6.9%)	
GenderC			
1	512386 (52.1%)	1638829 (54.7%)	0.8631
2	470505 (47.9%)	1358963 (45.3%)	
OccupationStatus			
1	275983 (29.2%)	1049159 (36.8%)	0.2700
2	48221 (5.1%)	22367 (0.8%)	
3	132381 (14%)	389893 (13.7%)	
5	421723 (44.6%)	1391986 (48.8%)	
6	66469 (7%)	0 (0%)	
MaritalStatus			
1	758360 (77.2%)	1890920 (68%)	0.6668
2	8119 (0.8%)	122121 (4.4%)	

3	26897 (2.7%)	218062 (7.8%)	
4	151401 (15.4%)	350332 (12.6%)	
5	0 (0%)	47945 (1.7%)	
6	38114 (3.9%)	151643 (5.5%)	
AgeGrpB			
1	36088 (3.7%)	72616 (2.5%)	0.2942
2	186840 (19%)	459316 (16.1%)	
3	48463 (4.9%)	859674 (30.1%)	
4	397487 (40.4%)	599209 (21%)	
5	314013 (31.9%)	862590 (30.2%)	
EducA			
1	82973 (8.4%)	87465 (3.1%)	0.7477
2	211533 (21.5%)	438494 (15.8%)	
3	337295 (34.3%)	1009398 (36.3%)	
4	351089 (35.7%)	1245667 (44.8%)	
HHInc			
1	50939 (6.1%)	194233 (6.9%)	0.3479
2	95292 (11.4%)	432989 (15.4%)	
3	127574 (15.2%)	329639 (11.7%)	
4	82568 (9.9%)	872065 (31%)	
5	481141 (57.4%)	982310 (34.9%)	
MedConditions_Depression			
1	199367 (20.3%)	516535 (17.5%)	0.7787
2	783524 (79.7%)	2431383 (82.5%)	
EmotionalSupport			
1	825242 (84%)	2713297 (92%)	0.3001
2	157649 (16%)	234621 (8%)	
SkinCancerHPExam			
1	0 (0%)	129471 (13.3%)	0.2102

2	38114 (10.2%)	0 (0%)	
3	334458 (89.8%)	844131 (86.7%)	
SkinCancerSelfCheck			
1	278829 (74.8%)	182882 (18.8%)	0.0056
2	0 (0%)	11770 (1.2%)	
3	93742 (25.2%)	778951 (80%)	
SpeakEnglish			
1	612114 (93.8%)	1633673 (92.5%)	0.9833
2	40214 (6.2%)	133044 (7.5%)	
PHQ4_cat			
above average	311563 (31.7%)	974058 (33.4%)	0.8939
average or lower	671328 (68.3%)	1943923 (66.6%)	
TotalScoreOfHealthSupport.new			
above average	407523 (43.8%)	950483 (33.7%)	0.5125
average or lower	523707 (56.2%)	1873139 (66.3%)	

Multivariate Analysis: Stage of Diagnosis

				Multivariate		
Name	**Levels**	**Ref**	**OR**	**low95**	**up95**	**pVal**
GenderC	2	1	**0.25**	**0.04**	**1.49**	**0.1330**
OccupationStatus	2	1	**0.00**	**0.00**	**0.03**	**0.0014**
	3	1	**0.07**	**0.00**	**1.83**	**0.1166**
	5	1	**0.07**	**0.01**	**0.70**	**0.0275**
	6	1	**0.00**	**0.00**	**0.00**	**0.0000**
Race2	Non-white	Non-Hispanic White	**65.37**	**0.77**	**5564.34**	**0.0703**
HHInc	2	1	**0.15**	**0.00**	**15.18**	**0.4237**
	3	1	**0.01**	**0.00**	**1.37**	**0.0727**

	4	1	**3.51**	**0.01**	**2414.02**	**0.7074**
	5	1	**0.01**	**0.00**	**1.10**	**0.0597**
MedConditions_Depression	2	1	**0.53**	**0.05**	**5.31**	**0.5896**
EmotionalSupport	2	1	**0.24**	**0.00**	**16.64**	**0.5149**
TotalScoreOfHealthSupport	average or lower	above average	**0.69**	**0.50**	**0.97**	**0.0350**