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Racial and Ethnic Differences in the Receipt of Metabolic Syndrome Risk Factor Screening and Treatment Among Prostate Cancer Patients Treated with Androgen Deprivation Therapy.

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DEDICATION

I dedicate this work to my lovely family who supported me emotionally and financially and made sacrifices that helped me achieve this success. My family is my source of inspiration in life and whose unconditional love and support always motivate me to set higher goals and keep moving forward. I could not have reached this point without their support.

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ABSTRACT

Background: Racial and ethnic health disparities in prostate cancer prevalence, incidence, mortality, quality of life, screening, and treatment constitute the largest of all cancer disparities. These health disparities are associated with higher morbidity and mortality rates in minority populations. Treatment with androgen deprivation therapy (ADT) has been the most widely used therapeutic modality to reduce the progression of prostate cancer to a worse disease stage and relieve potential obstructive symptoms. However, ADT is associated with possible toxic metabolic and cardiovascular (CVS) adverse events that may occur within six months of ADT initiation. These adverse events include metabolic syndrome, type II diabetes, hypertension, dyslipidemia and abdominal obesity. Due to increased recognition of metabolic syndrome risk factor (MSRF) and CVS complications associated with ADT; several national medical and governmental organizations and professional societies have published several science advisory guidelines since 2010. The guidelines aimed to guide healthcare providers caring for prostate cancer patients treated with ADT and to promote interventions that can mitigate

ADT related metabolic and CVS complications. Adherence to science advisory guideline recommended screening and treatment of MSRF across racial and ethnic groups of prostate cancer patients initiating ADT is unknown.

Objectives: To assess racial and ethnic differences in the receipt of MSRF screening and treatment among prostate cancer patients treated with ADT at the University of New Mexico Comprehensive Cancer Center (UNMCCC) between 2010 and 2021. The study also sought to evaluate longitudinal changes in MSRF screening and treatment among prostate cancer patients treated with ADT during the study period. Lastly, the study aimed to identify patient and healthcare provider characteristics that influence MSRF among patients treated with ADT during the study period.

Methods: A retrospective observational cohort study of 803 patients treated with ADT for at least six months at the UNMCCC between 2010 and 2021 was conducted. Male adult (≥18 years) patients with a confirmed diagnosis of prostate cancer and who received primary care within the UNM health system during the study period were included. The study index date was the first ADT dose administered during the study period. Patients meeting the study inclusion criteria were followed three months before ADT initiation to 12 months post-ADT initiation to evaluate MSRF screening and treatment. Patients were screened for MSRF if they were referred to primary care provider for MSRF screening/treatment or received blood glucose, lipid profile, and blood pressure screening within six months post-treatment with ADT. Patients were considered treated for MSRF if they were started or continued therapy (within six months of ADT initiation) with an anti-platelet therapy and statin if they have a documented diagnosis of a CVS disease, blood glucose lowering agent if they have a confirmed

diagnosis of diabetes mellitus II, and blood pressure lowering agent if they have a confirmed diagnosis of hypertension. For the differences in the proportions of patients receiving MSRF screening/treatment, the independent variable was race/ethnicity, whereas the main dependent variable was the receipt of MSRF screening/treatment. Chi-square test was used to determine differences in the proportions of patients receiving MSRF screening/treatment across racial and ethnic groups of prostate cancer patients treated with ADT. Multiple logistic regression analysis was used to identify patient and healthcare provider characteristics that influence MSRF screening among prostate cancer patients treated with ADT. The main independent variable considered for the analysis was race/ethnicity and the dependent variable was the receipt of MSRF screening. An a-priori power analysis was conducted to determine the minimum required sample size in the current study. A p-value ≤ 0.05 was considered in determining statistical significance in the current study.

Results: Guideline-concordant MSRF screening mean rate approached 23.5%; MSRF treatment rate was 76.9%. We found a significant difference in the proportion of patients receiving screening across all racial and ethnic groups of prostate cancer patients treated with ADT (p=0.032). A significant difference in MSRF screening between Non-Hispanic White (NHW) and Hispanic men (p=0.008) and between African American and Hispanic men (p=0.0401) was observed. The study did not find a significant difference in the proportion of MSRF treatment across all racial and ethnic groups. However, a significant difference in MSRF treatment was found between NHW and Hispanic men (p=0.0214). MSRF screening rates from 13.9% to 35.6% throughout the 10-year data collection period did not show an expected upward trend as the guidelines became more

widely distributed. Hispanic men (p=0.0001), American Indian/Alaskan Native (p=0.007), and Asian/pacific islander (p=0.04) had significantly lower odds of having MSRF screening compared to NHW patients. Patients with dyslipidemia at baseline had significantly higher odds of having MSRF screening than patients without a dyslipidemia diagnosis at baseline (p<0.0001). Oncologists with >20 years of experience had significantly higher odds of providing MSRF screening than those with <10 years of experience (p=0.006).

Conclusions: Racial and ethnic health disparities exist in MSRF screening and treatment among prostate cancer patients treated with ADT. Minority populations had significantly lower odds of having MSRF screening than NHW patients after adjusting for clinical and socio-economic variables. The gap between MSRF screening and MSRF treatment rates indicate that having pre-existing MSRF was associated with closer MSRF treatment regardless of ADT initiation. Closer clinical attention and education, as well as the development and implementation of innovative practice tools and interventions to optimize MSRF screening and treatment are warranted to mitigate the harmful short & long-term effects of ADT in prostate cancer patients.

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LIST OF ACRONYMS

AA	African American
AACE	American Association of Clinical Endocrinologists
ACA	Affordable Care Act
ACE	Angiotensin Converting Enzyme
ACS	American Cancer Society
ADA	American Diabetes Association
ADT	Androgen Deprivation Therapy
AHA	American Heart Association
AI/AN	American Indian/Alaskan Native
AJCC	American Joint Committee on Cancer
ALK	Alkaline Phosphatase
ALSYMPCA	ALpharadin in SYMptomatic Prostate CAncer
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
ASCO	American Society of Clinical Oncology
ATP	Adult Treatment Panel
AUA	American Urological Association
BMI	Body Mass Index
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
BRFS	Behavioral Risk Factor Surveillance System
CBC	Complete Blood Count
CCB	Calcium Channel Blocker
CDC	Center for Disease Control and Prevention
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Clinical Modification
CMH	Cochran Mantel Haenszel
CNP	Clinical Nurse Practitioner
Cr Cl	Creatinine Clearance
CRPC	Castration-Resistant Prostate Cancer
CT	Computed Tomography
CVD	Cardiovascular Disease
CVS	Cardiovascular
CY	Cytochrome
DEXA	Dual-X-ray Absorptiometry
DM	Diabetes Mellitus

DO	Doctor of Osteopathic Medicine
DPP	Dipeptidyl Peptidase
DRE	Digital Rectal Examination
EAU	European Association of Urology
ECG	Electrocardiogram
EGIR	European Group for the study of Insulin Resistance
EMR	Electronic Medical Record
ERSPC	European Randomized Study of Screening for Prostate Cancer
ESRD	End Stage Renal Disease
ESTRO	European Society for Radiotherapy & Oncology
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
FSH	Follicular-Stimulating Hormone
GLP	Glucagon-Like Peptide
GnRH	Gonadotropin-releasing hormone
H0	Null Hypothesis
HbA1C	Glycosylated Hemoglobin (A1C)
HCP	Healthcare Provider
HDL-C	High-Density Lipoprotein Cholesterol
HIPAA	The Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRPR	Human Research Protection Programs
HTN	Hypertension
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IM	Intra-Muscular
IRB	Institute Review Board
ISUP	International Society of Urological Pathology
LBGT	Lesbian, Gay, Bisexual, and Transgender
LDH	Lactic Dehydrogenase
LH	Luteinizing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MD	Medical Doctor
MENA	Middle East and North Africa
MEPS	Medical Expenditure Panel Survey
MeSH	Medical Subject Headings
MRN	Medical Record Number
MSRF	Metabolic Syndrome Risk Factor

NAMCS	National Ambulatory Medical Care Survey
NCCN	National Comprehensive Cancer Network
NCEP	National Cholesterol Education Panel
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHW	Non-Hispanic White
NM	New Mexico
NMTR	New Mexico Tumor Registry
NP	Nurse Practitioner
OR	Odds Ratio
PA	Physician Assistant
PAD	Peripheral Arterial Disease
PCa	Prostate Cancer
PCP	Primary Care Provider
PRISMA	Preferred Reporting Items for Systematic Reviews & Meta-Analysis
PSA	Prostate Specific Antigen
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
RR	Relative Risk
SC	Subcutaneous
SD	Standard Deviation
SGLT	Sodium-glucose Cotransporter-2
SIOG	International Society of Geriatric Oncology
TG	Triglycerides
TNM	Tumor Node Metastasis
UNM	University of New Mexico
UNMCCC	University of New Mexico Comprehensive Cancer Center
UNMHSC	University of New Mexico Health Sciences Center
US	United States
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

This chapter provided an overview of prostate cancer (PCa) and PCa treatment with androgen deprivation therapy (ADT). Racial and ethnic health disparities in PCa prevalence, incidence, mortality, screening, and treatment in the United States (U.S.) and among the New Mexican population were then presented. An overview of metabolic syndrome definition and epidemiology, its association with ADT and metabolic syndrome risk factor (MSRF) screening and treatment consensus recommendations among PCa patients treated with ADT were presented. An overview of the conceptual framework of "Integration of Targeted Health Interventions into Health Systems" was then presented. Lastly, we discussed current gaps in related literature, study significance, specific aims, and research hypotheses.

PCa and Treatment with ADT

PCa is the number one cancer affecting men in the U.S., accounting for more than 20% of all new cancer diagnoses in men, and the second highest cause of cancer-related deaths in men, with 34,500 predicted to die of this disease in 2022.[1,2] In 2018, the PCa age-adjusted incidence rate approached 107.5 per 100,000 individuals and 18.9 per 100,000 deaths in the U.S. with an estimated incidence count of 211,893 across all racial and ethnic groups.[3]

Despite advances in pharmacological and other treatment modalities for patients with PCa, treatment with ADT has been the most widely used therapeutic modality when there is evidence of rising prostate-specific antigen (PSA), or when hormonal therapy is indicated.[4,5] It is reported that nearly 50% of

patients who survived PCa received treatment with ADT at one point of their lives.[6] In a recent cross-sectional U.S. study, almost 25% (n=22,700) of all PCa patients received treatment with ADT during the period (January 1, 2010 – December 31, 2017).[7]

PCa depends on androgen production for its continued growth.[4] Nearly 90-95% of androgen production occurs in the testes, which is regulated by the hypothalamic-pituitary axis. The rest of androgen production is carried out by the adrenal glands.[4] These observations provide rationale for the use of ADT, which can be accomplished with either pharmacological (i.e., medical/chemical castration) or surgical castration (i.e., bilateral orchiectomy).[4]

Surgical castration is considered a simple and cost-effective intervention and is indicated when there is an urgent need to reduce testosterone levels (e.g., when the patient suffers from urinary tract outlet obstruction or spinal compression) or when cost or adherence to pharmacological ADT is an issue.[4]

Medical/chemical castration suppresses androgen production through its effect on the hypothalamic-pituitary axis. This includes treatment with gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide, goserelin, buserelin, triptorelin), GnRH antagonists (e.g., degarelix, relugolix) and antiandrogens (e.g., bicalutamide and flutamide).[4] In a meta-analysis of 10 trials that included 1,908 patients, medical/chemical castration using GnRH agonists was shown to be equivalent to surgical castration in terms of overall survival, progression-related outcomes and time to treatment failure.[8]

Overall, treatment with ADT is recommended for patients with advanced PCa and/or symptomatic metastases.[9] It is debatable whether asymptomatic metastatic patients should be started on ADT or delay treatment until significant symptoms develop.[9] Despite substantial beneficial evidence of ADT in improving survival, reducing the progression of PCa and relieving potential obstructive symptoms, ADT are associated with likely toxic cardiovascular (CVS) and metabolic adverse events.[10–13] Thus, it is essential to balance potential benefits and risks before and during treatment with ADT.

Health Disparities in PCa in the U.S.

Racial and ethnic health disparities in PCa prevalence, incidence, mortality, screening and treatment constitute the largest of all cancer disparities.[2] Despite improvements in understanding the pathophysiology of PCa and the availability of effective screening methods, non-pharmacological (surgery, radiation) and pharmacological agents, patients have not benefitted equally with screening and treatments as racial and ethnic disparities in the treatment of PCa persist.[2]

African American (AA) men suffer disproportionally from PCa, facing a 78% higher incidence rate than Non-Hispanic White (NHW) men.[2,14] They are more likely to be diagnosed at a younger age and present with more advanced and aggressive disease.[2,14] They also have more than 2 times higher mortality rates than NHW men.[2,14] These health disparities have been mostly associated with several clinical and socioeconomic factors. AA men are more likely to experience delays in PCa diagnosis as well as treatment than insured NHW

individuals.[15,16] They are also less likely to be screened for PCa than NHW men.[2,15,17–26] Despite AA men having an increased risk of developing aggressive PCa; lack of PCa testing awareness and general PCa knowledge, differential medical decision-making and access to testing were reported reasons for poor PCa screening among AA men.[24,25]

AA men are also less likely to receive treatment with radical prostatectomy or radiotherapy and more likely to receive treatment with ADT compared with NHW men.[27–30] The following are reported reasons for PCa treatment disparities in AA men: poorer quality of care, worse disease prognosis, low income, lack of insurance, higher cost of care for AA treated with radical prostatectomy than in NHW, fewer treatment options offered, less treatment information provided, differential provider-specific PCa screening and treatment, selection bias in definitive treatment (i.e., AA men are less likely to be offered the option to undergo radical prostatectomy or radiation independent of disease stage or prognosis), and the choice for less aggressive therapy.[27–30]

Hispanics, American Indian/Alaskan Native (AI/AN) and some Asian groups are more likely to present with advanced stages of PCa than NHW men because of lower PSA screening rates, raising concerns about under-diagnosis in these populations.[2,17–19,22,25,31–33] Lack of early diagnosis also contributes to higher mortality among these minority populations.[2,17–19,22,25,31–33] Some of the reported contributing factors of PCa screening disparities in these minority populations include low socioeconomic status, lack of cancer care services, differential access to healthcare and medical decision-making, limited knowledge

of cancer care, perceived discrimination by the healthcare provider, negative attitudes and beliefs toward cancer treatment and language differences.[17–19,31]

Among Hispanics/Latinos, Mexican Latinos have a lower reported incidence of PCa compared to Caribbean Latinos.[2] Among Asians living in the U.S., Japanese or Filipino patients have lower PCa incidence rates compared to other Asian groups.[2] Variations among Hispanics and some Asian groups have been mostly attributed to modifiable risk factors like red meat intake,[2,34] calcium and vitamin D intake,[2,35] increased body mass index (BMI), and agricultural exposure.[2,36,37]

Underwood et al. (2004) reported that among patients with well-differentiated PCa, definitive therapy (i.e., radical prostatectomy and/or external beam radiation or brachytherapy) was significantly more often administered in NHW (68.8%) compared to AA (64.6%) and Hispanics (64.9%).[23] This disparity widened in men with moderately or poorly differentiated disease. This indicates an ethnic difference in the type of treatment received, independent of disease stage or prognosis.[23]

New Mexico (NM) is one of five “majority-minority” states in the U.S. and has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI).[38] PCa is the most commonly diagnosed cancer among men in NM with an incidence rate of 82.7 and 19.4 deaths per 100,000 individuals during the period of 2014-2018. During the 2014-2018 time period, PCa diagnosis was represented by 87.8% NHW men, 29% Hispanics, 3.7% AI/AN, 3% AA, and 1.3% Asian/Pacific Islander.[3] Gilliland et al. (1998) reported

that increased PCa screening was a significant determinant of the rising incidence rate of PCa among NHW compared to AI during 1969-1994 in NM. The burden of PCa among AI compared to NHW was reflected in disproportionally high mortality rates in relation to incidence rates. Mortality rates were high because AI cases were more advanced at diagnosis (23.3%) compared to 11.6% among NHW.[39] These rate estimates may have been biased by ethnic differences in access to medical care.[39]

Minority populations in NM are more likely to present with advanced PCa disease stage, poorer prognosis and lower survival than NHW men.[39–43] They are also less likely to receive treatment with radical prostatectomy and more likely to receive treatment with ADT compared with NHW men.[39–42]

Metabolic Syndrome Risk Factor (MSRF) & Association with ADT

The clustering of diabetes mellitus type II, hypertension, dyslipidemia and abdominal obesity while being treated with ADT suggest "metabolic syndrome."[44–47] Other known names for metabolic syndrome are syndrome X, insulin resistance syndrome, obesity dyslipidemia syndrome, and the deadly quartet.[48,49] According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III definition, metabolic syndrome is present among men if ≥3 of the following five criteria are met: waist circumference over 40 inches, blood pressure (BP) over 130/85 mmHg, fasting triglycerides (TG) level over 150 mg/dl, fasting high-density lipoprotein cholesterol (HDL-C) level less than 40 mg/dl, and fasting blood glucose (FBG) over 100 mg/dl.[50] Although there are several other proposed definitions and diagnostic criteria for metabolic

syndrome, the criteria proposed by the NCEP ATP III represent the most commonly agreed-upon criteria.[51] It incorporates the key features of hyperglycemia, insulin resistance, visceral obesity, dyslipidemia and hypertension.[50] It also uses measurements and laboratory results that are readily available to physicians, facilitating its clinical and epidemiological application.[50]

Despite its wide utilization in PCa management, treatment with ADT is associated with an increased risk of developing metabolic syndrome and CVS complications, usually within 6 months of ADT initiation.[7,52–56] The metabolic complication risks have been primarily attributed to a biological mechanism. ADT alters body composition as low testosterone levels (i.e., male hypogonadism) are associated with a decline in lean body mass and an increase in fat mass.[57] Increased fat mass increases insulin levels (i.e., hyperinsulinemia) which might be the inciting event leading to metabolic dysregulation. Increased body fat mass also alters fatty acid metabolism and reduces glucose uptake by muscle cells, resulting in insulin resistance and diabetes that may predispose patients with PCa to increased risks of cardiovascular diseases (CVDs).[57–60] Tzortzis et al. (2017) reported that nearly 36-55% of PCa patients treated with ADT would develop metabolic syndrome within 12 months independent of age, race and PCa stage.[61] In addition to increased fat mass, circulating blood glucose levels, insulin resistance and lipids, ADT increases arterial stiffness resulting in increased risks of developing CVDs, including acute myocardial infarction (AMI), incident diabetes, and sudden cardiac death.[60,62,63]

Metabolic Syndrome Risk Factor (MSRF) Screening & Treatment Consensus Recommendations Among PCa Patients Treated with ADT

In 2010, due to increased recognition of metabolic changes associated with ADT, the American Heart Association (AHA), American Society for Radiation Oncology, American Urological Association (AUA) and American Cancer Society (ACS) published a science advisory guideline to guide healthcare providers caring for PCa patients receiving ADT.[54] This included recommendations to evaluate *MSRF (blood glucose, lipid profile and BP)* within 6 months of ADT initiation.[54] The guideline also recommended an annual assessment of these measures among patients with long-term ADT (≥12 months).[54] Primary care providers (PCPs) should also be provided information by the treating oncologist on the potential metabolic adverse events associated with ADT.[54] Oncologists should also weigh the risks and benefits of ADT before treatment initiation.[54] PCa patients treated with ADT and concomitant CVDs should also receive appropriate secondary preventive measures as recommended by the AHA and other expert organizations, including, when appropriate, exercise, anti-hypertensive and glucose-lowering medications (e.g., metformin), statins and aspirin.[54,64] These interventions are effective in mitigating some of the metabolic complications of ADT.[54,65–68]

Shortly after the science advisory guideline publication, the U.S. Food and Drug Administration (FDA) released in May 2010 a drug safety communication regarding possible increased risks of certain CVDs (AMI, stroke and sudden cardiac death) and type II diabetes among patients treated with one class of ADT medications, the GnRH agonists.[69] In March 2021, the National Comprehensive

Cancer Network (NCCN) clinical practice guideline of PCa recommended screening for and intervention to prevent and treat metabolic and CVS complications among patients treated with ADT.[70]

Integration of Targeted Health Interventions into Health Systems Conceptual Framework

We have adopted the conceptual framework "Integration of Targeted Health Interventions into Health Systems" proposed by Atun et al. (2010) [71] to guide the research and to precisely guide/answer study Specific Aim 4: To identify patient and healthcare provider factors influencing the receipt of MSRF screening among different racial/ethnic groups of PCa patients treated with ADT. The model builds on previous theoretical propositions and empirical research in innovation studies, particularly the adoption and diffusion of innovations within health systems.[71]

Bowser et al. (2017) utilized this framework to identify health system barriers and enablers that impact access to early screening, detection, and diagnosis of breast cancer both globally and more specifically in the Middle East and North Africa (MENA) region.[72] The framework was used to examine health system barriers and enablers to breast cancer screening at the broader macro health system level, the health provider, and the individual level. Authors found that health insurance coverage status and access, healthcare provider gender, type (i.e., degree) and specialty and having regular contact with the physician influence breast cancer screening.[72] More details about the conceptual framework and its application will be discussed in chapters 2 & 3.

In addition to using the conceptual framework described above, we also explored the literature to identify other patient and healthcare provider factors that predicted PCa and MSRF screening. Unfortunately, despite the substantial amount of evidence that evaluated healthcare provider and patient factors influencing the receipt of PCa screening [73–81], the evidence available about healthcare provider and patient factors influencing MSRF screening is scarce.

Edlefsen et al. (1999) found that healthcare provider gender, years of experience and specialty influence PSA screening.[73] Ramirez et al. (2009) found that female physicians were more likely to discuss general health prevention activities with patients than male physicians, especially sensitive issues, including substance use, violence and physical activity. Male physicians more often indicated that they felt that PSA screening was very effective in detecting potential PCa compared to female physicians.[74] Physicians' gender has predicted attitude toward PSA effectiveness.[74] In a similar study, female physicians were less likely to believe that their skills in performing prostate examination were excellent compared to male physicians.[76]

The influence of healthcare insurance coverage status on PCa disease screening, diagnosis and treatment has been studied extensively.[77–79] In a large national observational population-based study that included 85,203 patients diagnosed with PCa, insured individuals were significantly less likely to present with advanced PCa disease stage and more likely to receive definitive treatment (i.e., surgery or radiation) compared with uninsured individuals.[79]

Previous literature showed that marital status is an independent predictor for PCa-specific mortality and overall mortality.[80] Unmarried men had a statistically significant higher risk of PCa-specific mortality compared to married men of similar age, race, stage, and tumor grade.[80] Huang et al. (2017) also found that marital status is an independent prognostic factor for PCa. Unmarried individuals had significantly higher Gleason scores at diagnosis (i.e., poorer disease prognosis) compared to married men mainly due to lack of social support.[81]

Understanding patient and healthcare provider factors that predict differential MSRF screening among PCa patients treated with ADT could help us better understand patients' interaction with the U.S. healthcare system in NM and provide recommendations to implement necessary changes to optimize MSRF screening among all patients, and particularly among minority populations treated with ADT. Such an effort will help to achieve the goal of eliminating racial disparities in health and healthcare of PCa patients.

Gaps in the Related Literature

Despite the increasing recognition of metabolic syndrome and CVS complications associated with ADT among PCa patients, limited evidence is reported in the literature on whether healthcare providers are aware of, and following, the 2010 (AHA, AUA and ACS) science advisory guideline publication, and FDA drug safety communication related to GnRH agonist use.[54,69]

Few studies have reported population-based adherence to metabolic and CVS screening and treatment consensus recommendations among PCa patients

treated with ADT.[7,82,83] Studies identified mainly assessed screening for CVS outcomes measures, including risks of AMI, stroke, pulmonary embolism and statin medications utilization among PCa patients treated with ADT.[7,82,83] However, the studies did not report racial/ethnic differences in the receipt of MSRF screening and treatment while receiving ADT therapy for PCa.

This study evaluated racial/ethnic disparities in receiving MSRF screening and treatment among PCa patients treated with ADT. Our study also determined longitudinal changes in MSRF screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT. This time period was chosen to assess temporal changes of MSRF screening and treatment rates after ADT metabolic syndrome and CVS risks assessment consensus scientific guideline recommendations published in 2010.[54] This provided us with evidence about the rate of physicians' awareness, adoption and adherence to the evidence-based recommendations between 2010 and 2021. Additionally, the study identified patient and healthcare provider factors influencing the receipt of MSRF screening among different racial/ethnic groups of PCa patients treated with ADT. This provided us with valuable information and added a unique contribution to the current knowledge of PCa health disparities and MSRF screening and treatment while on ADT for PCa.

Significance

According to the U.S. Census Bureau, NM is one of five "majority-minority" states in the U.S. and has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI).[38] The Hispanic population

grew in NM from 953,403 (46.3% of the entire NM population) in 2010 to 1.043 million (49.3%) in 2021.[84,85] Similarly, the population of AI/AN grew (yet at a lower growth rate) from 193,222 (9.3% of the entire NM population) in 2010 to 232,747 (11%) in 2021.[84,85] This makes NM one of the most ethnically diverse states in the US.

Minority populations diagnosed with PCa are more likely to receive treatment with ADT and less likely to receive treatment with radiation or radical prostatectomy compared with NHW men which increases their risks of developing metabolic syndrome, CVDs and mortality.[2,23,28,29,86] Underwood et al. (2004) reported that among patients with well-differentiated PCa, definitive therapy (i.e., radical prostatectomy, external beam radiation, brachytherapy) was significantly more often administered in NHW (68.8%) compared to AA (64.6%) and Hispanics (64.9%). This disparity widened in men with moderately or poorly differentiated disease. This might indicate an ethnic disparity in the type of treatment received, independent of disease stage or prognosis.[23]

In summary, the following were reported reasons of differential PCa screening and treatment among minority populations in the U.S: low socioeconomic status, lack of insurance coverage, worse disease prognosis, lack of cancer care services and limited treatment options offered, patient choice for less aggressive therapy, limited knowledge of cancer care, perceived discrimination by the healthcare provider, negative attitudes and beliefs toward cancer treatment and language differences.[17–19,24,25,27–29,31] Lack of early diagnosis also contributes to higher mortality among these populations.[2,17–

[19,22,25,31–33] Minority populations in NM are also more likely to present with advanced PCa disease stage, poorer prognosis and lower survival compared with NHW men.[39–43]

Previous population-based studies found that metabolic syndrome is significantly more prevalent in Hispanics compared with NHW.[87–91] Ford et al. (2002) found a higher prevalence of metabolic syndrome among Hispanics (~32%) compared with NHW (~24%).[87] Schumacher et al. (2008) found that the prevalence of metabolic syndrome among AI/AN men from the southwest U.S. approached nearly 43%.[92] A high prevalence of metabolic syndrome is associated with increased risks of developing CVDs and mortality. Risks of these serious metabolic complications increase with the use of ADT among PCa patients.[60,62,63]

Assessing racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT between 2010 and 2021 provided us with information on whether healthcare providers are aware of and following 2010 (AHA, AUA and ACS) science advisory guideline publication [54], and FDA drug safety communication related to GnRH agonist use.[69] This also included providing information about whether PCa patients treated with ADT were screened and treated equally for MSRF. Adherence to the science advisory guideline could reduce risks of developing CVDs and mortality among all racial and ethnic groups, specifically among minority populations.

Understanding patient and healthcare provider factors that predict MSRF screening among PCa patients treated with ADT could help us better understand

patients' interaction with the U.S. healthcare system in NM and provide recommendations to implement necessary changes to optimize MSRF screening among all patients and particularly among minority populations treated with ADT. Such an effort will help to achieve the goal of eliminating racial disparities in health and healthcare.

This study is the first to explore racial/ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT among an ethnically diverse population in a southwestern state (NM) in the US. Previous population-based observational studies did not report the impact of race/ethnicity on MSRF screening and treatment in PCa patients treated with ADT.[7,82,83] The previous studies assessed different outcome measures, including risks of AMI, stroke, pulmonary embolism and statin medications utilization, among PCa patients treated with ADT.[7,82,83] We believe that our study findings provided valuable information and contributed to the current knowledge of PCa health disparities and MSRF screening and treatment among PCa patients treated with ADT.

Specific Aims and Research Hypotheses

Specific Aim 1: To determine racial/ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT.

Null hypothesis (H_0): There are no racial/ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT.

Specific Aim 2: To determine racial/ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT and with an indication to treat MSRF.

H_0: There are no racial/ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT and with an indication to treat MSRF.

Specific Aim 3: To determine longitudinal changes in MSRF screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT.

H_0: There is no difference in the MSRF screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT.

Specific Aim 4: To identify patient and healthcare provider factor influencing the receipt of MSRF screening among racial/ethnic groups of PCa patients treated with ADT.

H_0: There are no differences in patient factors (patient race/ethnicity, age at index date, marital status at index date, insurance coverage status at index date, PCa disease stage at index date, Gleason score at index date, number of co-morbidities at index date, baseline MSRF including “diagnoses of hypertension, diabetes mellitus II, obesity and dyslipidemia before treatment with ADT”) or healthcare provider factors (healthcare provider gender, specialty, and years of experience) in the receipt of MSRF screening among PCa patients treated with ADT.

CHAPTER 2: LITERATURE REVIEW

This chapter was divided into seven sections. First, the anatomy of the prostate gland, the pathophysiology, epidemiology, etiology, prognosis, screening, and diagnostic workup of PCa were presented. In the second section, advanced PCa and metastatic PCa, and current therapeutic options for the treatment of these PCa were presented. This included a discussion of ADT classes of medications, mechanisms of action, approved indications and dosage, contraindications, dose adjustments, available U.S. market dosage forms, common CVS and adverse metabolic effects.

In the third section, PCa health disparities in the U.S. and among the New Mexican population, including the use of ADT across different racial/ethnic groups were presented. The fourth section presented the definition of metabolic syndrome, epidemiology, association with ADT, and MSRF screening and treatment consensus guideline recommendations in PCa patients.

In the fifth section, reported studies that evaluated MSRF screening and treatment among different racial/ethnic groups of PCa patients treated with ADT were reviewed and discussed. The sixth section presented the conceptual framework used to guide the research. Lastly, we summarized the study's literature review results.

Anatomy of the prostate gland

The prostate gland is surrounded by a capsule located below the bladder and separated from the rectum by a layer of fascia named the denovillers aponeurosis.[93]

Both of base of prostate gland and bladder are supplied by the inferior vesicle artery.[93] The neurovascular bundle on either side of the prostate is derived from the pelvic plexus, which is essential for erectile function. These nerve plexuses arise from thoracic (T 10-12) and sacral (S 2-4) nerve roots.[93] Figure (1) describes the anatomy of the prostate gland.[94]

Pathophysiology of PCa

Several underlying mechanisms have been reported by the literature to better inform healthcare providers about the pathophysiology of PCa.[95] These include the ongoing androgen biosynthesis by the adrenal glands, upregulation of androgenic receptors and prostatic tumor-mediated cytochrome P17 (CYP17), and the activation of androgen receptors via different pathways.[96,97] Like other cancers, an imbalance between cell death rates and growth can lead to PCa.[95] However, this transformation is aggravated by subsequent gene mutations including the genes for retinoblastoma and P53, which will eventually cause tumor progression and metastasis.[95]

Nearly 90-95% of PCa cases are adenocarcinomas, 4% have transitional cell morphology and are thought to arise from the urothelial lining of the prostatic urethra and 1% have squamous cell carcinomas.[95,98] Although PCa can arise either from the peripheral zone (70%), central zone (15-20%), or transitional zone (10-15%), most of PCa cases involve multiple zones.[95]

When PCa is locally invasive, the transitional zone tumor cells spread to the bladder neck, whereas the peripheral zone tumor cells spread into the seminal vesicles and ejaculatory ducts.[95]

Figure 1. Anatomy of the prostate gland [94]

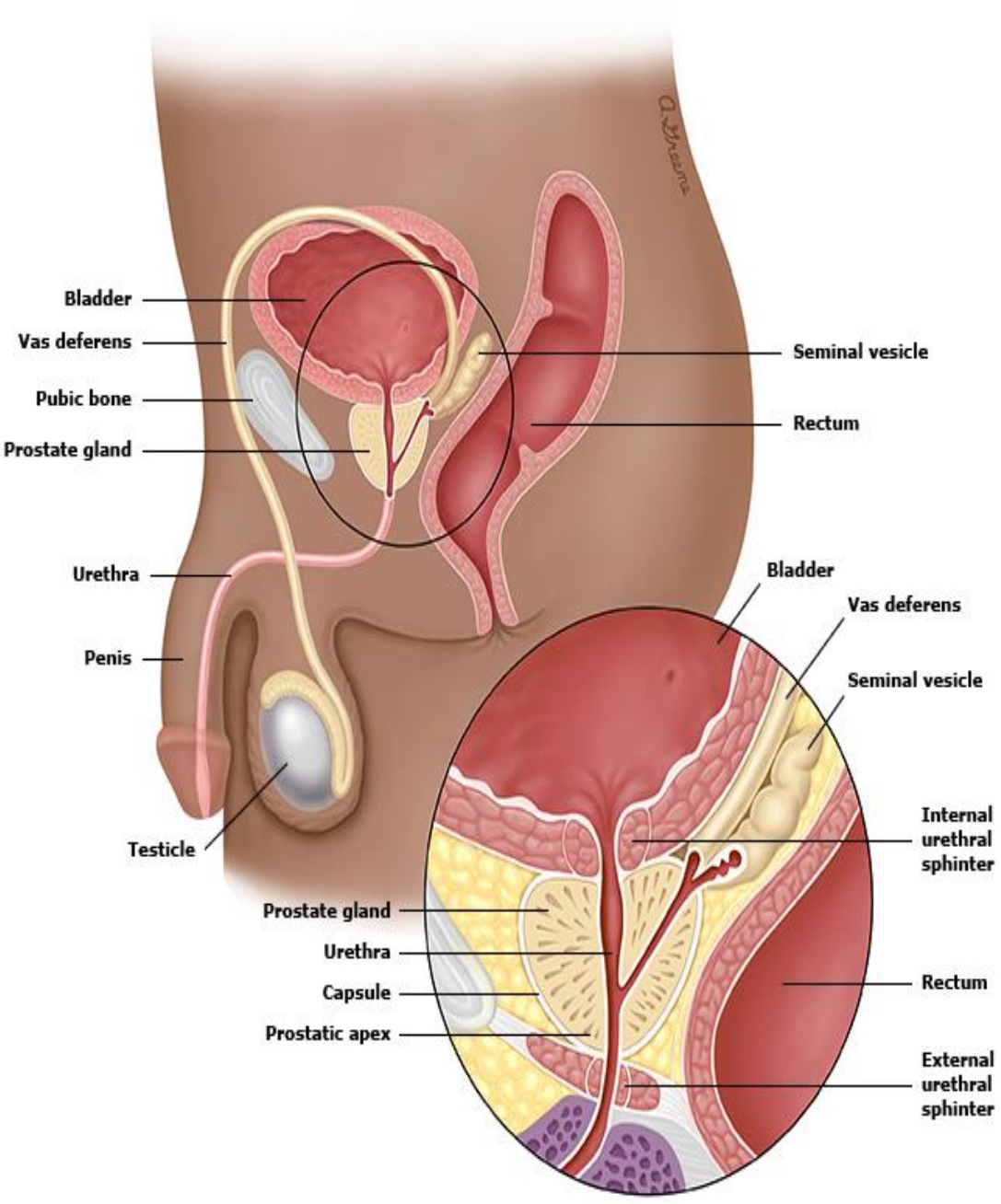


Figure 1 [Reproduced with permission from Benway BM, Andriole GL. Prostate biopsy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 8, 2022) ©2022 UpToDate, Inc. For more information, visit www.uptodate.com. Please refer to appendix (A) for the granted permission to use or reproduce copyrighted material].

For the case of metastatic PCa, the mechanical theory and the seed-and-oil theory are two current theories that explain how locally invasive PCa becomes metastatic.[99]

The mechanical theory attributes the spread of PCa through the lymphatic system. Investigators or proponents of the seed-and-oil theory believe that tissue factors facilitate the growth and the spread of cancerous cells.[99]

Epidemiology

PCa varies across geographical regions, depending primarily on different diagnostic workups rather than known risk factors (i.e., diet, lifestyle, race, age and androgen status).[100] The following are the reported age-adjusted PCa rates around the world: 104.2 cases of PCa per 100,000 person-years in Australia and New Zealand, 93.1 cases per 100,000 person-years in western Europe, 73.1 cases per 100,000 person-years in northern Europe, 85.6 cases per 100,000 person-years in North America; the least is 7.2 cases per 100,000 person-years in Asia due to familial and dietary factors.[101] The age-adjusted mortality is the highest in the Caribbean (26.3 cases per 100,000 person-years) and Southern Africa (19.3 cases per 100,000 person-years), followed by South America (16.2 cases per 100,000 person-years) and Northern Europe (15.4 cases per 100,000 person-years).[101] These variations have been mostly attributed to inherent genetic variation and dietary factors, although further studies are needed to confirm the underlying biological mechanism.[101]

In the U.S., the Center for Disease Control and Prevention (CDC) reported a PCa age-adjusted incidence rate of 107.5 per 100,000 and 18.9 per 100,000

deaths.[3] In 2018, the estimated incidence counts of PCa cases approached 211,893 across all racial and ethnic groups.[3]

Etiology

For many years, it was believed that testosterone, a steroid hormone produced mainly by the testes and the adrenal cortex, is responsible for rapid prostate growth and cancer.[102] AA men have a higher incidence of PCa, and studies reported that they have 15% higher testosterone levels than Hispanics and NHW.[103] However, a meta-analysis published by Boyle et al. (2015) concluded that both endogenous and exogenous testosterone are not independent risk factors for PCa.[104]

Rates of PCa vary among different geographical areas worldwide, suggesting that genetic variation may be considered an important etiological factor.[105] For example, the risk of PCa tends to be higher among AA and Caribbean men of African descent, followed by NHW, Hispanics, and finally, Asian men living in their native countries.[105] However, U.S. immigrant Asians tend to have higher risks of PCa compared to native Asians, which suggests that a diet high in calcium and red meat and familial predisposition may be contributing factors of PCa.[106]

Positive family history of PCa increases the risk of developing the disease 6-7 years earlier than someone without a positive family history.[107,108] Familial predisposition is responsible for 5-10% of PCa cases.[108] A positive BRCA-2 gene mutation may also increase the risk of developing aggressive PCa at a younger age.[109] The use of 5-alpha reductase inhibitors for treating benign prostatic

hyperplasia (BPH) has also been attributed to increasing risks of developing aggressive high-grade PCa compared to placebo.[110] In 2011, FDA issued a boxed warning for prescribing 5-alpha-reductase inhibitor products in patients with higher risks of developing PCa.[110]

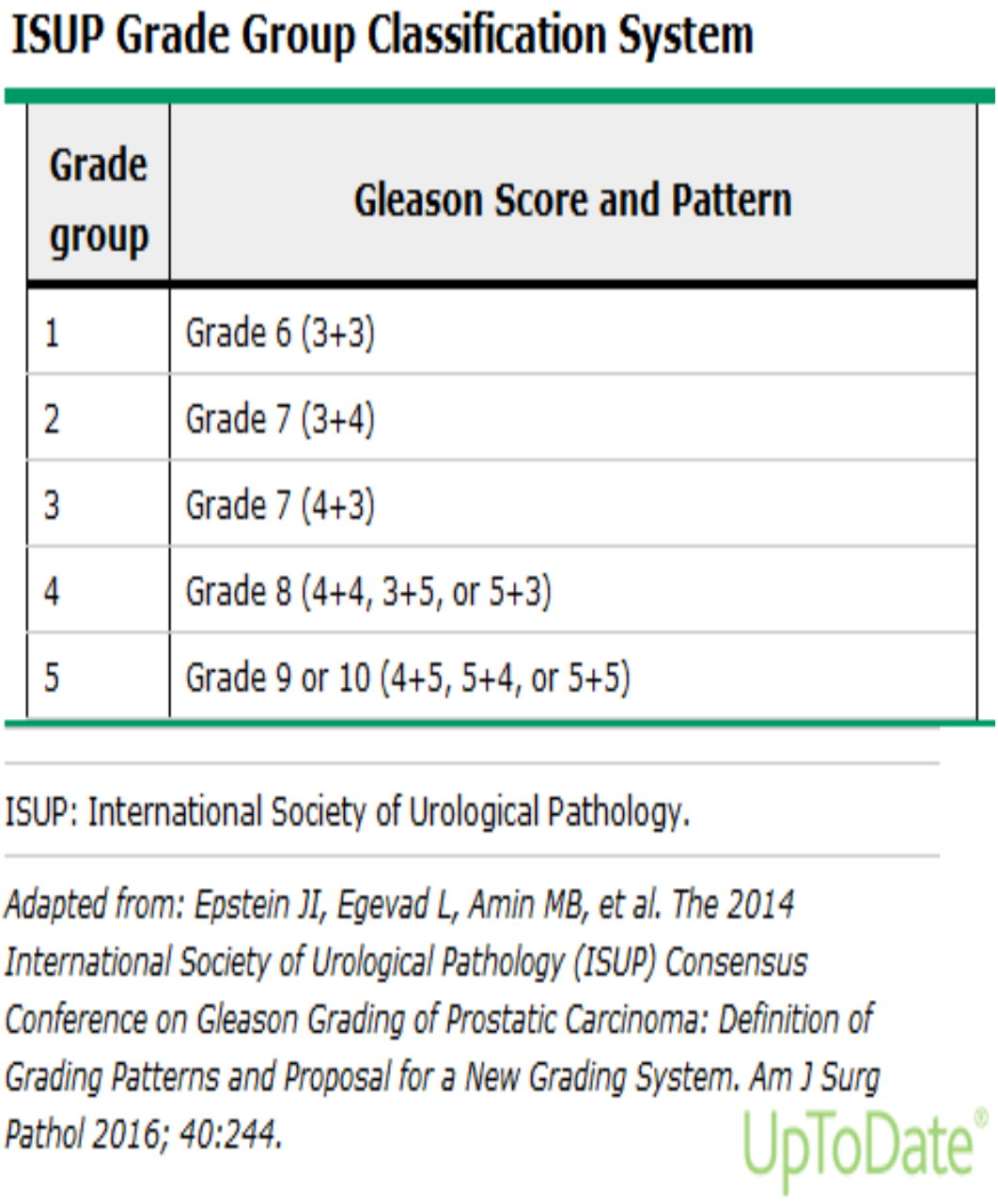
Prognosis

The main indicators of PCa prognosis have been well described in the literature. The first diagnostic indicator is the Gleason pattern which is a scoring system used to determine the aggressiveness of PCa and assists in choosing appropriate treatment options.[111] Scores may range from 1 to 10.[112] Higher Gleason pattern scores (>7) suggest poorly differentiated PCa cells and/or poor prognosis.[112] Scores between 1 and 6 indicate a well-differentiated or low-grade tumor, whereas a score of 7 is suggestive of a moderately-differentiated tumor.[112,113] However, Gleason pattern scores have changed recently because scores 2-5 are rarely seen. Figure (2) demonstrates the Gleason pattern for determining PCa prognosis. Other important indicators are age at diagnosis, capsular penetration and the extent of tumor volume.[113] Nearly 30% of localized PCa will spread despite treatment based on diagnostic PSA level, histologic grade and pathologic stage of the tumor.[111]

The literature has also reported that three consecutive increases in PSA levels after radiation therapy or an increase in PSA level by 0.2 ng/ml after radical prostatectomy may indicate metastasis.[114] In addition, performing biopsy and the clinical stage of PCa may indicate failure of localized PCa treatment.[115]

Figure 2. Gleason's Pattern of Prostate Cancer [116]

International Society of Urological Pathology (ISUP) Grade Group Classification System



ISUP Grade Group Classification System

Grade group	Gleason Score and Pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

ISUP: International Society of Urological Pathology.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

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*Figure 2 [Reproduced with permission from Yang XJ. Interpretation of prostate biopsy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 8, 2022) ©2022 UpToDate, Inc. For more information, visit www.uptodate.com. Please refer to appendix (A) for the granted permission to use or reproduce copyrighted material].

Another prognostic indicator is the type of anesthesia used in radical prostatectomies. In a retrospective study conducted to evaluate the association of tumor progression due to anesthesia after radical retropubic prostatectomies, 1,642 procedures were reviewed for patients who had general anesthesia and 1,642 had an opioid-sparing approach to anesthesia (neuraxial block). Results showed that patients who had general anesthesia during prostatectomy had higher mortality risk (Hazard Ratio (HR)= 1.32, 95% CI: 1.00–1.74, p=0.047) and greater risk of systemic progression (HR=2.81, 95% CI: 1.31–6.05, p=0.008) compared to patients who received opioid-sparing approach.[117]

The literature has also identified several biochemical and genetic markers that help determine the prognosis of PCa. However, none of the following genetic measures is routinely used in practice; mutations in MYC, P53, PTEN and ERG-TMPRSS2 chromosomes.[118]

Screening

Several organizations have issued screening guidelines for PCa. Examples of these organizations are the ACS, AUA and the NCCN clinical practice guideline of PCa. Although these organizations differ in their recommendation regarding PSA routine testing, age groups, and life expectancy, they all agreed on the importance of an informed shared decision-making process that considers patient value, preferences and quality of life.[9,70,119–121] Elevated PSA is proportionally associated with the odds of having PCa. When the PSA level is 1 ng/ml, PCa is detected in 8% of men. This increases to 25% if the PSA is between 4-10 ng/ml.[122]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) recommends that a PSA value of 3 ng/ml warrants lateralized sextant biopsy.[123] Preston et al. (2016) published a study reporting the association between high PSA levels in midlife and the odds of having deadly PCa in the future.[121] The study included men aged 40-59 years with PSA levels in the upper quartile versus those below the 50th percentile. Results indicated that the odds of having deadly PCa among patients with PSA level in the upper quartile versus those with levels below the median percentile was 8.7 if the person is 40-49 years old, 12.6 if the person is 50-54 years old and 6.9 if the person is 55-59 years old.[121]

ACS recommends that average-risk men aged 50 receive information about the potential risks of PCa and the importance of PSA screening. It further suggests men having a positive family history of PCa, high-risk men at age 45 and AA men receive PSA screening.[124]

PSA retesting every 2 years is considered if PSA level falls below 2.5 ng/ml and annual retesting is required if PSA level is ≥ 2.5 ng/ml.[125] However, AUA does not recommend routine PSA testing for the following categories[126]:

1. Men over 70.
2. Men under 40.
3. Men who are 40-54 years old with average risk.
4. Men with at least a life expectancy of less than 10-15 years.

Conversely, the NCCN clinical practice guideline of PCa is more conservative and recommends baseline evaluation, physical examination and

obtaining family history as well as digital rectal examination (DRE) for patients who are 45-75 years old.[70] The published literature has also suggested other approaches that may help determine the likelihood of developing PCa. Assessing PSA velocity is the first approach where the velocity is calculated by evaluating three consecutive PSA measurements over at least a period of 18-24 months.[127]

Free versus bound PSA is another approach that is used to differentiate elevated PSA due to BPH from cancer.[128] A lower percentage of free PSA is associated with higher odds of having PCa. The percentage is calculated relative to the total PSA level. A percentage of free PSA more than 25% is considered normal. However, a biopsy is recommended if the free PSA level is below 18% and others recommend a cutoff point of 12%.[129] Measuring free PSA level would help physicians determine whether to perform a patient's biopsy if PSA level falls within 4-10 ng/ml.[128] This approach would also help in patients with either a large prostate gland and who had one biopsy with negative results.[128] Although screening and earlier PCa detection reduce mortality, long-term treatment complications may offset treatment benefits, including bowel dysfunction and sexual and urinary complications that are common and long-lasting. For example, nearly 50-70% of patients that underwent radical prostatectomy suffer from sexual impotence and about 40-50% have urinary leakage.[130–133]

Diagnostic Workup

Most PCa patients are asymptomatic.[134] Abnormal PSA level and/or DRE are diagnostic measures used to identify prostate abnormality and/or cancer by performing a biopsy.[134] Multiple biopsies are usually required since false-

negative results often happen.[135] DRE helps detect nodules, asymmetry, or differences in prostate gland texture which warrantee the need for biopsy.[135] Most PCa patients have negative DRE and elevated PSA.[135]

PCa patients often present with urinary retention, urinary frequency, hematuria, adenopathy, bone pain, obstructive signs like decreased urine steam and over-distended bladder because of BPH.[134] However, patients with advanced stages of PCa may manifest skeletal abnormalities due to bone metastases. Other manifestations include weight loss, anemia and back pain due to spinal compression.[134,136] In addition to PSA, DRE and performing biopsy as part of the diagnostic workup, kidney and liver function tests are also warranted in advanced stages.[113] Computed Tomography (CT) scan is also often required in case of lymph node involvement.[113]

Tumor Node Metastases (TNM) Staging System of PCa

The American Joint Committee on Cancer (AJCC) issued a staging system for PCa based on the Gleason score and grade group of staging.[137] Generally, the clinical stage of PCa, PSA level, DRE findings, biopsy findings and imaging study results indicate PCa prognosis.[70,134] The TNM staging of PCa is described based on the extent of tumor size, involvement of lymph nodes and whether the tumor is metastasized. The following classification helps physicians determine the patient's prognosis and select the most appropriate therapy tailored for the stage of PCa. This may also help patients understand their disease condition and share their thoughts and decisions with the healthcare provider regarding treatment. Table (1) describes the TNM staging of PCa. In the

next section, we explored advanced and metastatic PCa, and their current therapeutic options. This included discussing ADT classes of medications, mechanisms of action, approved indications and dosage, contraindications, dose adjustments, common CVS, and adverse metabolic effects (≥10%), and available dosage forms in the U.S. market.

Advanced and Metastatic PCa

When localized PCa involves any combination of blood, lymphatic, or contiguous local spread, it is defined as advanced PCa.[138] Advanced PCa becomes metastatic when there is a distant spread to the bone(s) or other sites/tissues with or without bone involvement.[138] Patients with advanced and metastatic PCa often present with weight loss, pain, hematuria, urinary retention, urinary incontinence ureteral and/or bladder outlet obstruction, pathological fractures, bone marrow suppression, chronic renal failure, lower-extremity edema, adenopathy, and symptoms related to bony or soft-tissue metastases.[138]

Nearly 13% of PCa cases spread to lymph nodes, and 6% have distant metastasis.[138] Weiner et al. (2016) reported that the incidence of localized PCa had dropped by 37% during the period 2007-2013 compared to 2004 because of US Preventive Services Task Force (USPSTF) recommendations against routine PSA screening.[139] Underdiagnosis of PCa at early stages (i.e., localized disease stage) due to lower PSA screening rate resulted in a 72% higher incidence of metastatic PCa disease during the period (2007-2013) compared to 2004.[139]

Table 1. Tumor Nodes Metastases (TNM) Staging of Prostate Cancer [137,140]

T (Tumor size)	
Localized disease	Tx: Primary tumor cannot be assessed
	T0: No evidence of primary tumor
	T1: Clinically inapparent tumor, neither palpable nor visible by imaging
	T1a: Tumor incidental histologic finding in ≤5% of resected tissue
	T1b: Tumor incidental histologic finding in >5% of resected tissue
	T1c: Tumor identified by needle biopsy
	T2: Tumor confined within the prostate
	T2a: Tumor involves one-half of one lobe or less
	T2b: Tumor involves more than one-half lobe but not both lobes
	T2c: Tumor involves both lobes
Local extension	T3a: Extracapsular extension (unilateral or bilateral)
	T3b: Tumor invades seminal vesicles
	T4: Bladder invasion, fixed to the pelvic side wall, or invasion of adjacent structures
Metastatic disease	N: Positive regional lymph nodes
	M1: Distant metastasis
N (Nodal stages)	
NX	Regional lymph node metastasis
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M (Metastasis)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s), with or without bone disease

Despite advances in pharmacological options for patients with advanced and metastatic PCa, treatment with ADT has been the most widely used therapeutic modality when there is evidence of rising PSA, or when hormonal

therapy is indicated.[4,5] It is reported that nearly 50% of patients who survived PCa received treatment with ADT at one point of their lives.[6] PCa depends on androgen production for its continued growth.[4] Nearly 90-95% of androgen production occurs in the testes, which is regulated by the hypothalamic-pituitary axis. The rest of androgen production is carried out by the adrenal glands.[4] These observations provide rationale for the use of ADT, which can be accomplished with either pharmacological (i.e., medical/chemical castration) or surgical castration (i.e., bilateral orchiectomy).[4]

Surgical castration is considered a simple and cost-effective intervention. It is indicated when there is an urgent need to reduce testosterone levels (e.g., when the patient suffers from urinary tract outlet obstruction or spinal compression) or when cost or adherence to pharmacological ADT is an issue.[4] Medical/chemical castration suppresses androgen production through its effect on the hypothalamic-pituitary axis. This includes treatment with GnRH agonists (e.g., leuprolide, goserelin, buserelin, triptorelin), GnRH antagonists (e.g., degarelix, relugolix) and antiandrogens (e.g., bicalutamide and flutamide).[4]

GnRH agonists are synthetic molecules that bind to GnRH receptors on the pituitary gonadotropin-producing cells.[141] This causes an initial release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which causes a subsequent transient increase in androgen production from the testes (known as the flare phenomenon). However, GnRH receptors become downregulated on the gonadotropin-producing cells after one week of treatment initiation, causing a decline in LH and FSH production, subsequently reducing

androgen production from the testes.[141] Significant drop in testosterone production from the testes is usually noticed after 3-4 weeks of GnRH agonists initiation.[142] Despite this drop, continued treatment with GnRH agonists is essential to keep serum testosterone at castration levels. In a meta-analysis of 10 trials that included 1,908 patients, medical/chemical castration using GnRH agonists was shown to be equivalent to surgical castration in terms of overall survival, progression-related outcomes, and time to treatment failure.[8] Table (2) summarizes available GnRH agonists in the U.S. market.

GnRH antagonists were developed to reduce testosterone levels while avoiding flare phenomenon associated with GnRH agonists. GnRH antagonists also bind to the GnRH receptors on pituitary gonadotropin-producing cells but do not cause an initial release of FSH or LH.[4] Therefore, initial treatment with GnRH antagonists is preferable for patients with severe bladder obstruction and/or painful bone metastases.[143] Two large meta-analyses have evaluated the safety and efficacy of GnRH agonists and GnRH antagonists. In a meta-analysis of 8 randomized clinical trials (RCTs) that included nearly 2,600 patients, GnRH antagonists were associated with fewer CVS adverse events (Relative Risk (RR)= 0.52, 95% CI: 0.34-0.80, $p<0.05$) and lower mortality rate (RR= 0.48, 95% CI: 0.26-0.90, $p<0.05$) compared to GnRH agonists.[10] In the second meta-analysis of 5 RCTs that included nearly 1,900 patients, degarelix was associated with higher overall survival among patients with baseline PSA levels of >20 ng/ml (HR= 0.47, $p=0.023$) and >2 ng/ml (HR= 0.36, $p=0.006$) compared to patients receiving GnRH agonists.

Table 2. Gonadotropin-releasing hormone (GnRH) Agonists Medications [4]

Generic Name	United States Brand Name	FDA [a] Approval for PCa [b]	Approved indications for adults	Dosage for PCa indication	Cardiovascular and metabolic adverse events (≥10%)	Contraindications	Dosage adjustment	Dosage forms
Leuprolide	Eligard® (2004) Viadur® (2000) Lupron Depot® (1997/2011) [c]		Advanced PCa, Endometriosis, Uterine leiomyomata.	Varies based on dosage form [d]	Increased cholesterol level (7-59%), elevated triglycerides level (5-32%), hot flash (≤98%).	Hypersensitivity to leuprolide, or GnRH-agonist [e] analogs.	No dose adjustment required in renal or hepatic failure.	IM (Lupron Depot®) SC (Eligard®) SC (Viadur®) SC (Leuprolide acetate)
Goserelin	Zoladex®	1998	Advanced breast cancer, Endometrial thinning, Endometriosis, Advanced PCa.	28-day implant: 3.6 mg every 28 days, 12-week implant: 10.8 mg every 12 weeks.	Hot flash (64%).	Hypersensitivity to goserelin or GnRH-agonist analogs.	No dose adjustment required in renal or hepatic failure.	SC (Zoladex®)
Triptorelin	Trelstar Mixject®	2000	Advanced PCa, Controlled ovarian hyperstimulation.	3.75 mg once every 4 weeks, 11.25 mg once every 12 weeks, or 22.5 mg once every 24 weeks.	Hot flashes (59-73%) increased serum glucose.	Hypersensitivity to triptorelin or GnRH-agonist analogs.	No dose adjustment required in renal or hepatic failure.	IM (Trelstar Mixject®),
Histrelin	Vantas®	2004	Advanced PCa.	50 mg implant surgically inserted every 12 months.	Cardiovascular adverse events occur in less than 2% of patients.	Hypersensitivity to histrelin or GnRH-agonist analogs.	No dose adjustment required in renal or hepatic failure.	SC implant (Vantas®)

Footnote:

a. Food and Drug Administration.
b. Prostate Cancer.
c. Lupron depot 7.5mg, 22.5 mg, and 30 mg received FDA approval in 1997. In 2011, the 45 mg strength formulation received FDA approval.
d. IM: Lupron depot 7.5 mg (monthly): 7.5 mg every month **or** Lupron depot 22.5 mg (3 months): 22.5 mg every 12 weeks **or** Lupron depot 30 mg (4 months): 30 mg every 16 weeks **or** Lupron depot 45 mg (6 months): 45 mg every 24 weeks. SC: Eligard: 7.5 mg monthly **or** 22.5 mg every 3 months or 30 mg every 4 months **or** 45 mg every 6 months. Leuprolide acetate 5 mg/mL solution: 1 mg daily.
e. GnRH: Gonadotropin-releasing hormone.

Despite significant survival and safety advantages associated with GnRH antagonists, they are associated with localized injection site reactions (e.g., degarelix is associated with nearly 40% of injection site reactions).[11] Table (3) summarizes current GnRH antagonists in the U.S. market.

Third, anti-androgens (e.g., bicalutamide and flutamide) are add-on therapies to GnRH agonists used in advanced and metastatic PCa to reduce risks of flare phenomenon.[144] They bind to androgen receptors and inhibit their interaction with dihydrotestosterone and testosterone.[145] Monotherapy with anti-androgens has been shown ineffective in reducing testosterone levels because anti-androgens do not block the hypothalamic-pituitary axis.[4,145] Bicalutamide (Casodex®) was approved by the FDA in 2008 to treat advanced and metastatic PCa. It is a pure nonsteroidal anti-androgen receptor inhibitor and given as 50 mg orally once daily in combination with GnRH agonists.[146]

Casodex® is the preferred anti-androgen medication because of its favorable toxicity profile and efficacy relative to other anti-androgens. Conversely, flutamide which the FDA approved in 1989, is a less widely used anti-androgen because of limited effectiveness and worse adverse events profile. It has a short half-life (~5 hours) and is associated with frequent anti-androgenic and gastrointestinal adverse events.[147]

Loblaw et al. (2006) reported that treatment with combined androgen blockade therapy is controversial because several RCTs did not show survival benefits. However, a limited number of studies reported a 3-6 months survival benefit with complete androgen blockade therapy.[148]

Table 3. Gonadotropin-releasing hormone (GnRH) Antagonists Medications [4]

Generic Name	U.S. Brand Name	FDA [a] Approval Date	Approved indications for adults	Dosage for PCa [b] indication	Cardiovascular and metabolic adverse events (≥10%)	Contraindications	Dosage adjustment	Dosage forms
Degarelix	Firmagon®	2008	Advanced PCa	Loading dose: 240 mg administered as two 120 mg (3 mL) injections. Maintenance dose: 80 mg administered as one 4 mL injection every 28 days (beginning 28 days after the initial loading dose).	Hot flashes (26%) increased gamma-glutamyl transferase (≥10%).	History of severe hypersensitivity to degarelix.	Use with caution in moderate-severe renal failure (CrCl) [c] <50 ml/min), and severe hepatic failure (Child-Pugh class C).	Subcutaneous (Firmagon®)
Relugolix	Orgovyx®	2020	Advanced PCa	360 mg on day 1, followed by 120 mg once daily thereafter.	Hot flash (54%), increased serum glucose (44%), increased serum Triglycerides (35%).	The manufacturer lists no contraindications.	No dose adjustment required in renal or hepatic failure.	Oral tablets (Orgovyx®)

Footnote:
a. Food and Drug Administration.
b. Prostate Cancer.
c. Creatinine Clearance.

Continuation of Loblaw et al. (2006) study discussion: The number of negative studies was explained by the anti-androgen withdrawal phenomenon, where PSA levels are reduced when ADT is stopped because of modifications in androgen receptors that facilitate tumor growth. Thus, many patients' clinical conditions deteriorated because they did not stop ADT sooner. However, based on survival benefits provided by more recent clinical trials, it was suggested by the American Society of Clinical Oncology (ASCO) and NCCN clinical practice guideline of PCa to consider combined androgen blockade therapy in patients with hormonal sensitive and resistant PCa patients as well as in metastatic and high-risk localized disease stage.[70] Complete blockage of androgen receptors reduces symptoms of a flare-up (rise of testosterone levels) that may happen with GnRH agonists. The blockage approach should be continued unless PSA progression occurs.[148–150]

Overall, treatment with ADT is recommended for patients with advanced PCa and/or symptomatic metastases.[9] It is debatable whether asymptomatic metastatic patients should be started on ADT or delay treatment until significant symptoms develop.[9] Despite substantial beneficial evidence of ADT in reducing the progression of PCa and relieving potential obstructive symptoms, ADT are associated with likely toxic CVS and metabolic adverse events.[10–12,148,151] Thus, it is crucial to balance potential benefits and risks before and during treatment and consider patient preferences, values and quality of life.

Castration-Resistant Prostate Cancer (CRPC)

Castration is a treatment modality aimed at suppressing androgen production that contributes to stimulating growth of PCa cells. CRPC occurs when the patient is no longer responding or refractory to ADT. Thus, there is disease progression either in rising PSA levels and/or clinical progression despite treatment with ADT.[152] However, treatment with ADT in conjunction with newer therapeutic agents is still recommended by the NCCN clinical practice guideline in CRPC patients to maintain serum level of testosterone at castration level.[70]

CRPC is clinically characterized by 2 to 3 consecutive elevated PSA levels obtained at intervals of greater than 2 weeks and/or documented pathological findings of disease progression on CT scan despite pharmacological and surgical interventions aimed to reduce testosterone levels.[9,153] CRPC patients have low testosterone levels, classically below 50 ng/ml or even less than 20 ng/ml.[154] CRPC can be non-metastatic or metastatic. The non-metastatic form is M0, whereas the metastatic form is M1 or mCRPC. The main goals of CRPC treatment are prolonging survival, preventing recurrence, minimizing complications, and maintaining patient quality of life. Despite treatment with ADT, nearly 70% of PCa patients will develop mCRPC in their lifetime. Thus, starting treatment with chemotherapy or with other novel therapies (discussed next page) would be warranted in these cases as a first-line treatment for managing mCRPC.[70,155,156]

Until February 2018, there were no U.S. FDA-approved novel therapeutic agents to treat non-metastatic CRPC and patients were treated with ADT

alone.[157,158] However, apalutamide received U.S. FDA approval in February 2018 to treat non-mCRPC patients based on a randomized, double-blind, multicenter trial that included 1,207 patients. About 401 patients received ADT alone and 806 patients received apalutamide 240 mg orally plus ADT. The primary efficacy outcome was to assess metastasis free-survival. Results showed that patients receiving apalutamide and ADT had longer survival duration than ADT alone (40.5 months vs. 16.5 months).[157,158]

All therapeutic options described in figure (3) are indicated for metastatic stages of CRPC and are given in conjunction with ADT. Both abiraterone and docetaxel are combined with ADT when cancer is disseminated. Patients who have higher risks of developing metastasis based on clinical and/or PSA progression are also started on enzalutamide, apalutamide and ADT.[159–165]

Many crucial factors play a role in determining the course of treatment among patients with CRPC. This includes site and rate of disease progression, patient preferences, medication route of administration, side effects profile, drug-drug interactions, and regulatory and reimbursement statuses.[151] The site of metastatic involvement is the most crucial factor that affects survival in CRPC patients.[166] In addition to site involvement, the presence of visceral metastasis, poor performance status, use of opioids, presence of circulating tumor cells, increased PSA, alkaline phosphatase (ALK) and lactic dehydrogenase (LDH) levels, as well as low hemoglobin and serum albumin levels are all considered factors that affect survival among CRPC patients.[167]

Figure 3. Current Therapies for Castration-Resistant Prostate Cancer [159–165]

Overview of non-targeted therapies for metastatic castration-resistant prostate cancer (CRPC)

Approach	Indications	Route, schedule	Steroids	Symptoms, disease burden	Contraindications	PSA response to treatment	Median overall survival benefit for men with advanced disease*
Abiraterone	Metastatic CRPC	Oral, daily	Required	–	Severe liver dysfunction, hypokalemia, heart failure	Yes	Post-docetaxel: 4.6 months[1] compared with prednisone alone (HR for death 0.53, 95% CI 0.45-0.62) Chemotherapy naïve: 4.4 months[2] compared with prednisone alone (HR for death 0.81, 95% CI 0.70-0.93)
Enzalutamide	Metastatic CRPC	Oral, daily	Not required	–	Seizures	Yes	4.8 months[3]
Sipuleucel-T	Pre- or post-docetaxel	IV, every 2 weeks for 3 doses	Possibly contraindicated	Asymptomatic or minimally symptomatic	Steroids, opioids for cancer-related pain, GM-CSF, liver metastases	No	4.1 months[4]
Docetaxel	Metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction, cytopenias	Yes	2.5 months[5]
Cabazitaxel	Post-docetaxel, metastatic CRPC	IV, every 3 weeks	Required	–	Moderate liver dysfunction, cytopenias	Yes	2.4 months[6] compared with mitoxantrone/prednisone (HR for death 0.70, 95% CI 0.64-0.86)
Radium-223	Symptomatic bone metastases with no known visceral metastases	IV, every 4 weeks	Not required	Symptomatic bone metastases	Visceral metastases	Not reported	3.6 months[7]

PSA: prostate-specific antigen; HR: hazard ratio; IV: intravenous; GM-CSF: granulocyte-macrophage colony-stimulating factor.

* Docetaxel is also indicated for castration-sensitive disease in combination with androgen deprivation therapy for metastatic prostate cancer.

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*Figure 3 [Reproduced with permission from Dawson NA. Overview of the treatment of castration-resistant prostate cancer (CRPC). In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 8, 2022). ©2022 UpToDate, Inc. For more information, visit www.uptodate.com. Please refer to appendix (A) for permission to use or reproduce copyrighted material].

Several phase III clinical trials evaluated survival rates in patients who progress to worse disease condition despite treatment with docetaxel. Results showed that patients had longer overall survival rates when low number of serum circulating tumor cells was detected (<5 cells per 7.5 ml).[168–170]

Bone biomarkers have also been used to assess survival rates in patients with mCRPC since bone resorption and formation processes are disrupted in metastatic patients. Higher levels (>50th percentile) of bone resorption and formation biomarkers like N-telopeptide, pyridinoline, C-terminal collagen propeptide and bone ALK were associated with poorer prognosis and shorter overall survival (15 months vs. 22 months) compared with patients with normal biomarkers levels.[171]

Overall treatment goals for patients with bone metastasis include improving mobility, pain control and preventing complications such as spinal compression and pathological fractures. Radiation has been used extensively in patients with bone metastasis as a pain reliever since it benefits 80-90% of cases.[151]

The literature identified other therapeutic options that are used for mCRPC. Sipuleucel-T and radium-223 were introduced into the U.S. market in 2010 and 2013, respectively, as they showed a median survival benefit of 2-4 months compared to control.[160,172] Radium-223 is a radiopharmaceutical agent that improves patient quality of life by providing pain relief, improving overall survival and reducing complications. Radium-223 received FDA approval based on ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial to treat

mCRPC, symptomatic bone metastasis with no known visceral metastasis.[173,174] Results demonstrated higher survival rates compared to placebo (14.9 vs. 11.3 months). However, since both radium and sipuleucel have not been studied in patients with visceral metastases, the NCCN clinical practice guideline of PCa does not recommend either of both treatments to manage mCRPC with visceral metastasis.[70]

PCa Healthcare Disparities in the U.S.

Racial and ethnic health disparities in PCa prevalence, incidence, mortality, screening and treatment constitute the largest of all cancer disparities.[2] Despite improvements in understanding the pathophysiology of PCa and the availability of effective screening methods, non-pharmacological (surgery, radiation) and pharmacological agents, patients have not benefitted equally with screening and treatments as racial and ethnic disparities in the treatment of PCa persist.[2]

PCa Healthcare Disparities among African American (AA) men

AA men suffer disproportionally from PCa, facing a 78% higher incidence rate than NHW men.[2,14] They are more likely to be diagnosed at a younger age and present with more advanced and aggressive disease.[2,14] They also have more than 2 times higher mortality rates than NHW men.[2,14] These health disparities have been mostly associated with several clinical and socioeconomic factors. AA men are more likely to experience PCa diagnosis and treatment delays than insured NHW individuals.[15,16] They are also less likely to be screened for PCa compared to NHW men.[2,15,17–23] Steele et al. (2000) found that

AA men had lower PCa screening odds compared with NHW (OR: 0.3, 95% CI: 0.1-0.6).[24] Spencer et al. (2006) found that AA men had lower rate (42%) of PCa screening compared with NHW (48%) despite their increased risk of developing aggressive PCa.[25] After adjustment for demographic variables, they were 3% less likely to be screened for PCa than NHW men.[25] Comparable results were found by Etzioni et al. (2002).[26] Despite AA men having increased risks of developing aggressive PCa; lack of PCa testing awareness and general PCa knowledge, differential medical decision-making and access to testing were reported reasons for the low rate of PCa screening in AA men.[24,25]

AA men are also less likely to receive treatment with radical prostatectomy or radiotherapy and more likely to receive treatment with ADT compared with NHW men.[27–29] Moses et al. (2010) evaluated the influence of ethnicity on primary treatment received among patients with PCa.[27] NHW men were 48% less likely than AA men to receive ADT compared to surgery (p=0.02).[27] NHW with low-risk disease were 71% less likely to receive ADT than AA men with similar disease stage (p<0.01). Conversely, NHW men were more likely to receive surgical intervention compared to AA men with similar disease characteristics.[27] This indicates an ethnic disparity in the type of treatment received, independent of disease stage or prognosis.

Cobran et al. (2019), in a large population-based retrospective observational study that included 1,846 AA and 9,462 Caucasian patients with metastatic PCa evaluated the association between race and time to receive ADT during the period 2000-2011.[175] Results indicated that for AA men time to receive

ADT was longer compared to Caucasians (p<0.05).[175] Unmarried patients also had longer median time to receipt of ADT than married men, mainly due to lack of social support and difficulty in decision-making. Men residing in the South also had longer median time to receipt of ADT compared to men living in the Northeast US.[175]

Schmid et al. (2016) also reported that the proportion of AA men with localized PCa who underwent radical prostatectomy was (59.4%) compared to NHW men (69.5%) (p<0.05).[30]

In summary, the following were reported reasons for differential PCa treatment in AA men: poorer quality of care, worse disease prognosis, low income, lack of insurance, cost of care for AA treated with radical prostatectomy is higher than in NHW, fewer treatment options offered, less treatment information provided, differential provider-specific PCa screening and treatment, selection bias in definitive treatment (i.e., AA men are less likely to be offered the option to undergo radical prostatectomy or radiation independent of disease stage or prognosis), and the choice for less aggressive therapy.[27–30]

PCa Healthcare Disparities in Hispanics, American Indian/Alaskan Natives (AI/AN) and Other Minority Populations

Hispanics, AI/AN and some Asian groups are more likely to present with more advanced stage of PCa compared to NHW men because of lower PSA screening rates, raising concerns about under-diagnosis in these populations.[2,17–19,22,25,31–33] Lack of early diagnosis also contributes to higher mortality among AI/AN men.[176] Among Hispanics/Latinos, Mexican Latinos have a lower

incidence of PCa than Caribbean Latinos.[2] Among Asians living in the U.S., Japanese or Filipino patients have lower PCa incidence rates compared to other Asian groups.[2] Variations among Hispanics and some Asian groups have been mostly attributed to modifiable risk factors like red meat intake,[2,34] calcium and vitamin D intake,[2,35] increased BMI, and agricultural exposure.[2,36,37]

Haque et al. (2009) reported that Hispanics had a lower PSA screening rate (64.8%) compared with NHW (73.7%) men mainly due to varying clinical and socioeconomic factors (adjusted OR: 0.89; 95% CI: 0.84-0.96, $p<0.001$).[31] Glenn et al. (2012) also reported lower lifetime PSA and DRE screening rates for Hispanics compared with NHW men, mainly due to differential access to healthcare and medical decision-making ($p<0.05$).[17] Garg et al. (2013) also found that AA men (90%, OR: 0.52 (0.43–0.62)), Hispanics (84%, OR: 0.60 (0.53–0.68)) and “Other” minority populations (85.7%, OR: 0.84 (0.71–1.00)) had lower PSA screening rates compared with NHW men (93%, $p<0.01$) mainly due to varying socioeconomic and demographic factors.[18]

Goins et al. (2015) reported that PCa screening rates changed during the period 1996-2008 from 57.0% to 55.7% among AN/AN, 62.0% to 71.2% among AA, and 68.6% to 71.3% among NHW, indicating that disparity between NHW and AA shrank over time, however, it was virtually unchanged between NHW and AI/AN.[19] Potential contributing factors of health disparities in PCa screening in AI/AN men included low socioeconomic status, lack of cancer care services, limited knowledge of cancer care, perceived discrimination by the healthcare provider, and negative attitudes and beliefs toward cancer treatment.[19]

Gray et al. (2017) also reported that Hispanics (OR=0.92, 95% CI: 0.89-0.92, p<0.05), AA (OR=0.49, 95% CI: 0.48-0.50, p<0.05) and AI/AN (OR=0.89, 95% CI: 0.85-0.92, p<0.05) were less likely to receive radical prostatectomy compared to NHW men after adjusting for multiple clinical and socioeconomic variables.[29] Non-white race, increasing age, lack of insurance and low income were statistically significant predictors for not receiving definitive treatment (i.e., radical prostatectomy or radiation).[29]

Nguyen et al. (2019) found that 73.8% of AA men received ADT compared to NHW (77.2%) and Hispanics (80.7%). A significantly higher proportion of Hispanic (39.2%) and AA (59.5%) men were among the lowest income group compared to NHW men (20.7%). AA men had the highest proportion (57.7%) of stage IV PCa at diagnosis, followed by Hispanics (54%) and men of other minority populations (~54%) and then NHW (45%). Aggressive treatment using a combination of surgery, radiation and hormonal therapy was significantly most often administered in NHW men (19.2%) compared to AA (10.5%), Hispanics (17.4%) and other minority populations (15.5%). Access to care and treatment services, patient choice or knowledge, and service availability were reported as potential reasons for these health disparities in PCa minority populations.[86]

Underwood et al. (2004) reported that among patients with well-differentiated PCa, definitive therapy (i.e., radical prostatectomy, external beam radiation, brachytherapy, or combinations) was significantly more often administered in NHW (68.8%) compared to AA (64.6%) and Hispanics (64.9%), p<0.001. This disparity widened in men with moderately or poorly differentiated

disease, indicating an ethnic disparity in the type of treatment received, independent of disease stage or prognosis.[23]

In a nationwide study that included 72,036 patients with advanced PCa, Bagley, et al. (2020) identified factors associated with the receipt of ADT among patients 70 years and younger during the period 2004-2014.[28] The authors reported that AA men (OR=1.93, 95% CI: 1.74-2.14, p<0.001) and Hispanics (OR=1.36, 95% CI: 1.13-1.64, p<0.001) were more likely to receive ADT compared with NHW men.[28] Conversely, more NHW men received treatment with surgery or radiation (93%) compared to Hispanics (87%) and AA (87%) men, p<0.001. AA (OR= 1.46, 95% CI: 1.32-1.61, p<0.001) and Hispanic (OR= 1.36, 95% CI: 1.14-1.60, p<0.001) men were also more likely to receive no treatment compared to NHW men.[28] Compared with patients with managed care or private insurance, those with Medicaid, Medicare or with no insurance were more likely to receive treatment with ADT (Medicaid: OR, 2.92; 95% CI, 2.48-3.43, p<0.001; Medicare: OR,1.36; 95% CI, 1.20-1.53, p<0.001; no insurance: OR, 3.34; 95% CI, 2.81-3.98, p<0.001). Non-white race, low income, worse disease prognosis and high Charlson co-morbidity index were significant predictors for receiving treatment with ADT.[28]

PCa Healthcare Disparities in New Mexico (NM)

The state of NM is one of five “majority-minority” states in the U.S. and has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI).[38] PCa is the most commonly diagnosed cancer among men in NM with an incidence rate of 82.7 and 19.4 deaths per 100,000

individuals during the period of 2014-2018. During the 2014-2018 period, 5,351 new cases of PCa were diagnosed in NM and 1,044 PCa-related deaths.[3] PCa diagnosis was represented by 87.8% NHW men, 29% Hispanics, 3.7% AI/AN, 3% AA, and 1.3% Asian/Pacific Islander.[3]

Gilliland et al. (1998) reported that increased PCa screening was a significant determinant of the rising incidence rate of PCa among NHW compared to AI during the period 1969-1994 in NM. The burden of PCa among AI compared to NHW was reflected in disproportionally high mortality rates in relation to incidence rates. Mortality rates were high because AI cases were more advanced at diagnosis (23.3%) compared to 11.6% among NHW.[39] These rate estimates may have been biased by ethnic differences in access to medical care.[39] Minority populations in NM are more likely to present with advanced PCa disease stage, poorer prognosis and lower survival compared with NHW men.[39–42] They are also less likely to receive treatment with radical prostatectomy and more likely to receive treatment with ADT compared with NHW men.[39–42]

PCa Healthcare Disparities Among AI in NM

Gilliland et al. (1998) examined population-based PCa incidence, treatment and mortality among AI men in NM from 1969-1994.[39] During that period, age-adjusted incidence rate among AI had increased from 42.2 in 1969 to 64.6 in 1994 per 100,000 individuals.[39] However, AI men had lower incidence rates of localized PCa compared with NHW men during the same period. AI men were more likely to present with advanced and metastatic disease compared with NHW men. Underdiagnosis of PCa at early stages among AI men led to higher

incidence of aggressive metastatic PCa. Nearly 23% of PCa cases among AI men were diagnosed after distant spread compared with 11% for NHW men.[39] AI men also had a poorer 5-year PCa survival rate of 57% compared to 78% for NHW men.[39] In an earlier study, Gilliland et al. (1996) also reported that AI men were the least likely to be treated with radical prostatectomy (5%) and the most likely to be offered ADT (34.9%) compared to other racial/ethnic groups of PCa patients.[40]

PCa Healthcare Disparities Among Hispanics in NM

Gilliland et al. (1996) evaluated ethnic variation in PCa survival utilizing the NM tumor registry 1983-1992 data. Hispanics had a higher 12-month adjusted mortality risk (after PCa diagnosis) compared to NHW men (RR=1.2, 95% CI: 1.0-1.4) which may be explained by lower PSA screening rates and cancer awareness, worse disease prognosis and initial treatment choice.[40]

Overall, minority populations in the U.S. and NM were less likely to be screened for PCa, and more likely to experience delays in PCa diagnosis and treatment compared with NHW men. Some of the reported potential reasons of PCa health disparities in minority populations included poorer quality of care, worse disease prognosis, lack of insurance, high cost of care, low socioeconomic status, differential access to PCa testing and services, limited knowledge of cancer care, perceived discrimination by the healthcare provider, patient choice for less aggressive therapy, negative attitudes and beliefs toward cancer treatment and language differences. These health disparities were associated with higher morbidity and mortality rates in minority populations.[2,15,17–25,28,31,39–

[42,86]. Minority populations are also more likely to receive treatment with ADT and less likely to undergo radical prostatectomy compared with NHW men.[39–42] However, it is still essential to understand whether minority populations are at increased risk of developing metabolic syndrome due to ADT use compared with NHW men. The following section presented the definition of metabolic syndrome, risk factors, epidemiology, association with ADT, and its screening and treatment consensus recommendations.

Metabolic Syndrome Definition, Risk Factors and Epidemiology

The clustering of diabetes mellitus type II, hypertension, dyslipidemia and abdominal obesity while being treated with ADT suggest "metabolic syndrome."[44–47] Other known names for metabolic syndrome are syndrome X, insulin resistance syndrome, obesity dyslipidemia syndrome, and the deadly quartet.[48,49] Several definitions have been proposed by the literature for metabolic syndrome (Figure 4). This includes the NCEP ATP III definition, the International Diabetes Federation (IDF) definition, the European Group for the Study of Insulin Resistance (EGIR) definition, the World Health Organization (WHO) definition, and the American Association of Clinical Endocrinologists (AACE) definition. Despite having several proposed definitions for metabolic syndrome, the criteria proposed by the NCEP ATP III represent the most commonly agreed-upon criteria for metabolic syndrome.[51] It incorporates the key features of hyperglycemia, insulin resistance, visceral obesity, dyslipidemia and hypertension.[50] It also uses measurements and laboratory results that are readily available to physicians, facilitating its clinical and epidemiological application.[50]

Figure 4. Definition of Metabolic Syndrome [51,177]

Five definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%Δ; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance◇ or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol§	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides§	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)¥	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◇ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension of CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

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*Figure 4 [Reproduced with permission from Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 08, 2022). ©2022 UpToDate, Inc. For more information, visit www.uptodate.com. Please refer to appendix (A) for permission to use or reproduce copyrighted material].

In a large study that included 8,800 U.S. adults participating in the third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994), the overall prevalence of metabolic syndrome was 22% with an age-dependent increase (6.7%, 43.5%, and 42% for ages 20-29, 60-69, and >70 years, respectively).[87] The age-adjusted prevalence of metabolic syndrome was highest among Hispanics (~32%).[87] Additionally, the prevalence of metabolic syndrome was 57% and 27% higher in females than in males among AA and Hispanics, respectively.[87]

In an updated study using 2011 to 2016 NHANES III, the overall prevalence of metabolic syndrome was 34.7% among the study population. Similarly, the prevalence increased with age and among Hispanics.[88] In a similar study utilizing 1988-2012 NHANES III, Moore et al. (2017) have found that AA men were less likely to have metabolic syndrome (OR= 0.77, 95% CI: 0.66-0.89) compared to NHW men.[178] Both advanced age (OR= 1.73, 95% CI: 1.67-1.80) and low education attainment (OR= 1.56, 95% CI: 1.32-1.84) were independent predictors of increased likelihood of developing metabolic syndrome among the study population.[178]

Wilson et al. (2005) have also found that the age-adjusted prevalence of metabolic syndrome increased by 56% among males and 47% among females over 8 years.[91] In a large multiethnic cohort study that included 6,751 patients, the prevalence of metabolic syndrome was highest among Hispanics (29.6%), followed by NHW men (26.7%), AA (23.6%) and Chinese (20.1%).[89]

In summary, the age-adjusted prevalence of metabolic syndrome is higher among Hispanics compared to other racial groups.[87–89]

Association of Metabolic Syndrome with ADT

There is substantial evidence evaluating the risk of developing metabolic syndrome following ADT initiation among patients with PCa. Bosco et al. (2015) quantified these risks in a meta-analysis of nine studies, six conducted in the US. Results indicated a positive association between ADT and risks of metabolic syndrome (RR= 1.75, 95% CI: 1.27–2.41, p<0.05).[53] Chen et al. (2018) in an observational retrospective study that included 1,162 patients with PCa between 2006 and 2015, found that treatment with ADT (OR= 1.731, 95% CI: 1.367–2.193, p<0.001) is an independent risk factor for developing metabolic syndrome.[179] Rudman et al. (2016) also found that 31% of PCa patients treated with ADT developed metabolic syndrome; dyslipidemia (47%) and hypertension (68%) were the most common metabolic conditions.[180]

The metabolic changes associated with ADT use have been mainly attributed to a biological mechanism. ADT alters body composition as low testosterone levels (i.e., male hypogonadism) are associated with a decline in lean body mass and an increase in fat mass. Increased fat mass increases insulin levels (i.e., hyperinsulinemia) which might be the inciting event leading to metabolic dysregulation.[57] Increased body fat mass also alters fatty acid metabolism. It reduces glucose uptake by muscle cells, resulting in insulin resistance and diabetes that may predispose patients with PCa and on ADT to

increased risks of CVDs.[57–60] These metabolic changes can occur within 6 months of ADT initiation.[55–57,181–184]

Smith et al. (2008) used CT and dual X-ray absorptiometry (DEXA) scans to evaluate changes in body fat and lean mass among PCa patients who received ADT. Results showed that 80% of patients had significant reduction in lean body mass and an increase in body fat mass after 6 months of ADT.[185] Lage et al. (2007) also found a higher estimated relative risk for incident diabetes among ADT patients (RR= 1.36, p<0.001) compared to patients not on ADT after adjusting for demographic characteristics, general health condition, comorbidities and use of statins.[186]

Several other studies have shown that metabolic changes could worsen with long-term treatment with ADT (i.e. ≥12 months).[58,59,187,188] Physiologically, insulin resistance develops as glucose uptake by muscle cells is reduced 3-6 months following ADT initiation. As a result, the body compensates by increasing insulin secretion to maintain normal blood glucose levels. However, this compensatory mechanism fails during prolonged treatment, resulting in hyperglycemia (Figure 5).

In one cross-sectional study, ADT was associated with various components of metabolic syndrome. Patients who received ADT had higher abdominal obesity (p<0.007), hyperglycemia (p<0.006) and hypertriglyceridemia (p<0.06) compared with the non-ADT group.[58] Metabolic syndrome was prevalent in more than 50% of PCa patients who received 12 months of ADT compared to 22% among PCa patients not on ADT.[58]

Figure 5. Metabolic Changes During Short and Long-Term Androgen Deprivation Therapy

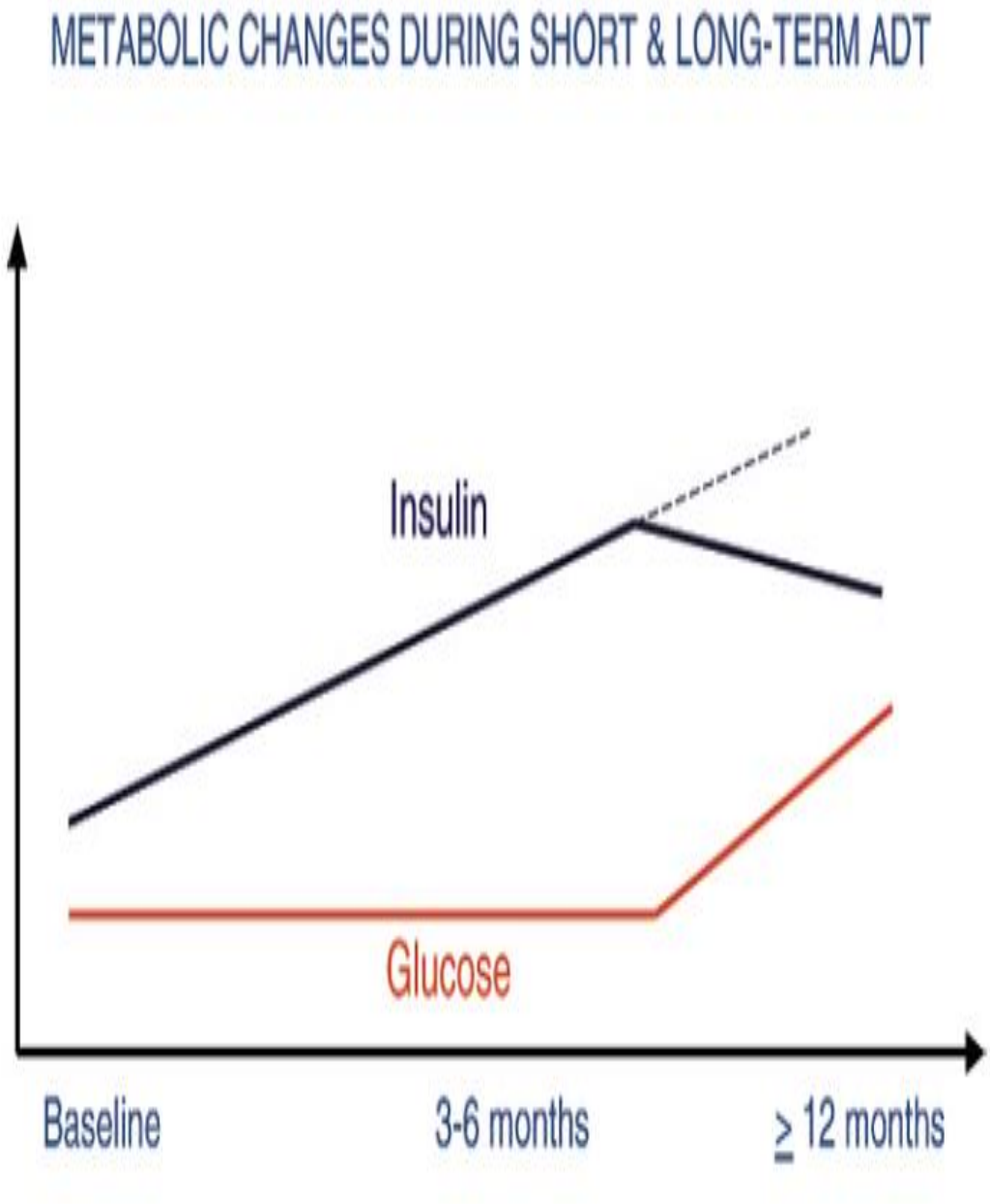


Figure 5: Proposed insulin and glucose biological dynamics during short and long-term ADT. A solid line suggests beta cell failure. The dashed line suggests continuing hyperinsulinemia. Color figure is available online at www.androlo gyjournal.org.

Tzortzis et al. (2017) reported that nearly 36-55% of PCa patients treated with ADT will develop metabolic syndrome within 12 months independent of age, race and stage of PCa.[61] Yuan et al. (2012) also evaluated metabolic complications' prevalence and changing trends among PCa patients treated with ADT. Nearly 30% of patients were diagnosed with metabolic syndrome 12 months following ADT initiation compared with the placebo group ($\chi 2=4.739$, $p=0.029$).[189] Patients had decreased HDL-C and increased TG levels within 4 months of ADT initiation.[189] Patients had also increased BP and FBG levels within 8 months of ADT initiation.[189]

Geng et al. (2020) in an observational retrospective study that evaluated the association between metabolic syndrome, time to ADT resistance (i.e., CRPC) and mortality found that metabolic syndrome is an independent predictor for CRPC (HR= 1.34, 95% CI: 1.02-1.75, $p=0.033$). Among patients with metabolic syndrome, patients who received statins had longer median time to CRPC (22.4 months) compared to 14.3 months among patients who did not receive statins ($p=0.002$).[190]

In addition to increased fat mass, increased circulating blood glucose levels, insulin resistance and lipid abnormalities, ADT increases arterial stiffness resulting in an increased risk of developing CVDs.[60] Liang et al. (2019) in a systematic review and meta-analysis of 19 studies estimated risks of cardiac events associated with ADT.[62] Results included an overall significant increase in AMI risks among PCa patients who received ADT (RR=1.19, 95% CI: 1.02-1.39,

p<0.05) compared with the control group. ADT was also associated with an overall increased CVD risk (RR= 1.25, 95% CI 1.11-1.40, *p*<0.05).[62]

Similarly, Keating et al. (2006) evaluated risks of incident diabetes, AMI, and sudden cardiac death among 73,196 Medicare enrollees aged 66 years or older with PCa treated with ADT. Patients had an increased risk of incident AMI (adjusted HR= 1.14, *p*<0.007) and incident diabetes (adjusted HR= 1.29; *p*<0.001) as early as 1-4 months following GnRH agonist treatment initiation. Additionally, patients had an increased risk of sudden cardiac death 5-12 months following treatment with GnRH agonists (adjusted HR= 1.31, *p*<0.001).[63]

Metabolic Syndrome and CVDs Risk Factor Screening & Treatment Consensus Recommendations Among PCa Patients Treated with ADT

In 2010, due to increased recognition of metabolic changes associated with ADT, the AHA, American Society for Radiation Oncology, AUA and ACS published a science advisory guideline to guide healthcare providers caring for PCa patients receiving ADT.[54] This included recommendations to evaluate MSRF (i.e. blood glucose, lipid levels and BP) within 6 months of ADT initiation. The science advisory guideline also recommended an annual assessment of these measures among patients with long-term ADT (≥12 months).[54]

PCPs should also be provided information by the treating oncologist on the potential metabolic adverse events associated with ADT.[54] Oncologists should also weigh the risks and benefits of ADT before treatment initiation.[54] Patients with preexisting CVDs should also receive appropriate secondary preventive measures as recommended by the AHA and other expert organizations including, when appropriate, exercise, anti-hypertensive and

glucose-lowering (e.g. metformin) medications, statins and aspirin.[54,64] These interventions effectively mitigate some of the metabolic complications of ADT.[54,65–68] Shortly after the science advisory guideline publication, the U.S. FDA released a drug safety communication in May 2010 regarding possible increased risks of certain CVDs (AMI, stroke and sudden cardiac death) and type II diabetes among patients treated with one class of ADT medications, the GnRH agonists.[69]

Utilizing the NCEP ATP III definition of metabolic syndrome, Grossman et al. (2011) provided more detailed recommendations for assessing and managing metabolic and CVS complications associated with ADT among PCa patients.[191] They recommended a baseline metabolic risk assessment before ADT initiation. This includes measuring BP, FBG, lipid levels and waist circumference. A follow-up assessment of these metabolic measures after 6 and 12 months of ADT was also recommended.[191] In a multidisciplinary consensus recommendation that aimed to guide physicians caring for mCRPC and hormonal-sensitive metastatic PCa patients, about 94% of panelists recommended regular metabolic assessments among patients treated with ADT.[192]

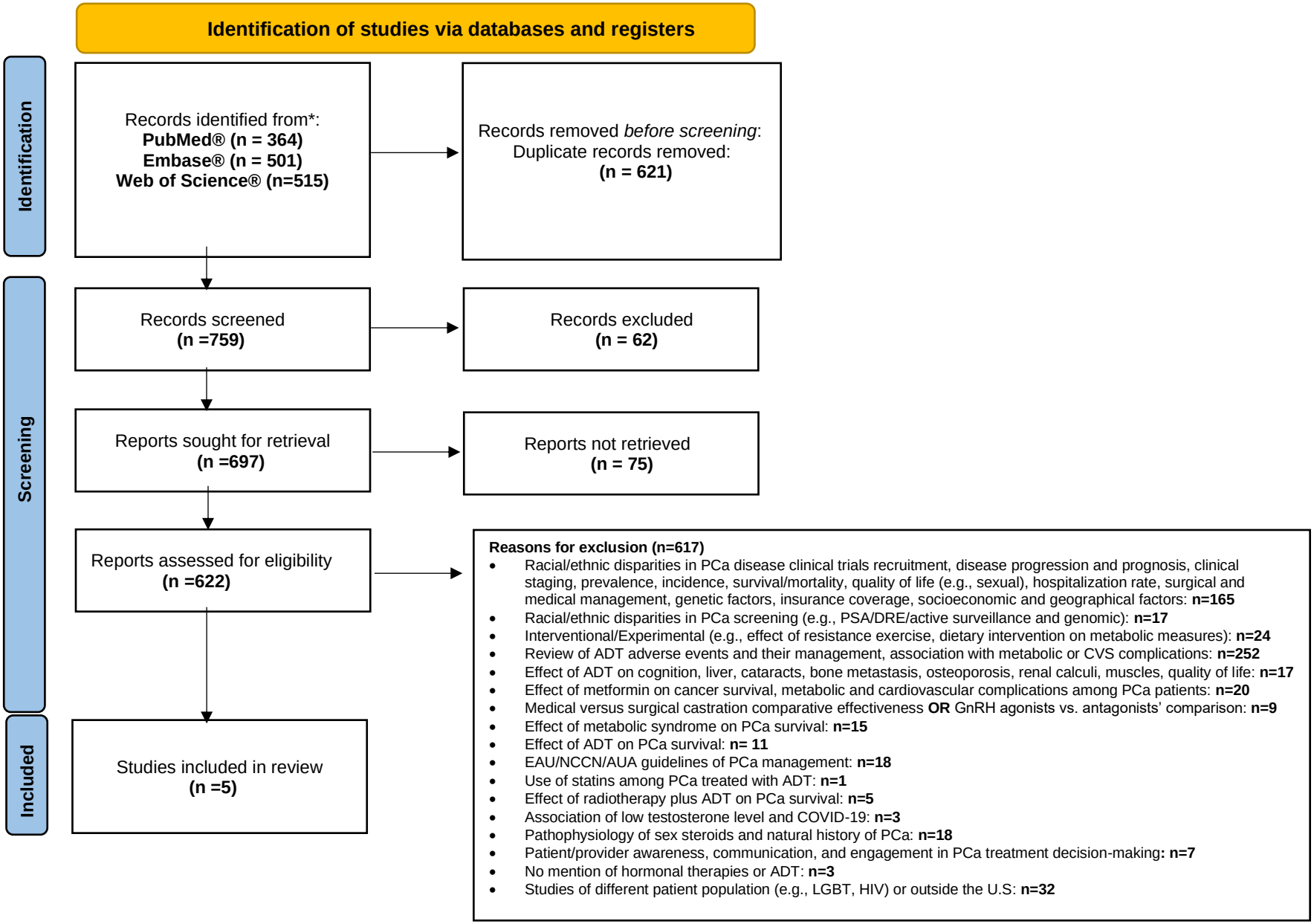
In March 2021, the NCCN clinical practice guideline for PCa recommended screening for and intervention to prevent and treat metabolic and CVS complications among PCa patients treated with ADT.[70] In the next section, we reviewed studies that evaluated MSRF screening and treatment among different racial/ethnic groups of PCa patients treated with ADT.

Review of studies that evaluated MSRF screening and treatment among different racial/ethnic groups of PCa patients treated with ADT

A systematic literature review using PubMed, Embase and Web of Science was conducted in May 2021 (updated on October 2022) to identify published studies that evaluated MSRF screening and/or treatment among different racial/ethnic groups of PCa patients treated with ADT.

Numerous combinations of the following search terms were used to identify relevant articles: "*Prostate cancer, neoplasm of the prostate, ethnic group, ethnicity, racial group, race, healthcare disparity, health disparities, African American, blacks, non-Hispanic White, Caucasians, Hispanics, Latinos, American Indian, Alaskan Native, metabolic syndrome, syndrome X, insulin resistance syndrome, obesity dyslipidemia syndrome, deadly quartet, androgen deprivation therapy, ADT, screening, assessment, treatment, management".* Both "MeSH" terms and "All" terms were used in the search strategy (Appendix B).

Three limitations to the search strategy were applied: (i) human studies, (ii) studies were restricted to "Male" sex, (iii) records were restricted to those of English language, unless a translation of the abstract/entire manuscript was available. No limitations were applied to geography, sample size, publication date, and study design. The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for reporting systematic literature review results was utilized to report identified studies (next page).[193] Table (4) summarized records identified using the three databases, screening process, eligibility and studies included in our final review. The following section discussed the conceptual framework used to guide our research.



**Adapted from:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj. n71. For more information, visit: http://www.prisma-statement.org/ [193]

Table 4. Studies evaluated screening/treatment of metabolic syndrome or cardiovascular risk factors among prostate cancer patients treated with Androgen Deprivation Therapy

Author (Year of publication)	Country	Type of article	Objective(s) of the study	Type of the study	Main outcomes	Main findings
Kenk et al. (2020)[194]	Canada	Journal Article	To provide recommendations for physicians caring for PCa [b] patients to assess CVDs [c] and minimize vascular and metabolic complications associated with ADT.	Review	N/A	<u>For every patient referred for ADT:</u> [a] [1] Collect routine medical history; perform a physical examination; determine the lipid profile; measure glycosylated hemoglobin A1c (HbA1c), uric acid, serum electrolytes, and creatinine; and CBC [d] and ECG [e]. [2] Patients should be started on "aspirin, glucose-lowering agent, statin, possible anticoagulation, renin-angiotensin antagonist, and b-blocker" (unless contraindicated) if they have either of the following pre-existing CVDs: stroke, transient ischemic attack, aortic disease, AMI [f] or CHD [g], PAD [h]. [3] Patients without pre-existing CVDs should be evaluated using the Framingham risk assessment tool or an equivalent CVD risk assessment tool. [4] Physicians should follow the ABCDE approach for CVDs risk assessment (A: assessment of risk, antiplatelet therapy, B: blood pressure, C: cholesterol, cigarette cessation, D: diabetes, diet, and weight management, E: exercise).

Castro-Alonso (2019)[82]	Mexico	Conference Abstract	To evaluate CVDs risk assessment among a sample of 100 patients with PCa treated with ADT.	Retrospective observational study.	Adherence with the guidelines.	Screening of CVS [i] comorbidities is sub-optimal among PCa patients treated with ADT. Nearly 6% of patients had significant CVDs including AMI, stroke, and pulmonary embolism. Note: "This record was identified using EMBASE database, and since it is a conference abstract, some of the findings were not retrievable."
Gan (2020)[83]	U.S.	Abstract	To evaluate CVDs risk assessment and statin prescription utilization among PCa patients treated with ADT.	Retrospective observational study.	Statin utilization and CVDs risk evaluation.	Nearly 48% (n=674) of patients who should have received statins did not receive statin therapy. In addition, nearly 25% of patients who received ADT developed an increase in blood pressure readings (*p<0.05*).
Sun et al. (2021)[7]	U.S.	Journal Article	To describe CVS risk factors assessment and treatment in men with PCa initiating ADT and overall.	Cross-sectional	Rate of CVS risk factors screening and treatment.	Nearly 25.1% of patients received ADT. Overall, there is a high CVS underassessment and undertreatment rate among PCa patients who received ADT.
Cornford et al. (2017)[195]	Global	Journal Article	To present a summary of the 2016 EAU [J] – ESTRO [K] – SIOG [L] guidelines on treating relapsing, mCRPC. [M]	Summary Review	Survival, progression of disease, quality of life, and adverse events of treatments.	Follow-up of ADT should include analysis of PSA, testosterone levels, and screening for cardiovascular disease and metabolic syndrome (within 3-6 months following treatment initiation, "*grade A recommendation*").

Footnote:

a. Androgen deprivation therapy.
b. Prostate Cancer.
c. Cardiovascular diseases.
d. Complete blood count.
e. Electrocardiogram.
f. Acute myocardial infarction.
g. Coronary heart disease.
h. Peripheral arterial disease.
i. Cardiovascular
j. European Association of Urology,
k. European Society for Radiotherapy & Oncology
l. International Society of Geriatric Oncology
m. Metastatic Castration-Resistant Prostate Cancer.

Kenk et al. (2020) aimed to provide recommendations for physicians caring for PCa patients. This included recommendations to assess CVDs and minimize ADT-related vascular and metabolic complications.[194] Although the study provided detailed screening and treatment recommendations for healthcare providers caring for PCa patients treated with ADT, it was a review article and did not aim to assess racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa treated with ADT.[194]

Castro-Alonso et al. (2019) in a retrospective observational study conducted in Mexico evaluated CVDs risk assessment among a sample of 100 patients with PCa treated with ADT.[82] The study's primary aim was to assess adherence to international and local guidelines of CVDs and metabolic syndrome risk assessment among PCa patients treated with ADT.[82] However, the study mainly assessed different outcomes (e.g. AMI, stroke and pulmonary embolism) and did not evaluate racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT.[82] The current study expanded Castro-Alonso et al. (2019) work by focusing on risk factor screening and treatment for metabolic syndrome. The current study also evaluated whether screening and treatment of MSRF occur equally across racial and ethnic groups of PCa patients treated with ADT.

Gan et al. (2020) aimed to evaluate CVDs risks and statin prescription utilization for men treated with ADT.[83] The study reported that nearly 50% of patients did not receive guideline-concordant statin therapy, and 25% had a significant increase in their BP readings. However, the study did not evaluate all

components of metabolic syndrome (e.g., TG level, HDL-C). It also did not assess racial and ethnic disparities in the receipt of MSRF screening and treatment.

In a nationwide U.S. study, Sun et al. (2021) evaluated CVS risk factors screening and treatment rates among PCa patients treated with ADT.[7] The study reported high CVS underassessment and undertreatment rate among PCa patients who received treatment with ADT.[7] Although this cross-sectional study shared some of the current study objectives, it did not primarily assess racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT. It did not report ethnicity data and also did not include all components of metabolic syndrome (e.g., data on TG and HDL-C were not collected).[7]

Lastly, Cornford et al. (2017) presented a summary of the 2016 European Society of Radiotherapy and Oncology (ESTRO) guideline on treating relapsing mCRPC. The guideline included recommendations to assess CVDs and MSRF within 3-6 months of ADT initiation, "*grade A recommendation"*.[195] However, this review article did not assess racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT.

In summary, few studies have reported population-based adherence to metabolic and CVS screening and treatment consensus recommendations among PCa patients treated with ADT.[7,82,83] Studies identified mainly assessed screening for different outcomes, including risks of AMI, stroke, pulmonary embolism and statin medications utilization among PCa patients treated with

ADT.[7,82,83] They also did not report racial and ethnic differences in receiving MSRF assessment and treatment. Therefore, we believe that our study provided valuable information and added a unique contribution to the current knowledge of PCa health disparities, metabolic syndrome, and treatment with ADT.

Conceptual Framework for The Current Study

We adopted Atun et al. (2010) conceptual framework "Integration of Targeted Health Interventions into Health Systems" [71] to guide the research and to specifically guide/answer study Specific Aim 4: To identify patient and healthcare provider factors influencing the receipt of MSRF screening among different racial/ethnic groups of PCa patients treated with ADT. The model builds on previous theoretical propositions and empirical research in innovation studies, particularly adoption and diffusion of innovations within health systems.[71]

This conceptual model was adopted because it facilitates analyzing factors that influence the integration process of targeted health interventions into health systems while aiming to improve health outcomes.[71] Atun et al. (2010) defined integration as the rate and extent pattern of health interventions adopted by the healthcare system. This conceptual model proposes that the adoption and diffusion of innovation and the extent to which it is integrated into healthcare system functions depend on five constituents described as follows[71]:

1. The health problem or its characteristics influence the rate at which the innovation gets integrated into the health system. For example, the problem's urgency may necessitate rapid introduction of an intervention

with limited integration, followed by gradual adaptation as the problem is better controlled.

2. The intervention/innovation refers to health technologies or organizational changes or modifications in decision-making, planning and service delivery processes. This includes innovative ideas, practices and institutional arrangements perceived as novel by individuals.
3. The adoption system refers to institutions and key actors of the healthcare system. This includes but is not limited to physicians, nurses, allied health professionals, patients, professional associations, patient groups, policy makers and civil society organizations. Each of these stakeholders may have different perceptions of the benefits and risks of an innovation and therefore occupy distinct roles and positions in the adoption system.
4. Health system characteristics involve organizational, clinical, financial, and regulatory changes involving multiple stakeholders. Therefore, integrating an innovation can occur at various health system levels (e.g., local, regional, national).

The context includes economic, political, ecological, legal, socio-cultural, and technological factors in the environment that may influence other constituents of the framework. For example, introducing a new diagnostic tool or prevention mechanism may provide opportunities for rapid adoption and easier integration into health systems. However, economic, and political factors may influence the desirability and hinder the integration of an intervention into the health system.

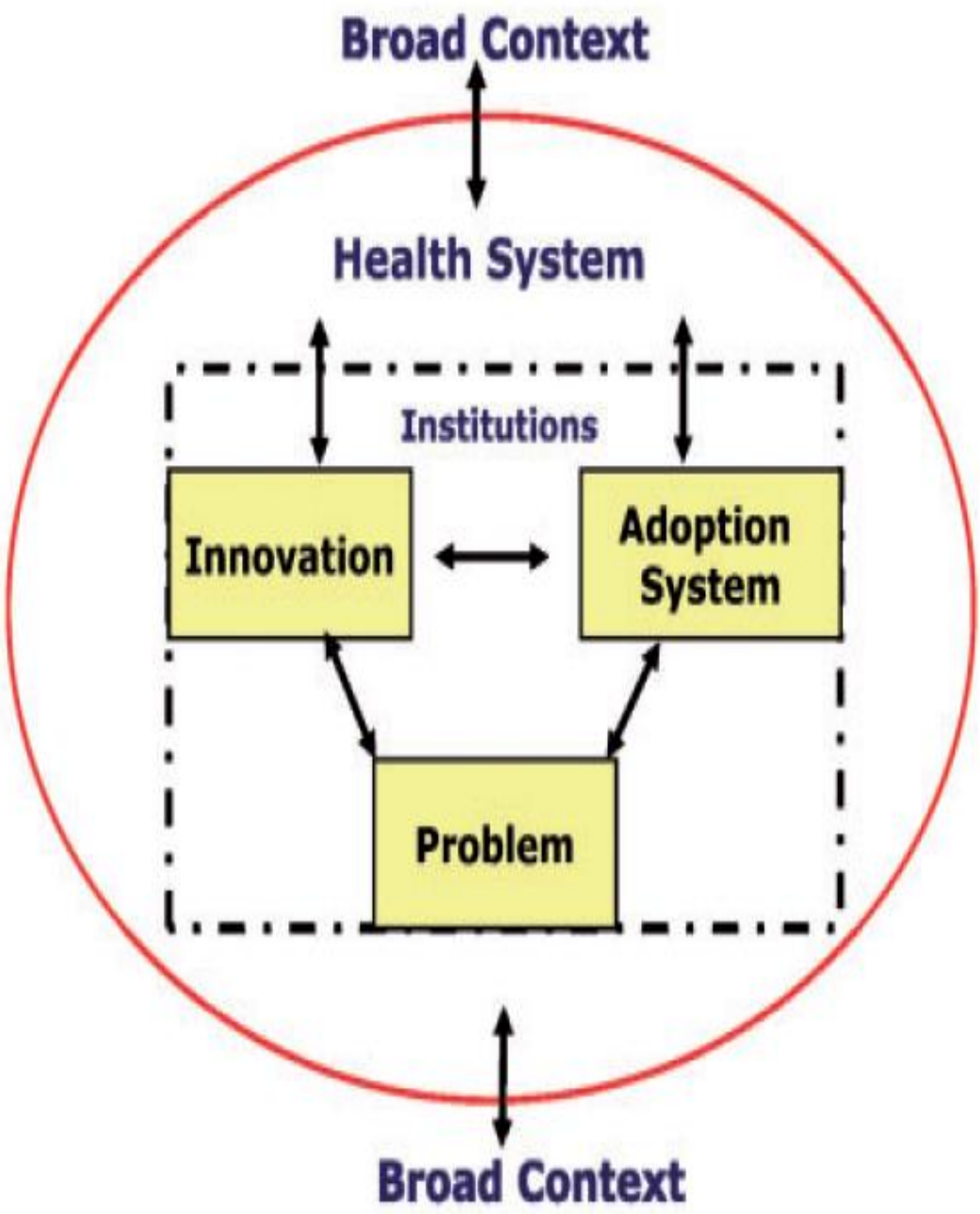
Figure (6) illustrates this conceptual model and its constituents. As illustrated in figure (6), the problem, the intervention/innovation, and the adoption system (i.e., stakeholders) influence each other within a health institution (e.g., hospital). For example, an investigator might be interested in understanding patient and healthcare provider factors influencing the receipt of breast cancer screening using a cutting-edge diagnostic tool in a tertiary care hospital where:

1. The problem is breast cancer.
2. The intervention is: breast cancer advanced screening tool.
3. Adoption system: healthcare system stakeholders.

The integration of breast cancer advanced screening tool in the hospital is influenced by the healthcare system stakeholders and the clinical, financial, and regulatory factors of a healthcare system. In addition, in a broader context, the healthcare system is influenced by economic, political, ecological, legal, socio-cultural, and technological factors in the innovation diffusion environment.

Bowser et al. (2017) utilized this framework to identify health system barriers and enablers that impact access to early screening, detection, and diagnosis of breast cancer both globally and more specifically in the MENA region. The framework examined health system barriers and enablers to breast cancer screening at the broader macro health system level, the health provider, and the individual level. Authors found that health insurance coverage status and access, healthcare provider gender, type (i.e. degree) and specialty, and having regular contact with the physician influenced breast cancer screening.[72]

Figure 6. Integration of Targeted Health Interventions into Health Systems Conceptual Framework [71]



*Adapted from [Atun R, de Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: a conceptual framework for analysis. Health Policy Plan. 2010;25(2):104-111. doi:10.1093/heapol/czp055].

Patwa et al. (2019) utilized the framework to investigate factors influencing the integration of safer conception services in a clinical setting. Specifically, the authors considered the “problem” as the risk of horizontal and vertical transmission of human immunodeficiency virus (HIV) horizontal and vertical transmission within families while trying to conceive. The “intervention” is safer conception care. The “health system characteristics” or the clinic characteristics refer to Witkoppen Clinic’s operation, a busy urban primary care clinic in sub-Saharan Africa.[196] Authors found that lack of HIV management skills and men and women trying to conceive within family planning may pose barriers to safer conception integration.[196]

In addition to using the conceptual framework described above to guide our research, we have also explored the literature to identify other patient and healthcare provider factors that predicted PCa and MSRF screening. Although there is a substantial amount of evidence that evaluated healthcare provider and patient factors influencing the receipt of PCa screening [73–81], the evidence available about patient and healthcare provider factors influencing MSRF screening is scarce. We summarized studies identified in the search below.

Healthcare provider characteristics

Franks et al. (2003) reported that female physicians are more likely to perform prevention procedures and make follow-up arrangements and referrals than male physicians.[75] Similarly, Ramirez et al. (2009) in a cross-sectional study that included 722 physicians evaluated physician gender differences in general and cancer-specific prevention attitudes and practices. Although both male and

female physicians shared many similarities, female physicians were more likely to discuss patients' general health prevention activities than male physicians, especially sensitive issues, including use of substances, violence, and physical activity. Male gender predicted belief in PSA screening.[74] Conversely, Lurie, et al. (1998) reported that female physicians were less likely to believe that their skills in performing prostate examination were excellent compared to male physicians (OR= 0.12, 95% CI: 0.06-0.22) mainly due to lower comfort level in performing sex-related examination and obtaining a sexual history from patients of opposite sex.[76]

Edlefsen et al. (1999) also reported that male physicians are more likely to perform DRE (98.5% vs. 91.2%) and order PSA (68% vs. 62%) compared to female physicians. Male physicians with ≤10 years of experience were also more likely to report routine PSA screening (23.3%) compared to physicians with ≥30 years of experience (8.6%). However, female physicians with ≥20 years of experience were more likely to report ordering PSA screening (22.2%) compared to physicians with ≤10 years of experience. Internal medicine physicians were also more likely to report ordering PSA screening (75.1%) compared to family practice physicians (63.3%).[73]

Patient-level characteristics

In addition to healthcare provider-level characteristics, the "adoption system" also includes patient-level characteristics that may influence the integration and adoption of healthcare intervention within the health system. We explored the literature to identify and understand patient-level variables

influencing MSRF screening among PCa patients treated with ADT. The description of these variables is below:

***Age*:** The incidence rate of PCa is exceptionally low/undetectable among patients who are <44 years. However, it increases among patients who are 45-64 years and is considered the highest among individuals who are 65-79 years.[3] Since the prevalence of PCa is highest among patients who are 65-79, we would expect a higher proportion of patients to receive ADT compared to other age groups. Therefore, it is likely that those patients would have higher odds of developing metabolic syndrome. However, it is still questionable (which was evaluated in the current study) whether patient age is a predictor of MSRF screening among PCa patients treated with ADT.

Marital status: Previous literature showed that marital status is an independent predictor for PCa-specific mortality and overall mortality.[80] Unmarried men have a higher risk of PCa-specific mortality (HR: 1.40, 95% CI: 1.35-1.44, p<0.0001) compared to married men of similar age, race, stage, and tumor grade.[80] Huang et al. (2017) also reported that marital status is an independent prognostic factor for PCa. Unmarried individuals had higher Gleason scores at diagnosis (i.e. poorer disease prognosis) compared to married men (HR: 1.12, p<0.007).[81] Despite screening of metabolic syndrome is initiated and mostly recommended by the healthcare provider, it is still questionable (which was evaluated in the current study) whether unmarried individuals had lower MSRF screening rate compared with married individuals mainly due to lack of social support and difficulty in decision-making.[81,175]

Insurance coverage status: The influence of healthcare insurance coverage status on PCa disease screening, diagnosis and treatment has been studied extensively.[77–79] In a large national observational population-based study that included 85,203 patients diagnosed with PCa, insured individuals were less likely to present with advanced PCa disease stage (adjusted OR=0.23, 95% CI: 0.20-0.27, *p* <0.001) and more likely to receive definitive treatment (i.e. surgery or radiation), (adjusted OR=2.29, 95% CI: 1.81-2.80, *p* <0.001) compared with uninsured individuals.[79] Therefore, we evaluated whether insurance coverage status predicts MSRF screening among racial and ethnic groups of PCa patients treated with ADT.

Comorbid disease conditions: Since treatment with ADT is indicated for patients with advanced and metastatic PCa [4,5], patients with a poorer prognosis and overall health condition are more likely to receive ADT and therefore at greater risk for developing metabolic syndrome and CVS complications. Therefore, it was essential to evaluate whether patients with poorer overall health condition (i.e., higher number of comorbidities) and PCa prognosis (i.e., worse PCa stage and Gleason scores) are more likely to receive MSRF screening compared to patients with better overall health condition and PCa prognosis.

In summary, guided by the conceptual framework “Integration of Targeted Health Interventions into Healthcare Systems,” we aimed to specifically guide/answer study Specific Aim 4: To identify patient and healthcare provider factors influencing the receipt of MSRF screening among different racial/ethnic groups of PCa patients treated with ADT. The model builds on previous

theoretical propositions and empirical research in innovation studies, particularly adoption and diffusion of innovations within health systems.[71] Understanding patient and healthcare provider factors that predict MSRF screening among racial and ethnic groups of PCa patients treated with ADT helped us better understand patients' interaction with the U.S. healthcare system in NM and provided recommendations to implement necessary changes to optimize MSRF screening among all patients and particularly among minority populations treated with ADT. Such an effort will help to achieve the goal of eliminating racial disparities in health and healthcare.

Summary of The Literature Review

In the U.S., the age-adjusted incidence rate of PCa approached 107.5 per 100,000 individuals and 18.9 per 100,000 deaths representing the most commonly diagnosed cancer among men.[3] NM is one of five "majority-minority" states in the U.S. and has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI).[38] 5,351 new cases of PCa were diagnosed and 1,044 PCa-related deaths were registered in NM during the period 2014-2018.[3] During the same period, PCa diagnosis was represented by 87.8% NHW men, 29% Hispanics, 3.7% AI/AN, 3% AA, and 1.3% Asian/Pacific Islander.[3] These rate estimates may have been biased by ethnic differences in access to medical care.[39]

Racial and ethnic health disparities in PCa prevalence, incidence, mortality, quality of life, screening and treatment constitute the largest of all cancer disparities. [2,17,27,29,30,86,175] Despite improvements in understanding the

pathophysiology of PCa and the availability of effective screening methods, non-pharmacological (surgery, radiation) and pharmacological agents; patients have not benefitted equally with these screening and treatments as racial and ethnic disparities in the treatment of PCa persist.[2]

Several population-based studies reported that racial and ethnic health disparities in ADT use among PCa patients persist.[27–30,86,175] Additionally, the rate of PCa under-diagnosis (mainly due to lower PSA/DRE screening rate) has been the highest for AI/AN and AA men followed by Hispanics and NHW men which raises concerns about under-detection in these minority populations.[2,17–22]

Minority populations in NM are more likely to present with advanced PCa disease stage, poorer prognosis and lower survival compared with NHW men.[39–42] They are also less likely to receive treatment with radical prostatectomy and more likely to receive treatment with ADT compared with NHW men.[39–42]

The literature has reported several reasons for PCa health disparities among minority populations. This included poorer quality of care, worse disease prognosis, lack of insurance, high cost of care, low socioeconomic status, differential access to PCa testing and services, limited knowledge of cancer care, perceived discrimination by the healthcare provider, patient choice for less aggressive therapy, negative attitudes and beliefs toward cancer treatment and language differences. These heath disparities were associated with higher morbidity and mortality rates in minority populations. [2,15,17–25,28,31,39–42,86]

Despite advances in pharmacological options for patients with advanced and metastatic PCa, treatment with ADT has been the most widely used

therapeutic modality when there is evidence of rising PSA, or when hormonal therapy is indicated.[4,5] Nearly 50% of survived PCa patients received treatment with ADT at one point in their lives [6], which can be accomplished with either pharmacological (i.e. medical/chemical castration) or surgical castration (i.e. bilateral orchiectomy).[4]

Despite substantial beneficial evidence of ADT in reducing the progression of PCa and relieving potential obstructive symptoms, ADT are associated with likely toxic metabolic and CVS adverse events that could occur within 6 months following ADT initiation. This includes metabolic syndrome, type II diabetes, hypertension, dyslipidemia and abdominal obesity.[55–57,181–184] In a large multi-ethnic cohort study that included 6,751 individuals, the prevalence of metabolic syndrome was highest among Hispanics (29.6%) followed by NHW men (26.7%), AA (23.6%) and Chinese (20.1%).[89]

Due to increased recognition of MSRF and CVS complications associated with ADT, the U.S. FDA released a drug safety communication regarding possible increased risks of certain CVDs (AMI, stroke and sudden cardiac death) and type II diabetes among patients treated with one class of ADT medications, the GnRH agonists.[69] This has been also supported by the science advisory guideline and recommendations published by various national medical organizations including the AUA, AHA, NCCN, ACS and American Society for Radiation Oncology that aimed to guide physicians caring for PCa patients treated with ADT and promote interventions that can potentially mitigate some of the metabolic and CVS complications.[54,70]

Few studies have reported population-based adherence to metabolic syndrome, CVS screening, and treatment consensus recommendations among PCa patients treated with ADT.[7,82,83] Studies identified mainly assessed screening and treatment for different outcomes measures including risks of AMI, stroke, pulmonary embolism and statin medications utilization among PCa patients treated with ADT.[7,82,83] They also did not report racial and ethnic differences in the receipt of MSRF assessment and treatment. Therefore, we believe that our study provided valuable information and added a unique contribution to the current knowledge of PCa health disparities, metabolic syndrome, and treatment with ADT. The next chapter discussed the methods employed to answer our research questions.

CHAPTER 3: METHODS

This chapter summarized the research methods used in the study. First, it described the study design and the conceptual framework that were utilized to guide the research. Next, study site/data source, inclusion/exclusion criteria, study variables, statistical tests/analyses and sample size calculation used in the study were presented. Lastly, we discussed the human subjects' approval to conduct this study.

Study Design

This study is a retrospective observational cohort study of PCa patients treated with ADT at the University of New Mexico Comprehensive Cancer Center (UNMCCC). The study's primary aim was to assess racial and ethnic disparities in the receipt of MSRF screening and treatment among PCa patients treated with ADT. The secondary aim of the study was to identify patient and healthcare provider factors influencing the receipt of MSRF screening among racial/ethnic groups of PCa patients treated with ADT. The study time period was January 1, 2010 – December 31, 2021. This time period was chosen to assess temporal changes of MSRF screening and treatment rates after ADT metabolic syndrome and CVS risks assessment consensus scientific guideline recommendations published in 2010.[54] This might provide evidence about the rate of physicians' awareness, adoption and adherence to the evidence-based recommendations between 2010 and 2021. Electronic medical record (EMR) systems were used to identify our study sample.

Table 5. List of Androgen Deprivation Therapy (ADT) products approved as formulary items at the University of New Mexico Comprehensive Cancer Center (2010-2021)

Class	Drug	Strength & Route of Administration
GnRH agonists [a]	Triptorelin (Trelstar Mixject®)	3.75 mg IM [b]
		11.25 mg IM
		22.5 mg IM
	Leuprolide (Lupron Depot®)	7.5 mg IM
		22.5 mg IM
		30 mg IM
		45 mg IM
	Leuprolide (Eligard®)	7.5 mg IM
		22.5 mg IM
		30 mg IM
		45 mg IM
	Goserelin (Zoladex®)	10.8 mg SC [c]
GnRH antagonists	Degarelix (Firmagon®)	240 mg SC

Footnote:

a. Gonadotropin-releasing hormone
b. Intra-muscular
c. Subcutaneous

The study index date was the first dose of ADT during the study period. The study was restricted to ADT products approved as formulary items at the UNMCCC during the study period. Table (5) summarizes the ADT (including class, medication, strength, and route of administration) included in the study.

Following index date determination, patients who met the study inclusion criteria were followed to determine MSRF screening and treatment. Patients' follow-up period ended 12 months after the index date. A baseline period of 3 months was used to assess MSRF (i.e., confirmed diagnoses of diabetes type II, obesity, hypertension, and dyslipidemia) prior to treatment with ADT. This also allowed us to identify patients with metabolic syndrome before ADT initiation.

Table 6. Metabolic Syndrome Risk Factor (MSRF) Screening Criteria [7,50,54]

Criteria (1): Referral for MSRF evaluation within 6 months post-index date documented in clinic visit notes. This included a referral to evaluate **all** the following MSRF: blood pressure, triglycerides, high-density lipoprotein cholesterol, blood glucose, or HbA1C. The 6 month post-index date was determined to allow adequate time to capture metabolic syndrome risk assessment prompted by the decision to start ADT.
Criteria (2): If there was **no referral** for MSRF evaluation documented in the patient chart within 6 months post-index date, the patient was considered screened if there was **at least 1 recorded measure or lab order for all the following** risk factors of metabolic syndrome in addition to blood pressure screening within 6 months post-index date: high-density lipoprotein cholesterol, triglyceride, blood glucose or HbA1C.
Determination of MSRF Screening: Patients who met **either of the screening criteria described above were considered** screened for MSRF.

Footnote: Guided by the NCEP ATP III definition of metabolic syndrome, cardiometabolic risk assessment consensus scientific recommendations (2010) and Sun et al. (2021) methods of CVS risk assessment among PCa treated with ADT, we determined to adopt the above-described screening criteria of MSRF assessment for the current study.[7,54]

We adopted both the 2010 CVS and MSRF consensus scientific assessment and treatment guideline recommendations and the Sun et al. (2021) screening criteria to serve as the study MSRF screening and treatment criteria.[7,54] Tables (6) and (7) summarize these criteria.

Study Site

The UNMCCC is one of only 51 comprehensive cancer centers across the U.S. and among the top 3% of the US elite cancer centers.[197] It has comprehensive cancer center designation by the National Cancer Institute (NCI) which provides the highest federal designation and ratings for cancer centers across the nation.[197] Nearly 60% of all adults and almost all children with cancer in NM receive treatment at the UNMCCC.[198] The center provides services for 10,000 visits per year and 13,900 prescription medications are filled annually at UNMCCC pharmacy.[198]

Table 7. Metabolic Syndrome Risk Factor (MSRF) Treatment Criteria [51,54,177,199]

Criteria (1): Patients **were started or continued therapy** with aspirin or other anti-platelet therapy (unless contraindicated) within 6 months post-index date if they had any of the following co-morbid disease conditions documented in the patient chart: acute myocardial infarction (ICD-10-CM: I21.xx **or** I22.x **or** ICD-9-CM:410.xx), coronary heart disease (ICD-10-CM: I24.xx **or** I25.xxx **or** ICD-9-CM: 414.xx), cardiac arrest (ICD-10-CM: I46.x **or** ICD-9-CM:427.5), heart failure (ICD-10-CM: I50.xxx **or** ICD-9-CM:428.xx), arrhythmias (ICD-10-CM: I49.xx **or** I48.xxx **or** I47.xxx **or** ICD-9-CM: 427.xx), stroke (ICD-10-CM: I63.xxx **or** ICD-9-CM: 434.xx **or** 433.xx) and peripheral vascular disease (ICD-10-CM: I73.xxx **or** ICD-9-CM: 443.9).[200,201] **Note:** Contraindications of anti-platelet therapy included: History of intracranial hemorrhage, significant thrombocytopenia, major surgery within 72 hours, hypersensitivity to the medication, acute clinically significant bleed, end-stage renal failure on hemodialysis, decompensated liver cirrhosis, severe hypertension with blood pressure over 200/110 mmHg[202]. Patients with a contraindication to anti-platelet therapy were exempted from this criterion.
Criteria (2): Patients **were started or continued therapy** with a blood glucose lowering agent within 6 months post-index date if they had a confirmed diagnosis of diabetes mellitus II (ICD-10-CM: E11 **or** ICD-9-CM: 250.00)[200,201] and eligible for pharmacological therapy. This included treatment with at least one or more of the following classes of medications: biguanides, alpha-glucosidase inhibitors, DPP-4 **a** inhibitor, GLP-1 **b** receptor agonists, meglitinides, SGLT-2 **c** inhibitors, sulfonylureas, thiazolidinediones, and insulin.
Criteria (3): Patients **were started or continued therapy** with a statin or other lipid-lowering agents within 6 months post-index if they had a confirmed diagnosis of dyslipidemia (ICD-10-CM: E78.xx **or** ICD-9-CM:272.x)[200,201] or other co-morbid conditions described in criteria (1) and eligible for pharmacological therapy. Treatment options included statins, fibrates (gemfibrozil, clofibrate, and fenofibrate), niacin/nicotinic acid, and bile acid binding resins (colestipol and cholestyramine).
Criteria (4): Patients **were started or continued therapy** with a blood pressure lowering agent within 6 months post-index date if they had confirmed diagnosis of hypertension (ICD-10-CM: I10 **or** I15.x **or** ICD-9-CM: 401.x)[200,201] and eligible for pharmacological therapy. This included treatment with at least one or more of the following classes of medications: diuretics, beta-blockers, ACE inhibitors **d**, ARBs **e**, CCBs **f**, alpha-blockers, alpha-2 receptor agonists, combined alpha and beta-blockers, central agonists, peripheral adrenergic inhibitors, and vasodilators.
Determination of Metabolic Syndrome Risk Factor Treatment: **(1)** Patients who met any of the above-described criteria were considered treated for MSRF. **(2)** Partially treated patients were considered NOT treated for MSRF (i.e., a PCa patient on ADT with a confirmed diagnosis of diabetes and dyslipidemia that was receiving diabetes treatment only). **(3)** Patients with **no** confirmed diagnosis of diabetes, CVDs, hypertension, or dyslipidemia were NOT evaluated for MSRF treatment.

Footnote:

a. dipeptidyl peptidase-4
b. glucagon-like peptide-1
c. Sodium-glucose transporter.
d. Angiotensin-converting enzyme
e. Angiotensin II receptor blocker
f. Calcium channel blocker

The center researches to find causes and cures for cancers affecting New Mexican residents. This includes developing new cancer drugs, genome sequencing, cancer prevention and cell signaling.[197] It collaborates with nearby resources and consortium partners including Sandia National Laboratories, Los Alamos National Laboratory, and NM State University scientists to provide important insights to unlock some of cancer's most challenging questions.[197] Guided by the New Mexico Tumor Registry (NMTR), the UNMCCC conducts cancer control and population science research, a joint program incorporating expertise in epidemiology, behavioral science, health economics, population genetics, biostatistics and environmental health across the cancer continuum.[197] It focuses on cancers with high incidence, mortality, or disparities in the multi-ethnic and underserved populations of NM.[203]

As NM is one of five "majority-minority" states in the U.S. and has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI)[38]; UNMCCC admits patients of various racial/ethnic groups which provides crucial insight about healthcare and socioeconomic challenges minority populations of NM face.[197] Nearly 52% of patients who receive treatment at the UNMCCC are from minority populations. About 35% of UNMCCC patients participate in clinical research, and 12% enroll in therapeutic trials testing new cancer treatments.[197,198]

Data Source

Our study utilized both the Mosaiq® Oncology and Cerner® millennium EMR systems. Mosaiq® Oncology is a comprehensive oncology information

system that serves as the primary EMR for cancer patients at UNMCCC. It helps healthcare professionals manage all aspects of chemotherapy from diagnosis through treatment and follow-up.[204] Mosaiq® Oncology incorporates all patient data, clinical regimens and pharmacy information to deliver comprehensive patient care. The system also allows users to access laboratory data and cancer registries.[204] Cerner® millennium is an EMR system used by UNMH health providers. The system includes information about patient demographics, medical history, clinic visits, medications, laboratory and vital signs, and several other clinical and administrative information.[205]

Study Inclusion/Exclusion Criteria

Patients were included in the study if they met **all** the following criteria:

1. Received treatment with ADT at the UNMCCC between January 1, 2010, and December 31, 2021.
2. Male patients.
3. ≥18 years old.
4. Had a diagnosis of PCa confirmed by ICD-10-CM/ICD-9-CM diagnosis codes:
    - C61: malignant neoplasm of prostate **or**,
    - D07.5: carcinoma in situ of prostate **or**,
    - 185: malignant neoplasm of prostate **or**
    - 233.4: carcinoma in situ of the prostate.
5. Received their 1st dose of any of the ADT listed in (table 5) during the study period (January 1, 2010 - December 31, 2021).

6. Received treatment with ADT for a minimum duration of 6 months.
7. Had an established care within the UNM health system during the study period.

Patients' exclusion criteria included meeting **any** of the following criteria:

1. Incomplete or missing data on race/ethnicity.
2. Evidence of unilateral or bilateral orchiectomy (i.e., surgical castration).
3. Received treatment with ADT for breast cancer management.

Application of The Conceptual Model in The Current Study

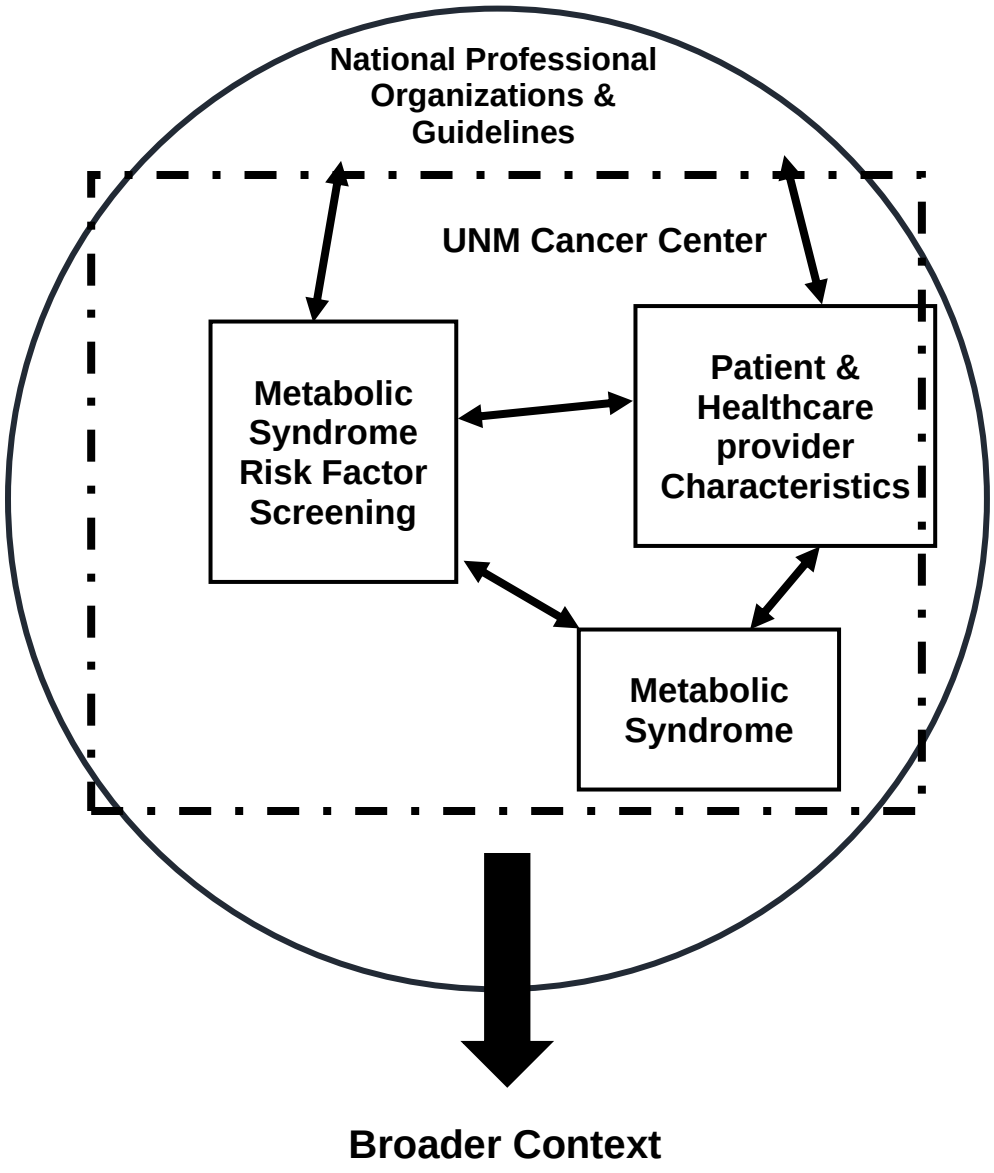
To answer our Specific Aim 4: "To identify patient and healthcare provider factors influencing the receipt of MSRF screening among racial/ethnic groups of PCa patients treated with ADT", the conceptual framework of "Integration of targeted health interventions into health systems" discussed in chapter (2) was adopted in this study.

Figure (7) illustrates the application of the conceptual model in the current study. We also summarized the application as follows:

1. *Problem*: metabolic syndrome.
2. *Intervention*: screening for MSRF within 6 months post-index date.
3. *The adoption system* included patient and healthcare provider characteristics that might influence the adoption of MSRF screening due to different perceptions of the benefits and risks of intervention and therefore occupied different roles and positions in the adoption system.

Chapter 2 explored the literature to identify which patient and healthcare provider variables might influence MSRF screening among PCa patients treated with ADT.

Figure 7. **Application of The Conceptual Framework**



Healthcare provider level characteristics: gender of the physician, specialty, and years of experience.

Patient level characteristics: health insurance coverage status, age, race/ethnicity, marital status, MSRF at baseline, number of co-morbidities, stage of PCa, and Gleason score.

*Adapted from [Atun R, de Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: a conceptual framework for analysis. Health Policy Plan. 2010;25(2):104-111. doi:10.1093/heapol/czp055].

Using our literature review results, this study evaluated whether healthcare provider gender, specialty and years of experience had an influence on the receipt of MSRF screening among PCa patients treated with ADT. In addition, we also evaluated whether patient health insurance coverage status, age, race/ethnicity, marital status, number of co-morbidities, having MSRF at baseline, stage of PCa, and Gleason score influenced the receipt of MSRF screening among PCa patients treated with ADT.

Study Participants' Characteristics Analyses

The baseline characteristics of the study population were presented in simple frequencies, means and percentages. Cochran-Mantel-Haenszel (CMH) chi-squared test was used to analyze differences in baseline characteristics across racial and ethnic groups of PCa patients treated with ADT. Proportions of patients with documented metabolic syndrome and CVS risk factors during 12 months of follow up post-index date were calculated. CMH chi-squared test was used to analyze racial and ethnic differences in the proportion of metabolic syndrome and CVS risk factors during 12 months of follow up among PCa patients treated with ADT. Proportions of patients who received guideline-concordant MSRF screening and treatment criteria were calculated. Healthcare providers characteristics that initiated guideline-concordant MSRF screening were presented in simple frequencies, mean and percentages.

Study Variables and Analyses by Specific Aim

The study's independent variables, dependent variables and analysis were presented by specific aim.

Specific Aim 1: To determine racial and ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT.

The Independent variable is race/ethnicity. Per the census bureau [206], the following patients' race/ethnicity demographic information were obtained from Mosaiq® Oncology and Cerner® millennium EMR databases:

- NHW/Non-Latino white,
- Hispanic or Latino,
- Black or AA,
- AI/AN/Native Hawaiian/Pacific Islander.
- Asian.

The dependent variable is the receipt of MSRF screening (Binary: Yes/No). Please refer to Table 6 for MSRF screening determination criteria summary.

Analyses: The proportion of patients who received MSRF screening was calculated and stratified by race and ethnicity. Chi-squared test was conducted to analyze the difference in proportions between racial and ethnic groups.

Specific Aim 2: To determine racial and ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT and with an indication of MSRF treatment.

The independent variable is race/ethnicity. Similarly, patients were categorized as NHW, Hispanic/Latino, AA, AI/AN/HN and Asian.

The dependent variable is the receipt of MSRF treatment (Binary: Yes/No). Please refer to Table 7 for more information on MSRF treatment determination criteria.

Analyses: The proportion of patients who received MSRF treatment was calculated and stratified by race and ethnicity. Chi-squared test was conducted to analyze the difference in proportions between racial and ethnic groups.

Specific Aim 3: To determine longitudinal changes in MSRF screening and treatment rates overtime (2010-2021) across different racial and ethnic groups of PCa patients treated with ADT.

The independent variable is race/ethnicity. Similarly, patients were categorized as NHW, Hispanic/Latino, AA, AI/AN/HN and Asian.

The dependent variables are the receipt of MSRF screening (Binary: Yes/No) and MSRF treatment (Binary: Yes/No).

Analyses: Two sets of analyses were conducted. One evaluated rate of MSRF screening (2010-2021), and one assessed MSRF treatment rates (2010-2021). Both were evaluated using the results obtained from specific aim 1. The sum of the proportion of patients screened and treated for MSRF was calculated for every year from 2010-2021. This provided us with rates of MSRF screening and treatment overtime.

Specific aim 4: To identify patient and healthcare provider factors influencing the receipt of MSRF screening among racial and ethnic groups of PCa patients treated with ADT.

The independent variables are patient race/ethnicity, age at the index date, marital status, stage of PCa at the index date, Gleason score at the index date, number of co-morbidities at the index date, health insurance coverage status at the index date, baseline diabetes mellitus II, baseline hypertension, baseline

dyslipidemia, baseline obesity, baseline metabolic syndrome, healthcare provider gender, specialty, and years of experience.

Patient race/ethnicity was categorized as NHW, Hispanic, AA, AI/AN/HN and Asian. Patient age was categorized as 18-44 years, 45-64 years, 65-79 years and ≥80 years based on available epidemiological evidence.[207] Per the U.S. bureau census, patient marital status was categorized as “Never Married/Single”, “Married/Partnered”,” Separated/Divorced” and “Widowed”.[208] Patient insurance coverage status was categorized as “Uninsured”, “Public Only”, “Public and Private” and “Private Only”. PCa disease stage was categorized based on the AJCC TNM staging system (I, II, III and IV).[112,137] Patient Gleason pattern scores were categorized as scores <7 (well-differentiated tumor), 7 (moderately differentiated tumor) and >7 (poorly differentiated tumor).[112,113] All MSRF at baseline (i.e. diabetes mellitus II, obesity, dyslipidemia and hypertension) were categorized as (binary: Yes/No).

Healthcare provider gender was categorized as (binary: male/female), whereas years of experience was categorized as “<10 years”, “10-20 years” and “>20 years” post-board certification/eligibility based on available literature.[73,209] Healthcare specialty were categorized as “Oncology,” “Family medicine,” “Internal medicine,” “Urology” and “Others” which included cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician. Healthcare provider variables were obtained from Mosaiq® Oncology, UNMCCC staff directory, LinkedIn and biography.
The dependent variable is the receipt of MSRF screening (Binary: Yes/No).

Analyses: Multiple logistic regression analyses were performed to determine significant factors influencing the receipt of MSRF screening. Bivariate logistic regression analyses were initially performed by taking each predictor at a time to determine its influence on receiving MSRF screening. Variables determined significant at $p<0.2$ in the bivariate analyses were incorporated in the final multiple regression model to predict the receipt of MSRF factor screening. We determined to test several interaction terms for possible inclusion in the model based on available evidence in the literature. This included interactions between "healthcare provider gender, years of experience, and specialty",[73] "baseline diabetes II, obesity, dyslipidemia, and metabolic syndrome",[58–60] "TNM stage and Gleason score",[210] and "patient race/ethnicity and insurance coverage status" [211(pp2010-2019)]. Stepwise regression deletion procedure was utilized to select variables and interaction terms to use in our model based on an iterative process of adding or removing variables. A p-value ≤ 0.05 was considered in determining statistical significance in the adjusted multiple logistic regression analyses. We determined to select the most parsimonious model with lowest Akaike information criterion (AIC) value.[212] Lastly, model fit statistics were performed to examine overall model fit. This included evaluating the Hosmer and Lemeshow model fit statistic, the receiver operating curve (ROC) and our response variable (MSRF) calibration curve. Hosmer and Lemeshow goodness of fit was used to evaluate whether or not the observed MSRF screening rates match expected rates in subgroups of our model population. A non-significant p-value indicates a non-poor model fit or good model fit.[213] The ROC was used to determine the best

cutoff value for predicting MSRF screening based on each patient and healthcare provider characteristics. The predicted probabilities from the model can take on all possible values between 0 and 1. The best-case ROC would look like a 90 degree angle or has a c-statistic value of 1.[214] Finally, the calibration curve evaluates whether there is an agreement between predicted and empirical probabilities in different percentiles of the predicted values. If the calibration curve is close to the diagonal reference line, the model can strongly predict the response variable. All analyses were conducted in SAS version 9.4 for Windows (SAS Institute, Cary, North Carolina).[215]

Sample Size Determination

An a-priori power analysis was conducted to determine the minimum required sample size to achieve Specific Aim # 4 of the study: “To identify patient and healthcare provider factors influencing the receipt of MSRF screening among racial and ethnic groups of PCa patients treated with ADT”. The main independent variable considered for the analysis was race/ethnicity and the dependent variable was the receipt of MSRF screening.

Limited evidence is available in the literature about racial and ethnic disparities in the receipt of metabolic syndrome screening. Therefore, we determined to explore the literature to identify studies that evaluated racial and ethnic differences in receiving MSRF screening. This included studies that evaluated racial and ethnic differences in diabetes, dyslipidemia, and hypertension screening.

Wilson et al. (2010) evaluated racial and ethnic differences in the access and quality of care for hyperlipidemia using the 2005 National Ambulatory Medical Care Survey (NAMCS). Half of patients were ≥65 years and male. Physician-ordered cholesterol screening was lower in Hispanics (30.3%) and AA (35.4%) compared to NHW (46.5%), (X^2, p<0.05).[216] Brown et al. (2001) also evaluated racial and ethnic disparities in cholesterol screening using the Behavioral Risk Factor Surveillance System (BRFSS). Hispanics (~60%, p<0.05), AA (69.9%) and Asians (62.7%, p<0.05) had lower cholesterol screening rate compared to NHW (73.1%).[217]

Shi et al. (2014) assessed diabetic retinopathy screening across racial and ethnic groups of diabetic patients using the Medical Expenditure Panel Survey (MEPS). Racial and ethnic groups were classified as NHW and minority populations. Minority populations had lower diabetic retinopathy screening rate compared with NHW. The largest significant racial gap of 15% was observed in 2008, followed by 11%, 10%, and 7% in 2006, 2009, and 2005, respectively, p<0.05.[218] Schneider et al. (2002) reported that minority populations had 6.8% (95% CI: 1.2-12.4, p<0.05) lower diabetic retinopathy screening rate compared to NHW.[219] Tung et al. (2016) evaluated racial and ethnic differences in diabetes screening between Asian Americans and other adults using BRFSS.[220(pp2012–2014)] Asian Americans had 34% lower adjusted odds of receiving recommended American Diabetes Association (ADA) diabetes screening compared with NHW (95% CI: 0.60-0.73, p<0.05).[220(pp2012–2014)]

Sun et al. (2021) evaluated CVS risk factors assessment and management among U.S. veterans with PCa with or without ADT. White race was associated with a 5.7% (95% CI: 5.0-6.4) lower probability of CVS risk factors screening compared with non-White race among the whole study sample.[7] Rates of CVS risk factors screening among patients on ADT and with preexisting atherosclerotic CVDs approached (75.3%, 95% CI: 73.6-76.9).[7] Conversely, CVS risk factors screening rates were lower among patients on ADT without preexisting atherosclerotic CVDs (67.1%, 95% CI: 65.9-68.2).[7] Patients on ADT were significantly more likely to have preexisting CVDs and advanced disease stage.[7] Marcondes et al. (2021) evaluated racial and ethnic differences in receiving guideline-directed preventive care among patients with diabetes mellitus. This included screening for cholesterol, BP, and other diabetic complications. Hispanics were less likely to have their BP checked compared to NHW (adjusted OR: 0.42; 95 % CI 0.28-0.65, p<0.001).[221] Table (8) summarized reported racial/ethnic differences in MSRF screening.

Based on the reported differences in screening rates between various racial and ethnic groups described in Table 8, we determined to use a difference of 10% (SD=5). This estimate assumes that minority populations may have a 10% (SD=5) lower probability of being screened for MSRF than NHW men due to varying clinical and socioeconomic factors. We also determined to use CVS risk factors event rates of 75% (95% CI: 70-80%) based on rates reported by Sun et al. (2021) to compute the minimum required sample size of the current study.[7]

Table 8. Summary of reported differences in screening rates among racial and ethnic groups

Study	Outcome	Racial/ethnic groups	Reported mean differences in screening rates
Wilson et al. (2010)[216]	Cholesterol	Hispanics, AA [a] NHW [b]	(-16.2% for Hispanic vs. NHW) * (-11.1% for AA vs. NHW) *
Brown et al. (2001)[217]	Cholesterol	Hispanics, AA, Asians, AI/AN [c], NHW	(-7.9% for AI/AN vs. NHW) (-10.4% for Asian vs. NHW) * (-13% for Hispanics vs. NHW) * (-3.2% for AA vs. NHW)
Shi et al. (2014) 222(pp2002-2009)	Diabetic retinopathy	NHW, minority populations	(-11% for minority populations vs. NHW) *
Schneider et al. (2012)[219]	Diabetic retinopathy	AA, NHW	(-6.8% for AA vs. NHW) *
Tung et al. (2016) 220(pp2012-2014)	Diabetes	Hispanics, AA, Asians, AI/AN, NHW	(-12.1% for Asians vs. NHW) * (-3.6% for AI/AN vs. NHW) * (-1.1% for Hispanics vs. NHW) * (+1% for AA vs. NHW) *
Sun et al. (2021)[7]	CVRFs [d]	White, AA, Other	(+5.7% for minority populations vs. White). **
Marcondes (2021)[221]	Blood pressure & Cholesterol	NHW, Hispanic, AA	(BP: -7.3% for Hispanics vs. NHW) * (Cholesterol: -7.2 % for Hispanics vs. NHW) * (BP: -1.3% for AA vs. NHW) * (Cholesterol: -1% for BP vs. NHW) *

Footnote:

a. African American.
b. Non-Hispanic White.
c. American Indian/Alaskan Native.
d. Cardiovascular risk factors.
e. * $p<0.05$

Using an alpha value = 0.05 (the power of rejecting the null hypothesis), a two-tailed test and a power level of 80%, **the current study required a minimum sample size of 654 patients**. Table (9) summarized the estimated sample size based on different values of “CVS risk factors event rates” and

Table 9. Sample Size Determination

		Differential Screening Rate (Minority populations vs. NHW*)		
	NHW Rate	**Small (-5%)**	**Medium (-10%)**	**Large (-15%)**
Metabolic Syndrome Risk Factor Screening Rate	70% *(low)*	OR = 1.26 Alpha = 0.05 Power = 0.80 **Sample Size = 2690**	OR = 1.56 Alpha = 0.05 Power = 0.80 **Sample Size = 707**	OR = 1.90 Alpha = 0.05 Power = 0.80 **Sample Size = 333**
	75% *(Medium)*	OR = 1.29 Alpha = 0.05 Power = 0.80 **Sample Size = 2443**	OR = 1.62 Alpha = 0.05 Power = 0.80 **Sample Size = 654**	OR = 2.00 Alpha = 0.05 Power = 0.80 **Sample Size = 308**
	80% *(High)*	OR = 1.33 Alpha = 0.05 Power = 0.80 **Sample Size = 2229**	OR = 1.71 Alpha = 0.05 Power = 0.80 **Sample Size = 596**	OR = 2.15 Alpha = 0.05 Power = 0.80 **Sample Size = 281**

*NHW: Non-Hispanic White, Small effect size was -5% difference in screening rate of minority populations compared to NHW (medium effect = -10%; large effect = -15%).

"differences in screening rates among racial and ethnic groups" using G*Power version 3.1.9.4 software.[223] Please refer to Appendix (C) for more information.

Human Subjects' Approval

The study was approved by the University of New Mexico Health Sciences Center (UNMHSC) Office of Human Research Protections Program (HRPR), study ID: 21:282. The research protocol was approved under category (5): Data, documents, records, or specimens. The IRB approval included a waiver of informed consent and The Health Insurance Portability and Accountability Act (HIPAA) authorization addendum. Please refer to Appendix (D) for the HRPR approval letter.

CHAPTER 4: RESULTS

This chapter provides the results of the study. The chapter begins with an overall description of the study sample including a presentation of baseline characteristics stratified by race and ethnicity. This is followed by presenting the proportion of metabolic syndrome & CVS risk factors during 12 months of follow-up post-index date among PCa patients treated with ADT. MSRF screening rates among PCa patients treated with ADT are then presented. This also includes discussing the characteristics of healthcare providers that initiated guideline-concordant MSRF screening among PCa patients treated with ADT. Results of MSRF treatment among PCa patients treated with ADT are then discussed. This is followed by a detailed description of the study results by each specific aim.

Study Sample

The UNMCCC Mosaiq® Oncology data analysis team identified a total of 1001 unique medical record numbers (MRNs). There were 143 patients excluded because they were not treated within the UNM health system during the study period. There were also 32 patients excluded because they received treatment with ADT for less than 6 months. A total of 17 patients were excluded because of missing race or ethnicity data. There were also 6 patients excluded because of missing PCa diagnosis or receiving treatment with ADT for breast cancer. This resulted in a total of 803 patients that met the study inclusion criteria. Table 10 presents a summary of the study's sample characteristics.

Table 10. Sample Characteristics

Variable	N=803
Race/Ethnicity	**n (%)**
Non-Hispanic White	455 (56.7)
Hispanic	242 (30.1)
African American	49 (6.1)
American Indian/Alaskan & Hawaiian Native	41 (5.1)
Asian	16 (2.0)
Age (Mean, SD[a])	69.7 (8.8)
18-44	1 (0.1)
45-64	238 (29.6)
65-79	455 (56.7)
≥80	109 (13.6)
ADT [b]/year	
2010	80 (10.0)
2011	42 (5.2)
2012	35 (4.4)
2013	51 (6.4)
2014	45 (5.6)
2015	73 (9.1)
2016	78 (9.7)
2017	72 (9.0)
2018	72 (9.0)
2019	101 (12.6)
2020	77 (9.6)
2021	77 (9.6)
Initial ADT received (at index date)	
GnRH [c] agonists	
Triptorelin pamoate (Trelstar®)	377 (46.9)
Leuprolide acetate (Lupron Depot®)	227 (28.3)
Goserelin (Zoladex®)	53 (6.6)
Leuprolide acetate (Eligard®)	32 (4.0)
GnRH antagonists	
Degarelix (Firmagon®)	114 (14.2)
ADT switch during 12 months of follow-up	
No treatment switch	599 (74.6)
Switch from GnRH antagonist to GnRH agonist	104 (13.0)
Switch from one GnRH agonist to another GnRH agonist	94 (11.7)
Switch from GnRH agonist to GnRH antagonist	6 (0.7)

Table 10.

Insurance status at index date [d]	
Private/commercial	377 (47.0)
Public/governmental	291 (36.2)
Public + Private	113 (14.1)
Uninsured/self-pay	22 (2.7)
Marital status at index date	
Married/partnered	528 (65.8)
Never Married/Single	139 (17.3)
Divorced/Separated	75 (9.3)
Widowed	61 (7.6)
TNM [e] Staging at index date	
I	26 (3.2)
II	270 (33.6)
III	133 (16.6)
IV	374 (46.6)
Gleason score at index date	
<7 (well-differentiated tumor)	49 (6.1)
7 (moderately-differentiated tumor)	290 (36.1)
>7 (poorly-differentiated tumor)	464 (57.8)
Number of co-morbid disease conditions at index date	
<5	472 (58.8)
5 to 10	323 (40.2)
>10	8 (1.0)
Confirmed diagnosis of diabetes mellitus II at baseline	190 (23.6)
Confirmed diagnosis of hypertension at baseline	524 (65.3)
Confirmed diagnosis of dyslipidemia at baseline	349 (43.5)
Confirmed criteria of obesity (BMI [f] ≥30) at baseline	276 (34.4)
Confirmed criteria of metabolic syndrome [g]	245 (30.5)

Footnote:

a. Standard Deviation.
b. Androgen Deprivation Therapy.
c. GnRH, Gonadotropin-Releasing Hormone.
d. Date of first dose of ADT administered during the study period.
e. Tumor, nodes, and metastases.
f. Body Mass Index.
g. Patients met the criteria set by the National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP) III definition for metabolic syndrome diagnosis.

Study Sample Baseline Characteristics by Race and Ethnicity

The study sample (N=803) included a total of 455 (57%) NHW patients, 242 (30%) Hispanics, 49 (6%) AA, 41 (5%) AI/AN/HN and 16 (2%) Asian. The mean age (69.7, SD=8.8) was not significantly different across all races and ethnicities, p=0.12. However, the proportion of AA men that were 45-64 years was higher (46.9%) compared to AI/AN/HN (34.1%), Hispanics (33.5%), NHW (25.5%) and Asian (25%).

There was a significant difference in the type of ADT received during the study period across all racial and ethnic groups, p=0.04. The proportion of AA men who received treatment with GnRH antagonist was lower (6.1%) compared to AI/AN/HN (19.5%), Hispanics (14.8%), NHW (14.5%), and Asian (6.2%). Conversely, more AI/AN/HN (19.5%) men switched treatment from GnRH antagonist to agonist during 12 months of follow up compared to NHW (13.4%), Hispanics (12.8%), Asian (6.2%) and AA (6.1%).

There was a significant difference in the type of insurance coverage across all racial and ethnic groups, p=0.01. The proportion of uninsured/self-pay patients was higher among Hispanics (6.2%) compared to AA (4.1%), AI/AN/HN (2.4%), NHW (0.9%) and Asian (0%). The percentage of unmarried men or men without a partner was significantly higher among AA (59.2%) compared to AI/AN/HN (46.3%), Hispanics (34.8%), Asian (31.3%) and NHW (30.3%), p<0.001. AI/AN/HN men with metastatic disease stage were higher (63.4%) compared to Asian (50%), AA (49%), Hispanics (45.9%) and NHW (45.1%), p=0.55. Both Asian (75%) and AI/AN/HN (73.2%) had worse PCa disease prognosis (Gleason score >7) compared to AA (59.2%), Hispanics (56.6%) and

NHW (56.2%), p=0.38. There was no significant difference in the number of co-morbidities at baseline across all racial and ethnic groups, p=0.35.

There was a significant difference in the proportion of patients with diabetes mellitus II (p<0.001), obesity (p=0.008) and metabolic syndrome (p<0.001) across all racial and ethnic groups of PCa patients treated with ADT. The proportion of AI/AN/HN with diabetes mellitus II (39%), dyslipidemia (46.3%) and metabolic syndrome (41.5%) was higher compared to other racial and ethnic groups. The percentage of Hispanic individuals with a BMI≥30 was significantly higher (43%) compared to AI/AN/HN (39%), AA (36.7%), NHW (29.5%) and Asian (25%), p=0.008. Table 11 summarizes baseline characteristics of the study sample by race and ethnicity.

Patients with Metabolic Syndrome & CVS Risk Factors during 12-month Post-index Date by Race/Ethnicity

Nearly 1 in 10 patients (9.8%, n=44) of NHW and 9.7% of AI/AN/HN had a documented diagnosis of AMI during 12 months of follow-up post-index date compared to Hispanics (8.3%), AA (4.1%) and Asian (0%), p<0.48. In addition, the proportion of NHW (14.7%) with documented cardiac arrhythmias was higher compared to AI/AN/HN (12.2%), Hispanics (8.7%), Asian (6.3%) and AA (6.1%), p<0.01. Similar to baseline data, the proportion of patients with diabetes mellitus II was significantly higher among AI/AN/AN (39%) compared to Hispanics (36.8%), AA (30.6%), NHW (16.9%) and Asian (12.5%), p<0.0001. More information about the prevalence of other metabolic syndrome and CVS risk factors during 12-month post-index date is presented in Table 12.

Table 11. Sample Characteristics by Race/Ethnicity

Variable	NHW [a]	Hispanic	AA [b]	AI/AN/HN [c]	Asian	*P* value [d]
Study Sample, n (%) [e]	455 (57%)	242 (30%)	49 (6%)	41 (5%)	16 (2%)	
Age (Mean, SD [f])	70.4 (8.4)	69 (9.2)	66 (7.8)	69.7 (11.5)	72.1 (9.9)	**0.007** [d!]
18-44, n (%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.12
45-64, n (%)	116 (25.5%)	81 (33.5%)	23 (46.9%)	14 (34.1%)	4 (25%)	
65-79, n (%)	275 (60.4%)	130 (53.7%)	23 (46.9%)	19 (46.4%)	8 (50%)	
≥80, n (%)	63 (13.8%)	31 (12.8%)	3 (6.2%)	8 (19.5%)	4 (25%)	
ADT at index date [g], n (%)						
GnRH agonists [h]						
Triptorelin pamoate (Trelstar®)	205 (45%)	121 (50%)	29 (59.2%)	15 (36.6%)	7 (43.8%)	**0.04**
Leuprolide acetate (Lupron Depot®)	136 (29.9%)	58 (24%)	14 (28.6%)	12 (29.3%)	7 (43.8%)	
Goserelin (Zoladex®)	23 (5.1%)	22 (9.1%)	1 (2.0%)	6 (14.6%)	1 (6.2%)	
Leuprolide acetate (Eligard®)	25 (5.5%)	5 (2.1%)	2 (4.1%)	0 (0%)	0 (0%)	
GnRH antagonists						
Degarelix (Firmagon®)	66 (14.5%)	36 (14.8%)	3 (6.1%)	8 (19.5%)	1 (6.2%)	
ADT switch within 12 months post-index date [i], n (%)						
No treatment switch	349 (76.7%)	174 (71.9%)	38 (77.6%)	27 (65.9%)	11 (68.8%)	0.40
Switch from GnRH antagonist to GnRH agonist (Yes)	61 (13.4%)	31 (12.8%)	3 (6.1%)	8 (19.5%)	1 (6.2%)	
Switch from one GnRH agonist to another GnRH agonist (Yes)	42 (9.2%)	35 (14.5%)	7 (14.3%)	6 (14.6%)	4 (25%)	

Table 11. Continuation						
Switch from GnRH agonist to GnRH antagonist (Yes)	3 (0.7%)	2 (0.8%)	1 (2%)	0 (0%)	0 (0%)	
Insurance status at index date, n (%)						
Private/commercial	222 (48.8%)	99 (40.9%)	28 (57.1%)	18 (43.9%)	10 (62.5%)	**0.01**
Public/governmental	162 (35.6%)	97 (40.1%)	14 (28.6%)	15 (36.6%)	3 (18.8%)	
Public + Private	67 (14.7%)	31 (12.8%)	5 (10.2%)	7 (17.1%)	3 (18.8%)	
Uninsured/self-pay	4 (0.9%)	15 (6.2%)	2 (4.1%)	1 (2.4%)	0 (0%)	
Marital status at index date, n (%)						
Married/partnered	317 (69.7%)	158 (65.2%)	20 (40.8%)	22 (53.7%)	11 (68.7%)	**<0.001**
Never Married/Single	76 (16.7%)	32 (13.2%)	19 (38.8%)	12 (29.3%)	0 (0%)	
Divorced/Separated	36 (7.9%)	28 (11.7%)	8 (16.3%)	1 (2.4%)	2 (12.5%)	
Widowed	26 (5.7%)	24 (9.9%)	2 (4.1%)	6 (14.6%)	3 (18.8%)	
TNM [j] Staging at index date, n (%)						
I	12 (2.6%)	11 (4.5%)	2 (4.1%)	1 (2.4%)	0 (0%)	0.55
II	158 (34.7%)	86 (35.5%)	13 (26.5%)	8 (19.6%)	5 (31.3%)	
III	80 (17.6%)	34 (14.1%)	10 (20.4%)	6 (14.6%)	3 (18.7%)	
IV	205 (45.1%)	111 (45.9%)	24 (49.0%)	26 (63.4%)	8 (50.0%)	
Gleason score at index date, n (%)						
<7 (well-differentiated tumor)	29 (6.4%)	17 (7.0%)	1 (2.0%)	1 (2.4%)	1 (6.2%)	0.38
7 (moderately-differentiated tumor)	170 (37.4%)	88 (36.4%)	19 (38.8%)	10 (24.4%)	3 (18.8%)	
>7 (poorly-differentiated tumor)	256 (56.2%)	137 (56.6%)	29 (59.2%)	30 (73.2%)	12 (75.0%)	

Table 11. Continuation

Number of co-morbid disease conditions at index date, n (%)						
<5	264 (58.0%)	143 (59.1%)	29 (59.2%)	25 (61.0%)	11 (68.7%)	0.35
5 to 10	189 (41.6%)	93 (38.4%)	20 (40.8%)	16 (39.0%)	5 (31.3%)	
>10	2 (0.4%)	6 (2.5%)	0 (0%)	0 (0%)	0 (0%)	
Diagnosis of diabetes mellitus II at baseline	71 (15.6%)	87 (36.0%)	14 (28.6%)	16 (39.0%)	2 (12.5%)	**<0.001**
Diagnosis of hypertension at baseline	294 (64.6%)	161 (66.5%)	35 (71.4%)	25 (61.0%)	9 (56.3%)	0.74
Diagnosis of dyslipidemia at baseline	194 (42.6%)	111 (45.9%)	21 (42.9%)	19 (46.3%)	4 (25.0%)	0.55
Criteria of obesity (BMI≥30) [k]	134 (29.5%)	104 (43.0%)	18 (36.7%)	16 (39.0%)	4 (25.0%)	**0.008**
Diagnosis of metabolic syndrome [l]	107 (23.5%)	100 (41.3%)	18 (36.7%)	17 (41.5%)	3 (18.8%)	**<0.001**

Footnote:

- **a.** Non-Hispanic White.
- **b.** African American.
- **c.** American Indian, Alaskan Native, Hawaiian Native.
- **d.** Cochran-Mantel-Haenszel (CMH) chi-square test value (whereas **d!** is the p-value calculated using ANOVA).
- **e.** Row percentage.
- **f.** Standard Deviation.
- **g.** Androgen Deprivation Therapy.
- **h.** Gonadotropin-Releasing Hormone.
- **i.** Date of first dose of ADT administrated during the study period.
- **j.** Tumor, Nodes and Metastases.
- **k.** BMI, Body Mass Index.
- **l.** Patients met the criteria set by the National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP) III definition for metabolic syndrome diagnosis.

Table 12. Patients with Metabolic Syndrome & Cardiovascular Risk Factors During 12-month Post-Index Date [a] by Race/Ethnicity

Metabolic/CVS [b] Disease Condition, n (%)	NHW [c] (n=455)	Hispanic (n=242)	AA [d] (n=49)	AI/AN/HN [e] (n=41)	Asian (n=16)	*P* value [f]
Acute myocardial infarction	44 (9.7%)	20 (8.3%)	2 (4.1%)	4 (9.8%)	0 (0%)	0.48
Coronary heart disease	118 (25.9%)	55 (22.7%)	9 (18.4%)	11 (26.8%)	1 (6.3%)	0.30
Heart failure	26 (5.7%)	15 (6.2%)	2 (4.1%)	3 (7.3%)	1 (6.3%)	0.97
Cardiac arrhythmia	67 (14.7%)	21 (8.7%)	3 (6.1%)	5 (12.2%)	1 (6.3%)	**0.01**
Stroke	18 (4.0%)	15 (6.2%)	3 (6.1%)	5 (12.2%)	0 (0%)	0.13
Peripheral vascular disease	71 (15.6%)	34 (14%)	5 (10.2%)	6 (14.6%)	1 (6.3%)	0.72
Diabetes mellitus II	77 (16.9%)	89 (36.8%)	15 (30.6%)	16 (39.0%)	2 (12.5%)	**<0.0001**
Hypertension	298 (65.5%)	163 (67.4%)	36 (73.5%)	25 (61.0%)	9 (56.3%)	0.62
Dyslipidemia	205 (45.0%)	113 (46.7%)	21 (42.6%)	19 (46.3%)	4 (25.0%)	0.56
Metabolic Syndrome	114 (25.1%)	104 (43.0%)	19 (38.8%)	17 (41.5%)	3 (18.8%)	**0.00001**

Footnote:

a. Date of the first dose of Androgen Deprivation Therapy (ADT) administered during the study period.
b. Cardiovascular.
c. Non-Hispanic White.
d. African American.
e. American Indian, Alaskan Native, Hawaiian Native.
f. Cochran-Mantel-Haenszel (CMH) chi-square test value.

Overall MSRF Screening among PCa Patients

Approximately 1 in 10 (12.3%, n=99) patients were referred to a healthcare provider to screen for MSRF within 6-months of ADT initiation. Nearly all patients (99.1%, n=796) had a documented BP reading within 6 months of ADT initiation. About 8 in 10 patients (76.2%, n=612) received HbA1C or blood glucose level assessment within 6 months of ADT initiation. Nearly 2 in 10 patients (22.9%, n=184) received a lipid profile screening (i.e., HDL-C and TG level) within 6-months of ADT initiation. This resulted in 189 patients (23.5%) receiving guideline-concordant MSRF screening among PCa patients treated with ADT. About 12% (n=99) who referred to a provider for MSRF screening and 11.2% (n=90) who had evidence of testing for all MSRFs within 6-months of ADT initiation. Additionally, (n=43, 5.3%) of patients met both MSRF screening criteria. For some patients (n=42, 5.2%), screening did not occur until months 7-12 after ADT initiation (late MSRF screening). Of those, about 67% (n=28) were of minority populations compared to 33% (n=14) NHW. Table 13 summarizes the proportion of patients who received guideline-concordant MSRF screening among PCa patients treated with ADT. Table 14 describes healthcare providers' characteristics (i.e., gender, years of experience and specialty) that initiated guideline-concordant MSRF screening among PCa patients treated with ADT.

Our study found that among patients who met the NCEP ATP III criteria of metabolic syndrome at baseline (n=245), nearly 38% (n=93) received guideline-concordant MSRF screening and 24% (n=59) were referred to a PCP to screen

Table 13. Metabolic Syndrome Risk Factor Screening Among Prostate Cancer Patients Treated with Androgen Deprivation Therapy

Metabolic Syndrome Risk Factor Screening Criteria [g]	N=803
Criteria (1): Referral initiated within 6-months post-index date	
Referral to a healthcare provider (i.e., PCP [a] or internal medicine or cardiology or endocrinology) to screen for MSRF within 6 months post-ADT [b] initiation (Yes)	99 (12.3%)
Criteria (2): Screening based on Lab Order/Test/Reading Evidence	
Blood pressure screening within 6 months post-ADT initiation (Yes)	796 (99.1%)
Blood glucose level or HbA1C [d] screening within 6 months post-ADT initiation (Yes)	612 (76.2%)
HDL-C [e] screening within 6 months post-ADT initiation (Yes)	184 (22.9%)
Triglyceride level screening within 6 months post-ADT initiation (Yes)	184 (22.9%)
Overall MSRF [c] screening – Science Advisory Guideline Concordant	
MSRF screening within 6 months of ADT initiation (Yes)	189 (23.5%)
Average time in months to receive MSRF screening	2.66 (SD=1.84) [f]
Late MSRF screening	
MSRF screening within 7-12 months of ADT initiation (Yes)	42 (5.2%) [h]
Average time in months to receive MSRF screening	9.7 (SD=1.86)

Footnote:

a. Primary Care Provider.
b. Androgen Deprivation Therapy.
c. Metabolic Syndrome Risk Factor Screening.
d. Glycated hemoglobin.
e. High-density lipoprotein-Cholesterol.
f. Standard Deviation.
g. MSRF Screening Criteria: These were the MSRF recommended screening criteria by the 2010 science advisory guideline recommendations for PCa patients treated with ADT. Patients were considered screened for MSRF if they got a referral to screen for MSRF AND/OR had at least 1 recorded measure or lab order for all the following MSRF in addition to BP screening within 6-months post-index date: Triglyceride level, HDL-C level, and blood glucose or HbA1c.
h. Late MSRF screening (n=42): about 67% (n=28) were of minority populations compared to 33% (n=14) NHW.

Table 14. Characteristics of Healthcare Providers that Initiated Guideline-concordant Metabolic Syndrome Risk Factor Screening

Characteristics of Healthcare providers (HCP)	N=189*
HCP gender	
Male	111 (58.7%)
Female	78 (41.3%)
HCP Years of Experience (Mean, SD)	24.6 (SD=14.7)
<10 years of experience, n (%)	47 (24.9%)
10-20 years of experience, n (%)	37 (19.6%)
>20 years of experience, n (%)	105 (55.5%)
HCP Specialties	
Oncology	49 (25.9%)
Family Medicine	39 (20.6%)
Internal Medicine	36 (19.0%)
Clinical Nurse Practitioner (Family Medicine)	30 (15.9%)
Urology	11 (5.8%)
Cardiology	10 (5.3%)
Physician Assistant	7 (3.7%)
Endocrinology	2 (1.1%)
Neurology	2 (1.1%)
Emergency Medicine	1 (0.5%)
Nephrology	1 (0.5%)
Pharmacist Clinician	1 (0.5%)

Footnote:
***N=189** refers to the total number of patients who received guideline-concordant metabolic syndrome risk factor (MSRF) screening by the HCP within 6 months post-index date. The Index date refers to date of the first dose of androgen deprivation therapy administered during the study period.

Continuation of discussion for page 102: for MSRF within 6 months post-index date. These findings suggest higher MSRF screening rates among this subpopulation compared to the entire study population.

Overall MSRF Treatment among PCa Patients

Among the study sample, 8 in 10 patients (81.3%, n=653) had at least one MSRF requiring treatment. Among those, 77% (n=502) of patients received guideline-concordant MSRF treatment within 6 months of ADT initiation. However, 23.1% (n=151) were partially treated for MSRF (Table 15).

Results of Specific Aim 1

Specific Aim 1 was to determine racial/ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT. Null hypothesis (H_0): There are no racial/ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT.

Nearly 27% (n=122) of NHW patients, 18% (n=43) of Hispanics, 31% (n=15) of AA, 15% (n=6) of AI/AN/HN and 19% (n=3) of Asian received MSRF screening within 6 months of ADT initiation. Results showed a significant racial/ethnic difference in the proportion of patients receiving MSRF screening among PCa patients treated with ADT, $\chi 2$ (4) = 10.563, p=0.032. Table 16 presents results of overall MSRF screening by race/ethnicity. Only comparison between NHW and Hispanic patients met the required sample size from the power analysis (n=654); therefore, while other comparisons against NHW are reported, the sample size is insufficient. We found a significant difference in MSRF screening between NHW and Hispanic patients, $\chi 2$ (1) = 7.15, p=0.008,

Table 15. Metabolic Syndrome Risk Factor Treatment Among Prostate Cancer Patients Treated with Androgen Deprivation Therapy

Overall MSRF Treatment				
Total number of patients with MSRFs [a] and treatment indication.	653	Among the whole study sample, nearly 81.3% (n=653) had MSRF and an indication for MSRF treatment (i.e., eligibility for pharmacological therapy, no treatment contraindication, or drug allergies).		
Number of patients fully treated for MSRF within 6 months post-ADT initiation.	502 (76.9%)	This reflects the percentage of patients who received guideline-concordant MSRF treatment within 6 months post-index date.		
Number of patients partially treated for MSRF within 6 months post-ADT initiation.	151 (23.1%)	Example of a partially treated patient for MSRF: a PCa patient on ADT with a confirmed diagnoses of diabetes mellitus II and dyslipidemia that is receiving treatment for diabetes mellitus II only).		
MSRF Treatment – Stratified by Each Risk Factor				
Patient population	**CVDs [b]**	**HTN [c]**	**DM II [d]**	**Dyslipidemia**
Number of patients with a MSRF and treatment indication.	335	522	186	355
Number of patients who received guideline-concordant MSRF treatment within 6 months post-ADT.	208 (62%)	510 (97.7%)	178 (95.7%)	311 (87.6%)

Footnote:

a. Metabolic Syndrome Risk Factor.

b. Cardiovascular diseases (CVDs) include a confirmed diagnosis of at least one of the following: acute myocardial infarction, coronary heart disease, heart failure, cardiac arrest, cardiac arrhythmia, stroke, and peripheral vascular disease. A prostate cancer patient with co-concomitant CVDs and on androgen deprivation therapy should be started on Aspirin and Statin therapy (unless contraindicated).

c. Hypertension.

d. Diabetes mellitus II.

and between AA and Hispanic, $\chi 2$ (1) = 4.2121, p=0.0401. There were no statistically significant differences in the proportions of patients receiving guideline-concordant MSRF screening between the other racial and ethnic groups of PCa patients treated with ADT. Tables 17-26 compare MSRF screening among various racial and ethnic groups of PCa patients treated with ADT.

Table 16. Overall Metabolic Syndrome Risk Factor Screening By Race/Ethnicity

MSRF [a] Screening	NHW [b]	Hispanic	AA [c]	AI/AN/HN [d]	Asian	Total
Yes	122 (26.8%)	43 (17.8%)	15 (30.6%)	6 (14.6%)	3 (18.8%)	**189 (23.5%)**
No	333 (73.2%)	199 (82.2%)	34 (69.4%)	35 (85.4%)	13 (81.2%)	**614 (76.5%)**
Total	**455 (100%)**	**242 (100%)**	**49 (100%)**	**41 (100%)**	**16 (100%)**	**803 (100%)**

There was **a statistically** significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [e] across all racial and ethnic groups, **$\chi 2$ (4) = 10.563, p=0.032.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Non-Hispanic White.
c. African American.
d. American Indian/Alaskan Native, Hawaiian Native.
e. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 17. Metabolic Syndrome Risk Factor Screening (Non-Hispanic White vs. Hispanic)

MSRF [a] Screening	NHW [b]	Hispanic	Total
Yes	122 (26.8%)	43 (17.8%)	165 (23.7%)
No	333 (73.2%)	199 (82.2%)	532 (76.3%)
Total	**455 (100%)**	**242 (100%)**	**697 (100%)**

There was **a statistically** significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [c] between NHW and Hispanics, **$\chi 2$ (1) = 7.15, p=0.008.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Non-Hispanic White.
c. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 18. Metabolic Syndrome Risk Factor Screening (Non-Hispanic White vs. African American)

MSRF [a] Screening	NHW [b]	AA [c]	Total
Yes	122 (26.8%)	15 (30.6%)	137 (27.2%)
No	333 (73.2%)	34 (69.4%)	367 (72.8%)
Total	**455 (100%)**	**49 (100%)**	**504 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [d] between NHW and AA, **$\chi 2$ (1) = 0.3226, p=0.5701.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Non-Hispanic White.
c. African American.
d. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 19. Metabolic Syndrome Risk Factor Screening (Non-Hispanic White vs. American Indian/Alaskan Native)

MSRF [a] Screening	NHW [b]	AI/AN/HN [c]	Total
Yes	122 (26.8%)	6 (14.6%)	128 (25.8%)
No	333 (73.2%)	35 (85.4%)	368 (74.2%)
Total	**455 (100%)**	**41 (100%)**	**496 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [d] between NHW and AI/AN/HN, **$\chi 2$ (1) = 2.914, p=0.0878.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Non-Hispanic White.
c. American Indian/Alaskan Native/Hawaiian Native
d. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 20. Metabolic Syndrome Risk Factor Screening (Non-Hispanic White vs. Asian)

MSRF [a] Screening	NHW [b]	Asian	Total
Yes	122 (26.8%)	3 (18.8%)	125 (26.5%)
No	333 (73.2%)	13 (81.2%)	346 (73.5%)
Total	**455 (100%)**	**16 (100%)**	**471 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [c] between NHW and Asian, **$\chi 2$ (1) = 0.5154, p=0.4728.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Non-Hispanic White.
c. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 21. Metabolic Syndrome Risk Factor Screening (Hispanic vs. African American)

MSRF [a] Screening	Hispanic	AA [b]	Total
Yes	43 (17.8%)	15 (30.6%)	58 (20%)
No	199 (82.2%)	34 (69.4%)	233 (80%)
Total	**242 (100%)**	**49 (100%)**	**291 (100%)**

There was **a statistically** significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [c] between Hispanic and AA, **$\chi 2$ (1) = 4.2121, p=0.0401.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** African American.
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 22. Metabolic Syndrome Risk Factor Screening (Hispanic vs. American Indian/Alaskan Native)

MSRF [a] Screening	Hispanic	AI/AN/HN [b]	Total
Yes	43 (17.8%)	6 (14.6%)	49 (17.3%)
No	199 (82.2%)	35 (85.4%)	234 (82.7%)
Total	**242 (100%)**	**41 (100%)**	**283 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [c] between Hispanic and AI/AN/HN, **$\chi 2$ (1) = 0.2406, p=0.6237.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. American Indian/Alaskan Native/Hawaiian Native
c. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 23. Metabolic Syndrome Risk Factor Screening (Hispanic vs. Asian)

MSRF [a] Screening	Hispanic	Asian	Total
Yes	43 (17.8%)	3 (18.8%)	46 (17.8%)
No	199 (82.2%)	13 (81.2%)	212 (82.2%)
Total	**242 (100%)**	**16 (100%)**	**258 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [b] between Hispanic and Asian, **$\chi 2$ (1) = 0.0099, p=0.9209.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 24. Metabolic Syndrome Risk Factor Screening (African American vs. American Indian/Alaskan Native)

MSRF [a] Screening	AA [b]	AI/AN/HN [c]	Total
Yes	15 (30.6%)	6 (14.6%)	21 (100%)
No	34 (69.4%)	35 (85.4%)	69 (100%)
Total	**49 (100%)**	**41(100%)**	**90 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [d] between AA and AI/AN/HN, **$\chi 2$ (1) = 3.1857, p=0.0742.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. African American.
c. American Indian/Alaskan Native/Hawaiian Native.
d. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 25. Metabolic Syndrome Risk Factor Screening (African American vs. Asian)

MSRF [a] Screening	AA [b]	Asian	Total
Yes	15 (30.6%)	3 (18.8%)	18 (27.7%)
No	34 (69.4%)	13 (81.2%)	47 (72.3%)
Total	**49 (100%)**	**16 (100%)**	**65 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF screening within 6-months post-index date [c] between AA and Asian, **$\chi 2$ (1) = 0.8476, p=0.3572.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. African American.
c. Date of the first dose of androgen deprivation therapy administrated during the study period.

Table 26. Metabolic Syndrome Risk Factor Screening (American Indian/Alaskan Native vs. Asian)

MSRF [a] Screening	AI/AN/HN [b]	Asian	Total
Yes	6 (14.6%)	3 (18.8%)	9 (15.8%)
No	35 (85.4%)	13 (81.2%)	48 (84.2%)
Total	**41 (100%)**	**16 (100%)**	**57 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving metabolic syndrome risk factor screening within 6-months post-index date [c] between AI/AN/HN and Asian, **$\chi 2$ (1) = 0.1466, p=0.7017.**

Footnote:

a. Metabolic Syndrome Risk Factor.
b. American Indian/Alaskan Native/Hawaiian Native.
c. Date of the first dose of androgen deprivation therapy administrated during the study period.

Results of Specific Aim 2

Specific Aim 2 was to determine racial/ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT. Null hypothesis (H_0): There are no racial/ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT.

Among the study sample, 81.3% (n=653) had at least one MSRF and an indication for MSRF treatment. Among those, 80.3% (n=298) NHW patients, 71.6% (n=144) Hispanic, 67.5% (n=27) AA, 83.9% (n=26) AI/AN/HN and 70% (n=7) Asian received MSRF treatment within 6 months of ADT initiation.

Results showed no significant racial/ethnic difference in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT, $\chi 2$ (4) = 8.6754, p=0.0697. Table 27 presents results of MSRF treatment by race/ethnicity. However, we found a statistically significant difference in MSRF treatment between NHW and Hispanic patients, $\chi 2$ (1) =5.5951, p=0.0214.There were no statistically significant differences in the proportions of patients receiving guideline-concordant MSRF treatment when other racial and ethnic were compared. Tables 27-37 compare MSRF treatment among different racial and ethnic groups of PCa patients treated with ADT.

Table 27. Overall Metabolic Syndrome Risk Factor Treatment by Race/Ethnicity

MSRF [a] Treatment	NHW [b]	Hispanic	AA [c]	AI/AN/HN [d]	Asian	Total
Yes	298 (80.3%)	144 (71.6%)	27 (67.5%)	26 (83.9%)	7 (70%)	**502 (76.9%)**
No	73 (19.7%)	57 (28.4%)	13 (32.5%)	5 (16.1%)	3 (30%)	**151 (23.1%)**
Total	**371 (100%)**	**201 (100%)**	**40 (100%)**	**31 (100%)**	**10 (100%)**	**653 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date across all racial and ethnic groups, **$\chi 2$ (4) = 8.6754, p=0.0697.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Non-Hispanic White.
- **c.** African American
- **d.** American Indian/Alaskan Native, Hawaiian Native
- **e.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies). Among a total sample of 803 in our study, nearly 81.3% (n=653) had an indication for MSRF treatment.

Table 28. Metabolic Syndrome Risk Factor Treatment (Non-Hispanic White vs. Hispanic)

MSRF [a] Treatment	NHW [b]	Hispanic	Total
Yes	298 (80.3%)	144 (71.6%)	442 (77.3%)
No	73 (19.7%)	57 (28.4%)	130 (22.7%)
Total	**371 (100%)**	**201 (100%)**	**572 (100%)**

There was **a statistically** significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between NHW and Hispanics, **$\chi 2$ (1) =5.5951, p=0.0214.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Non-Hispanic White
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents NHW and Hispanic patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 29. Metabolic Syndrome Risk Factor Treatment (Non-Hispanic White vs. African American)

MSRF [a] Treatment	NHW [b]	AA [c]	Total
Yes	298 (80.3%)	27 (67.5%)	325 (79.1%)
No	73 (19.7%)	13 (32.5%)	86 (20.9%)
Total	**371 (100%)**	**40 (100%)**	**411 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [d] between NHW and AA, **$\chi 2$ (1) = 3.5884, p=0.0665.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Non-Hispanic White.
- **c.** African American.
- **d.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents NHW and AA patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 30. Metabolic Syndrome Risk Factor Treatment (Non-Hispanic White vs. American Indian/Alaskan Native)

MSRF [a] Treatment	NHW [b]	AI/AN/HN c	Total
Yes	298 (80.3%)	26 (83.9%)	324 (80.6%)
No	73 (19.7%)	5 (16.1%)	78 (19.4%)
Total	**371 (100%)**	**31 (100%)**	**402 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [d] between NHW and AI/AN/HN, **$\chi 2$ (1) = 0.2302, p=0.6313.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Non-Hispanic White.
- **c.** American Indian/Alaskan Native/Hawaiian Native.
- **d.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents NHW and AI/AN/HN patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 31. Metabolic Syndrome Risk Factor Treatment (Non-Hispanic White vs. Asian)

MSRF [a] Treatment	NHW [b]	Asian	Total
Yes	122 (26.8%)	7 (70%)	129 (27.7%)
No	333 (73.2%)	3 (30%)	336 (72.3%)
Total	**455 (100%)**	**10 (100%)**	**465 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between NHW and Asian, **$\chi 2$ (1) = 0.6499, p=0.4247.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Non-Hispanic White.
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents NHW and Asian patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 32. Metabolic Syndrome Risk Factor Treatment (Hispanic vs. African American)

MSRF [a] Treatment	Hispanic	AA [b]	Total
Yes	144 (71.6%)	27 (67.5%)	171 (71%)
No	57 (28.4%)	13 (32.5%)	70 (29%)
Total	**201 (100%)**	**40 (100%)**	**241 (100%)**

There was **no statistically** significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between Hispanic and AA, **$\chi 2$ (1) = 0.2777, p=0.5982.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** African American
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents Hispanic and AA patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 33. Metabolic Syndrome Risk Factor Treatment (Hispanic vs. American Indian/Alaskan Native)

MSRF [a] Treatment	Hispanic	AI/AN/HN [b]	Total
Yes	144 (71.6%)	26 (83.9%)	170 (73.3%)
No	57 (28.4%)	5 (16.1%)	62 (26.7%)
Total	**201 (100%)**	**31 (100%)**	**232 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between Hispanic and AI/AN/HN, **$\chi 2$ (1) = 2.051, p=0.1521.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** American Indian/Alaskan Native/Hawaiian Native.
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents Hispanic and AI/AN/HN patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 34. Metabolic Syndrome Risk Factor Treatment (Hispanic vs. Asian)

MSRF [a] Treatment	Hispanic	Asian	Total
Yes	144 (71.6%)	7 (70%)	151 (71.6%)
No	57 (28.4%)	3 (30%)	60 (28.4%)
Total	**201 (100%)**	**10 (100%)**	**211 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [b] between Hispanic and Asian, **$\chi 2$ (1) = 0.0126, p=0.9106.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents Hispanic and Asian patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 35. Metabolic Syndrome Risk Factor Treatment (African American vs. American Indian/Alaskan Native)

MSRF [a] Treatment	AA [b]	AI/AN/HN [c]	Total
Yes	27 (67.5%)	26 (83.9%)	53 (74.6%)
No	13 (32.5%)	5 (16.1%)	18 (25.4%)
Total	**40 (100%)**	**31 (100%)**	**71 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [d] between AA and AI/AN/HN, **$\chi 2$ (1) = 2.4733, p=0.1158.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** African American.
- **c.** American Indian/Alaskan Native/Hawaiian Native.
- **d.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents AA and AI/AN/HN patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 36. Metabolic Syndrome Risk Factor Treatment (African American vs. Asian)

MSRF [a] Treatment	AA [b]	Asian	Total
Yes	27 (67.5%)	7 (70%)	34 (68%)
No	13 (32.5%)	3 (30%)	16 (32%)
Total	**40 (100%)**	**10 (100%)**	**50 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between AA and Asian, **$\chi 2$ (1) = 0.0230, p=0.8795.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** African American.
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents AA and Asian patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Table 37. Metabolic Syndrome Risk Factor Treatment (American Indian/Alaskan Native vs. Asian)

MSRF [a] Treatment	AI/AN/HN [b]	Asian	Total
Yes	26 (83.9%)	7 (70%)	33 (80.5%)
No	5 (16.1%)	3 (30%)	8 (19.5%)
Total	**31 (100%)**	**10 (100%)**	**41 (100%)**

There was **no** statistically significant difference in the proportion of patients receiving MSRF treatment within 6-months post-index date [c] between AI/AN/HN and Asian, **$\chi 2$ (1) = 0.2963, p=0.3780.**

Footnote:

- **a.** Metabolic Syndrome Risk Factor.
- **b.** American Indian/Alaskan Native/Hawaiian Native.
- **c.** Date of the first dose of androgen deprivation therapy administrated during the study period.

This table represents AI/AN/HN and Asian patients with a confirmed MSRF diagnosis(es) and a treatment indication for MSRF (i.e., eligible for pharmacological therapy with no known treatment contraindication or drug allergies).

Results of Specific Aim 3

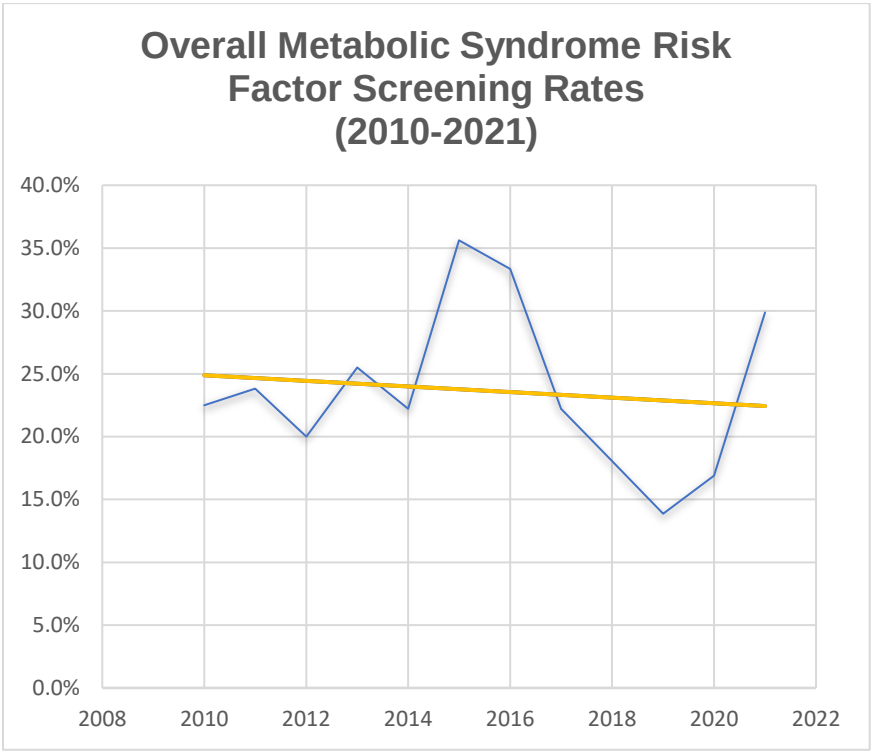
Specific Aim 3 was to determine longitudinal changes in guideline-concordant MSRF screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT.

Null hypothesis (H_0): There is no difference in the MSRF guideline-concordant screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT.

The mean rate of MSRF guideline-concordant screening among PCa patients treated with ADT was found to be considerably low (23.5%) and varied from 13.9% to 35.6% throughout the study period. MSRF screening rates varied between 20-25% during the first 5 years of follow-up post-index date. However, MSRF screening rate increased substantially to 35.6% in 2015 before dropping to its lowest (13.9%) in 2019. MSRF screening rates increased again to reach 29.9% in 2021. Figure 8 illustrates MSRF screening rates between 2010 and 2021 among the study sample, whereas Figure 9 describes MSRF screening rates across racial and ethnic groups of PCa patients treated with ADT.

Rates of MSRF screening among NHW men varied from 16.1% to 36.8% throughout the study period. Rates varied considerably during the first 8 years of follow-up post-index date (the lowest rate was 21.7% whereas the highest was 36.8%). However, the rate dropped to its lowest (16.1%) in 2019. In the last two years, MSRF screening rates increased again to reach 35.4% in 2021. Figure 10 describes MSRF screening rates among NHW men between 2010 and 2021.

Figure 8. Metabolic Syndrome Risk Factor Screening Rates Among Prostate Cancer Patients Treated with Androgen Deprivation Therapy (2010-2021)



Year	MSRF* Screening
2010	22.5%
2011	23.8%
2012	20.0%
2013	25.5%
2014	22.2%
2015	35.6%
2016	33.3%
2017	22.2%
2018	18.1%
2019	13.9%
2020	16.9%
2021	29.9%
Total	23.5%

*** MSRF: Metabolic Syndrome Risk Factor.**

Figure 9. Metabolic Syndrome Risk Factor Screening Rates by Race/Ethnicity (2010-2021)

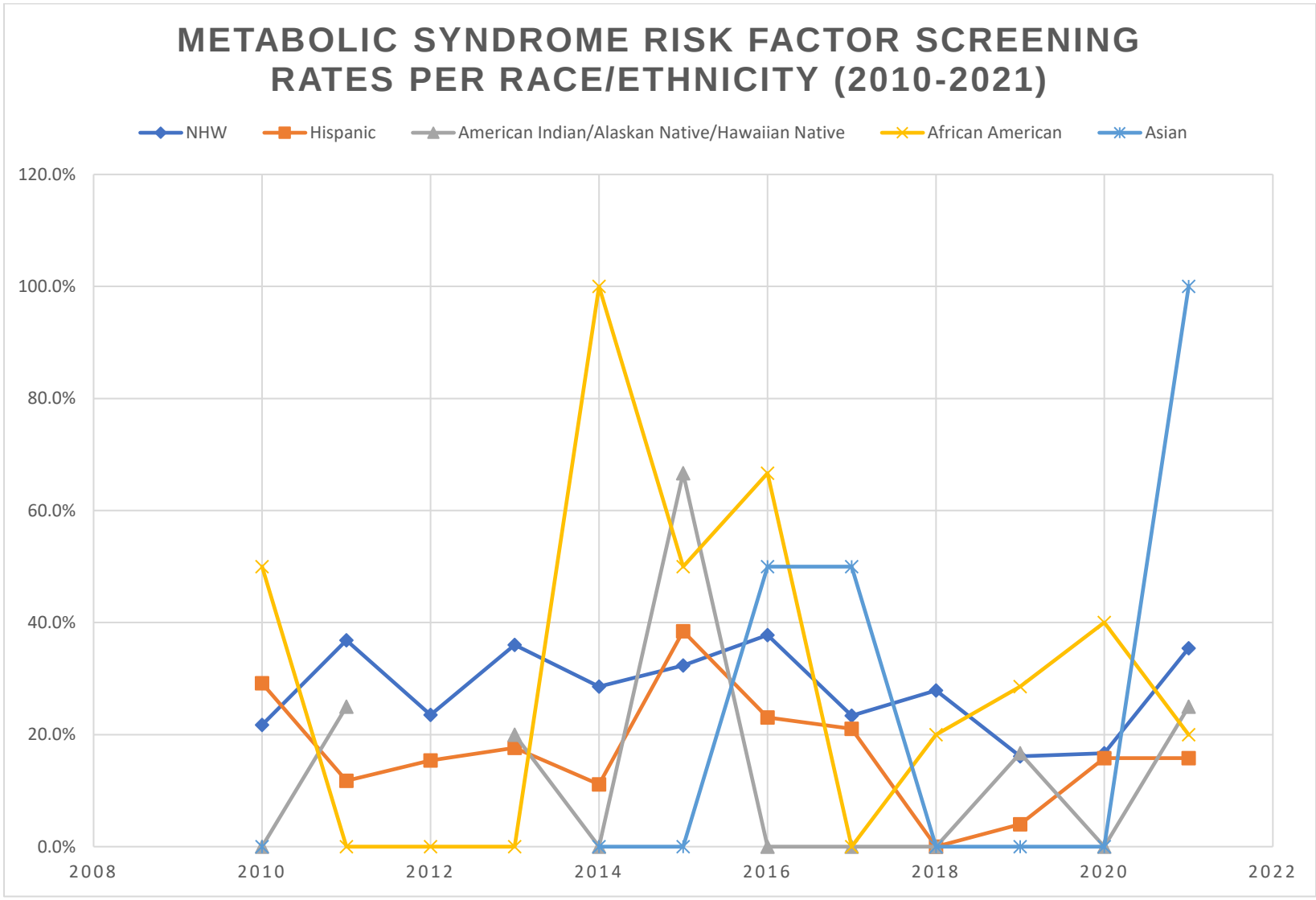
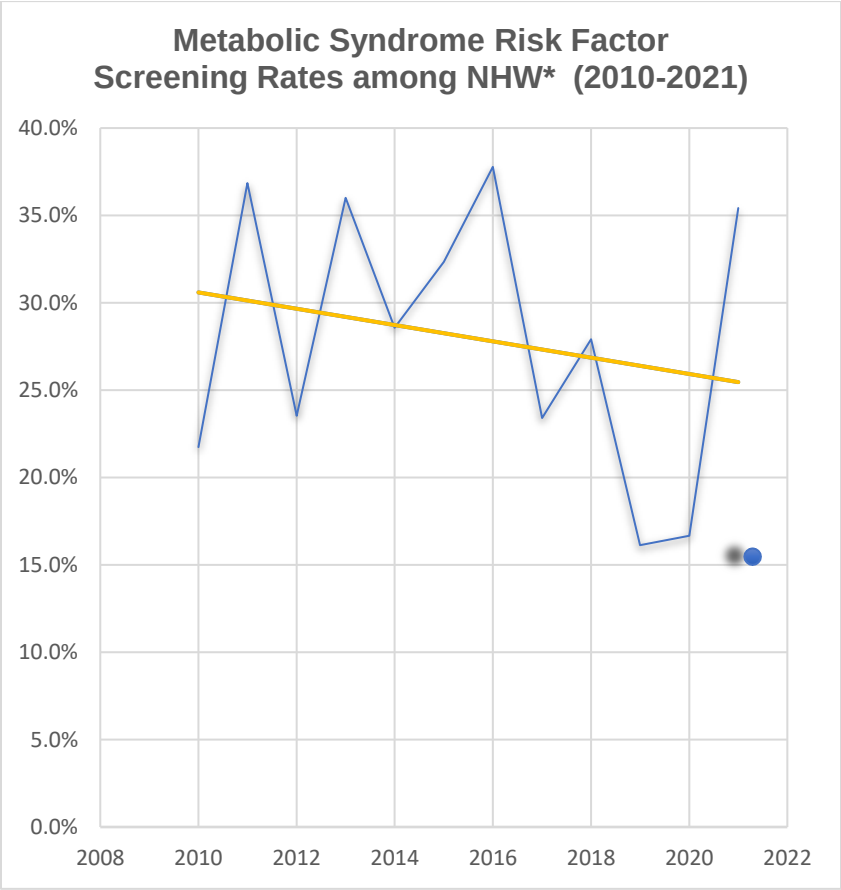


Figure 10. Metabolic Syndrome Risk Factor Screening Rates Among Non-Hispanic White (2010-2021)



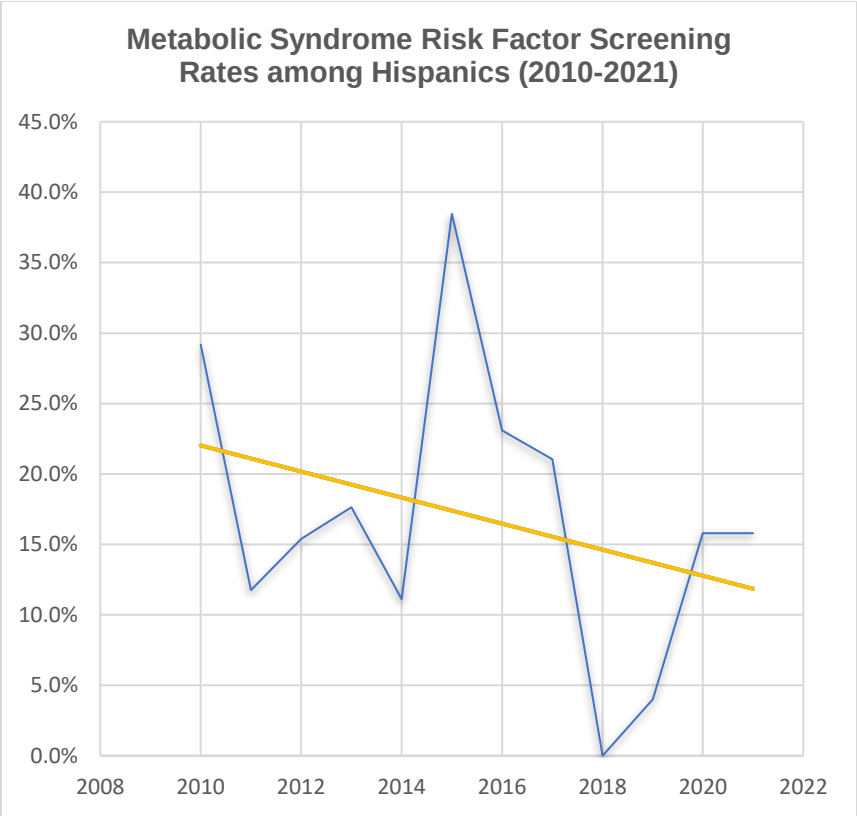
Year	MSRF* Screening
2010	21.7%
2011	36.8%
2012	23.5%
2013	36.0%
2014	28.6%
2015	32.4%
2016	37.8%
2017	23.4%
2018	27.9%
2019	16.1%
2020	16.7%
2021	35.4%
Total	26.8%

*NHW: Non-Hispanic White; MSRF: Metabolic Syndrome Risk Factor.

Rates of MSRF screening among Hispanic men varied substantially from 0.0% to 38.5% throughout the study period. Although MSRF screening rate was nearly 29.2% in 2010, it dropped to nearly 11% during 2011-2014. A sharp increase in MSRF screening rate was noticed in 2015 (38.5%) before it dropped sharply to 0% in 2018 (i.e., none of the 19 Hispanic individuals in 2018 received MSRF screening within 6 months post-ADT initiation). However, of the 19 Hispanic individuals with PCa and treated with ADT in 2018, 4 (~21%) received late MSRF screening (i.e., 7-12 months post-ADT initiation). Since 2018, the MSRF screening rate has increased to 15.8% in 2021. Figure 11 describes MSRF screening rates among Hispanic men between 2010 and 2021. Figure 12 compares MSRF screening between NHW and Hispanic men between 2010 and 2021.

Rates of MSRF screening among AI/AN/HN also varied from 0% to 66.7% during the study period. However, these rates should be interpreted with caution due to small sample size (i.e., 6 of 41 patients received MSRF screening between 2010 and 2021). AA and Asian men had also considerable variation in MSRF screening rates during the study period ranging from 0% to 100%. However, similar to AI/AN/HN, these rates should be interpreted with caution due to small sample size (i.e.,15 of 49 patients received MSRF screening between 2010 and 2021). Figure 13-15 illustrate MSRF screening rates among men of AI/AN/HN, AA and Asian populations between 2010 and 2021.

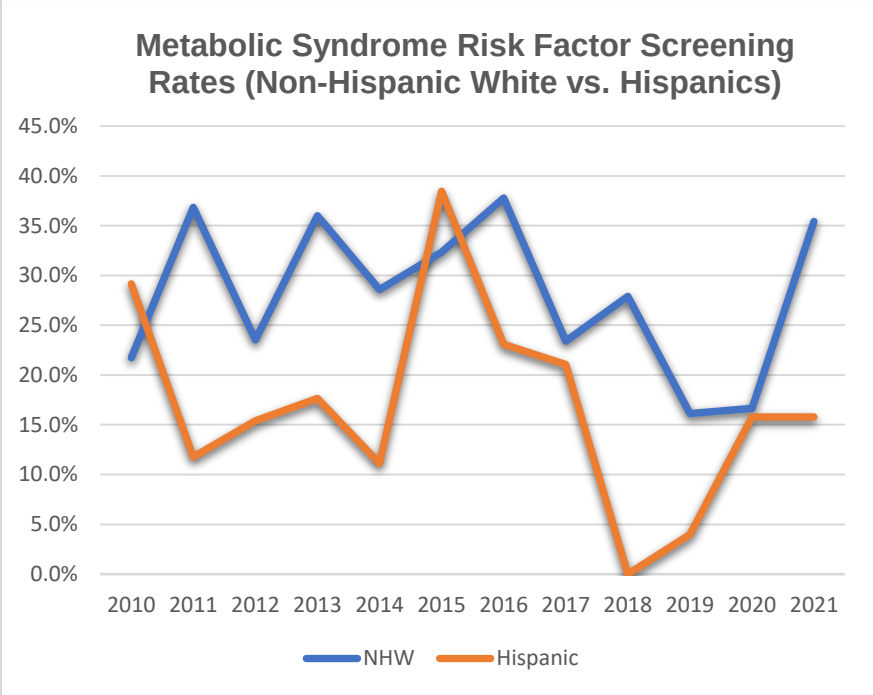
Figure 11. Metabolic Syndrome Risk Factor Screening Rates Among Hispanics (2010-2021)



Year	MSRF* Screening
2010	29.2%
2011	11.8%
2012	15.4%
2013	17.6%
2014	11.1%
2015	38.5%
2016	23.1%
2017	21.1%
2018	0.0%
2019	4.0%
2020	15.8%
2021	15.8%
Total	17.8%

*MSRF: Metabolic Syndrome Risk Factor.

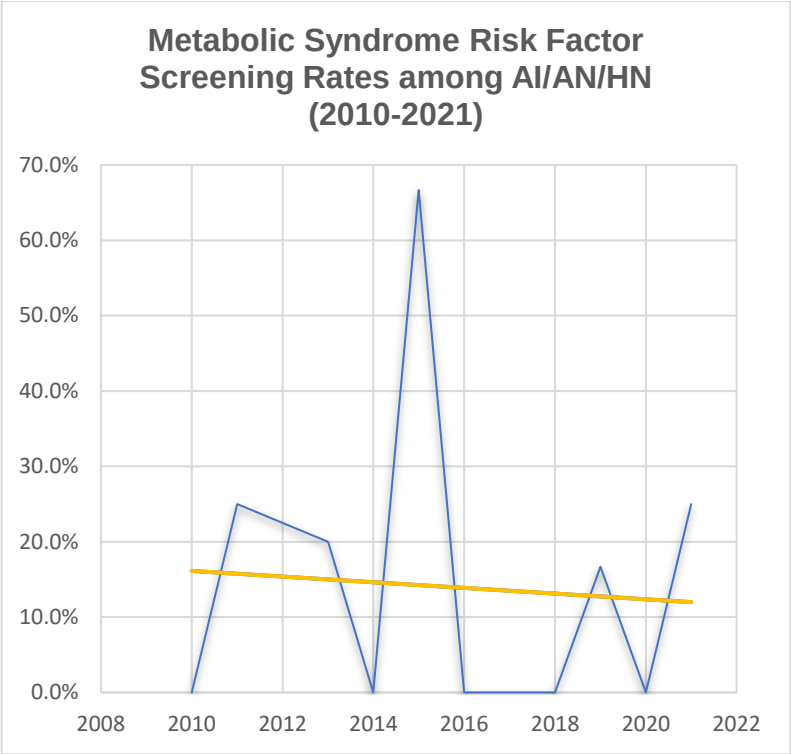
Figure 12. Metabolic Syndrome Risk Factor Screening Rates (Non-Hispanic White vs. Hispanics) (2010-2021)



MSRF* Screening		
Year	NHW*	Hispanic
2010	21.7%	29.2%
2011	36.8%	11.8%
2012	23.5%	15.4%
2013	36.0%	17.6%
2014	28.6%	11.1%
2015	32.4%	38.5%
2016	37.8%	23.1%
2017	23.4%	21.1%
2018	27.9%	0.0%
2019	16.1%	4.0%
2020	16.7%	15.8%
2021	35.4%	15.8%

*** MSRF: Metabolic syndrome Risk Factor.**
***Non-Hispanic White.**

Figure 13. Metabolic Syndrome Risk Factor Screening Rates Among American Indian/Alaskan Natives (2010-2021)

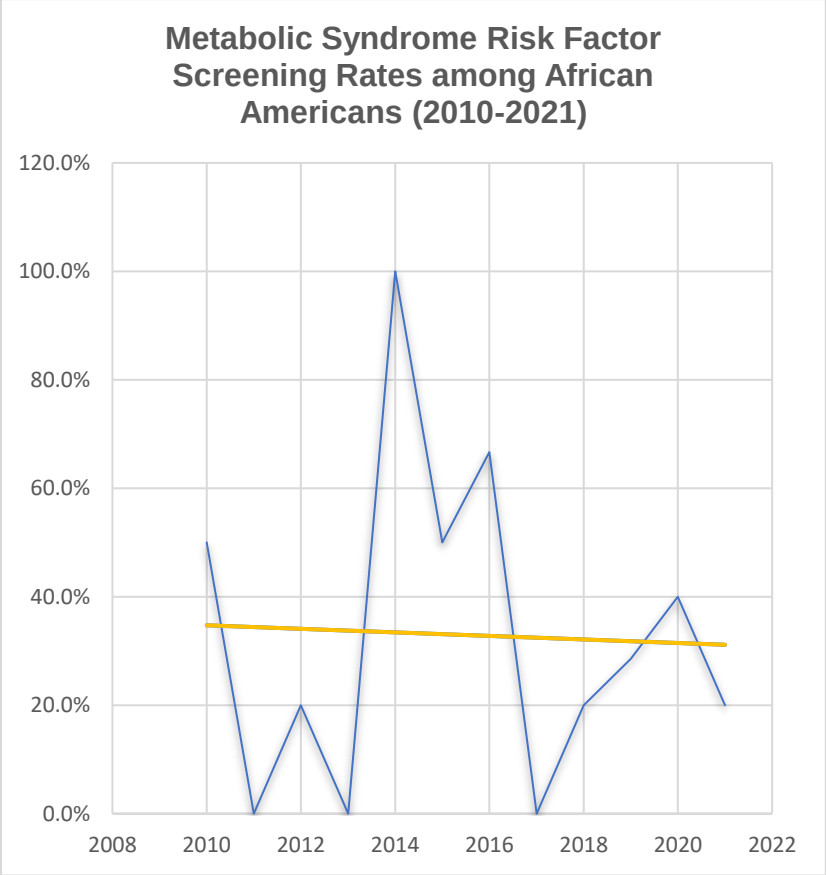


Year	MSRF* Screening
2010	0.0%
2011	25.0%
2012	Missing/ No patients
2013	20.0%
2014	0.0%
2015	66.7%
2016	0.0%
2017	0.0%
2018	0.0%
2019	16.7%
2020	0.0%
2021	25.0%
Total	14.6%

*AI/AN/HN: American Indian/Alaskan Native/Hawaiian Native.

MSRF: Metabolic Syndrome Risk Factor.

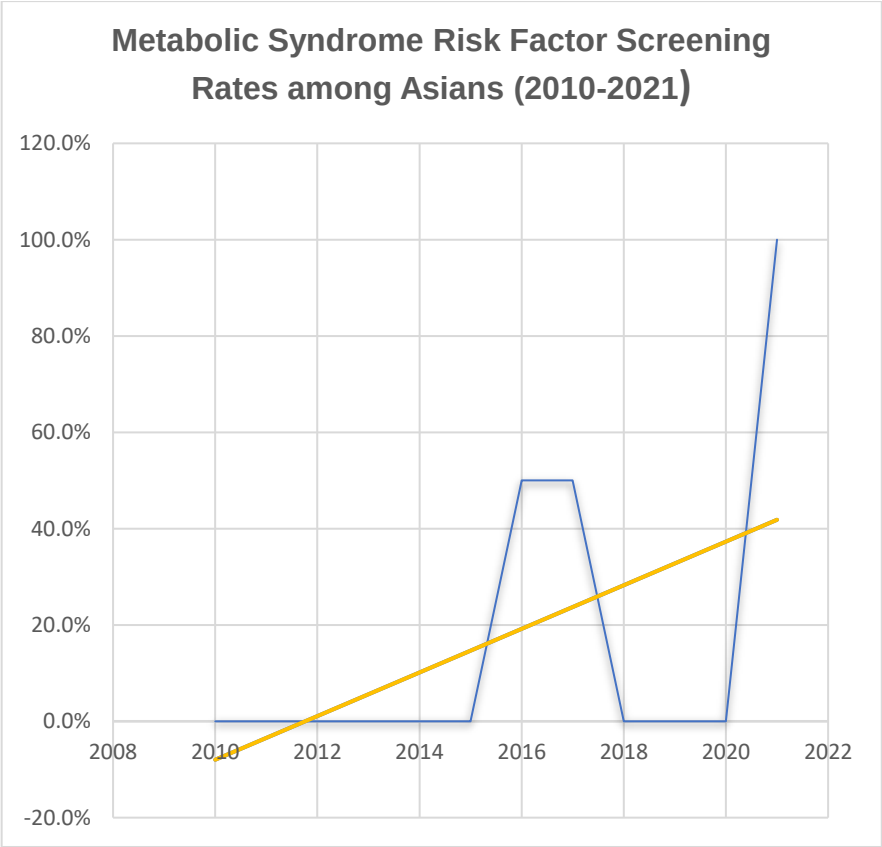
Figure 14. Metabolic Syndrome Risk Factor Screening Rates Among African Americans (2010-2021)



Year	MSRF* Screening
2010	50.0%
2011	0.0%
2012	20.0%
2013	0.0%
2014	100.0%
2015	50.0%
2016	66.7%
2017	0.0%
2018	20.0%
2019	28.6%
2020	40.0%
2021	20.0%
Total	30.6%

*** MSRF: Metabolic Syndrome Risk Factor.**

Figure 15. Metabolic Syndrome Risk Factor Screening Rates Among Asians (2010-2021)



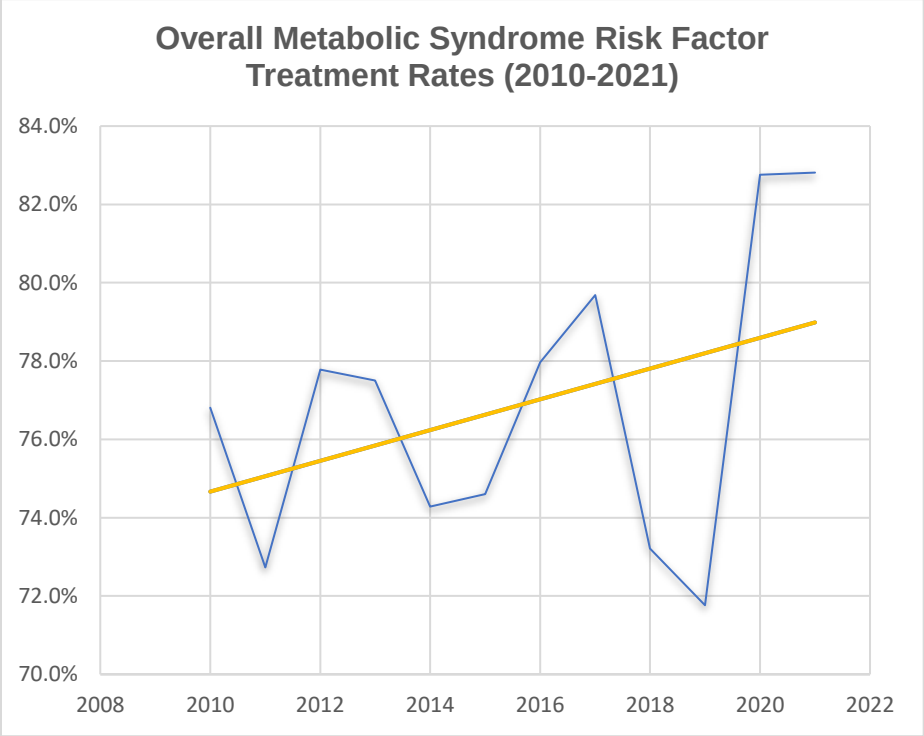
Year	MSRF* Screening
2010	0.0%
2011	Missing/ No patients
2012	Missing/ No patients
2013	Missing/ No patients
2014	0.0%
2015	0.0%
2016	50.0%
2017	50.0%
2018	0.0%
2019	0.0%
2020	0.0%
2021	100.0%
Total	18.8%

*MSRF: Metabolic Syndrome Risk Factor.

The mean rate of guideline-concordant MSRF treatment among PCa patients treated with ADT approached (76.9%, n=502) and varied from (71.8%, n=63) to (82.8%, n=53) throughout the study period. Rates of MSRF treatment varied between (73%, n=24) and (80%, n=51) during the first 8 years of follow-up post-index date before it dropped to its lowest (71.8%, n=61) in 2019 likely due to lower proportion of patients with confirmed diagnostic criteria of metabolic syndrome at baseline in 2019 (21%) compared to 2018 (26%) and 2020 (27%). However, MSRF treatment rates increased again to reach (82.8%, n=53) in 2021. Figure 16 illustrates MSRF treatment rates between 2010 and 2021 among the study sample, whereas Figure 17 describes MSRF treatment rates across racial and ethnic groups of PCa patients treated with ADT.

Rates of MSRF treatment among NHW men averaged nearly 80% (n=298) during the study period. Figure 18 describes MSRF treatment rates among NHW men between 2010 and 2021. Hispanic men had a significantly lower mean MSRF treatment rate (71.6%, n=144) compared to NHW men (80.3%, n=298) throughout the study period, $p<0.05$. Although slight variations were noticed throughout follow-up, treatment rates were generally considered consistent among NHW and Hispanic individuals. Figure 19 illustrates MSRF treatment rates among Hispanic men. Figure 20 compares MSRF screening between NHW and Hispanics. MSRF treatment rates among AI/AN/HN, AA and Asian varied considerably from 0% to 100% and should be interpreted cautiously due to small sample size (Figures 21, 22 and 23, respectively).

Figure 16. Metabolic Syndrome Risk Factor Treatment Rates Among Prostate Cancer Patients Treated with Androgen Deprivation Therapy (2010-2021)



Year	MSRF* Treatment
2010	76.8%
2011	72.7%
2012	77.8%
2013	77.5%
2014	74.3%
2015	74.6%
2016	78.0%
2017	79.7%
2018	73.2%
2019	71.8%
2020	82.8%
2021	82.8%
Total	76.9%

*** MSRF: Metabolic Syndrome Risk Factor.**

Figure 17. Metabolic Syndrome Risk Factor Treatment Rates By Race/Ethnicity (2010-2021)

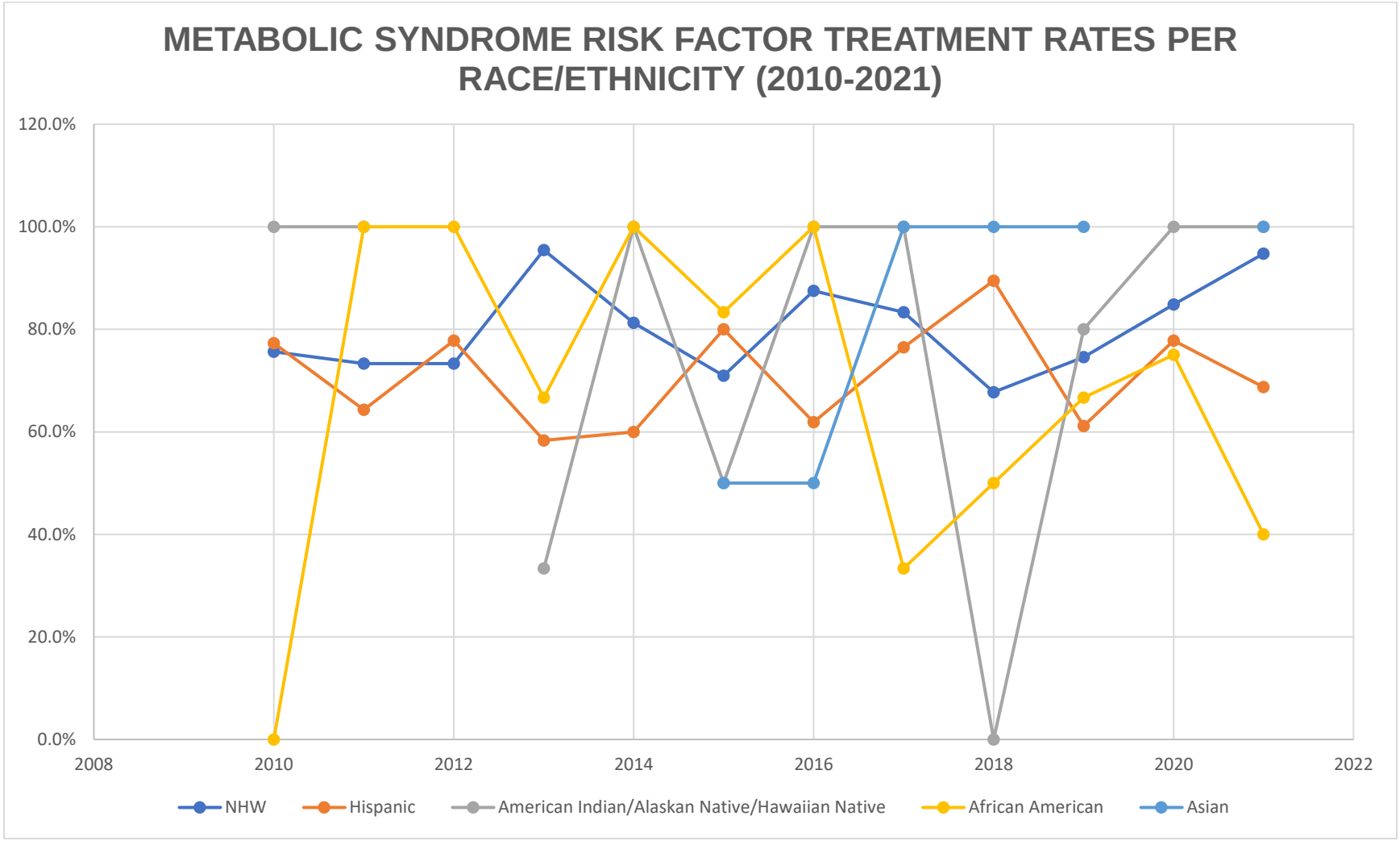
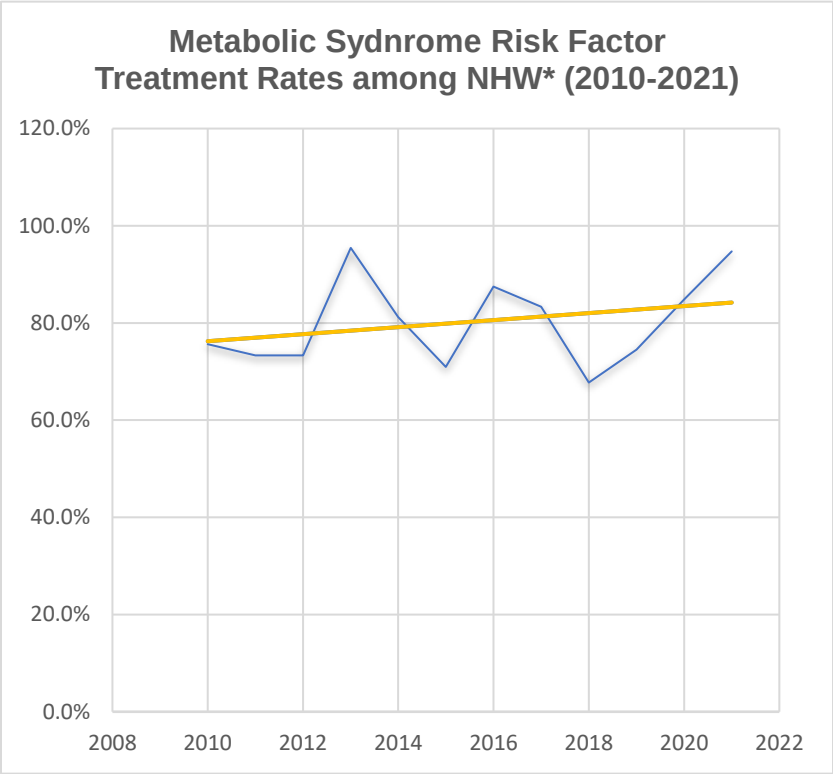


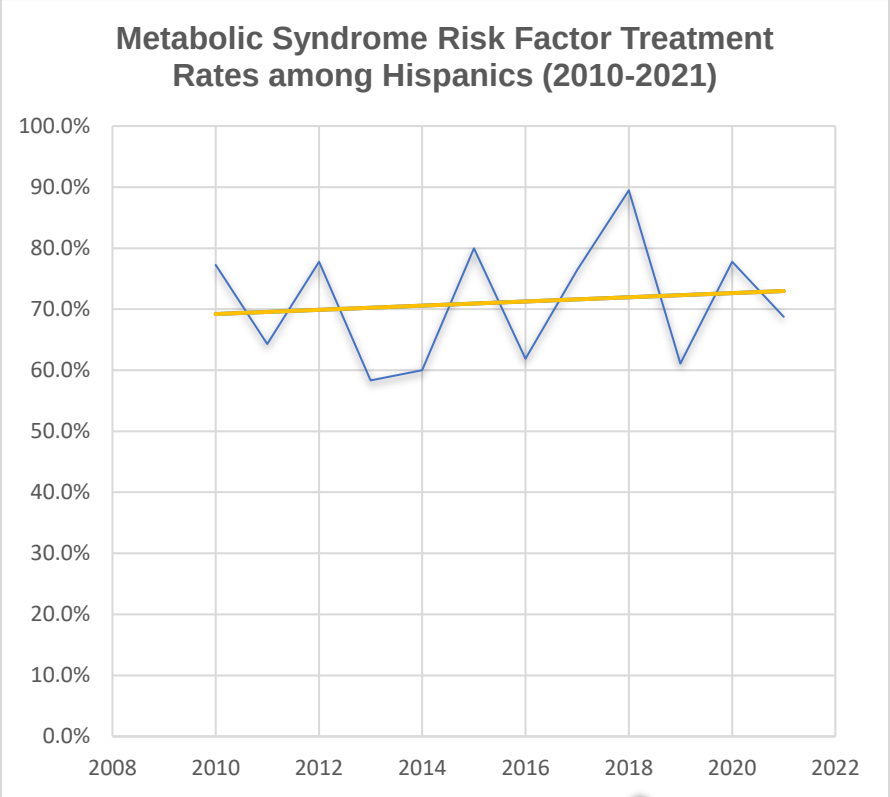
Figure 18. Metabolic Syndrome Risk Factor Treatment Rates among Non-Hispanic White (2010-2021)



Year	MSRF* Treatment
2010	75.6%
2011	73.3%
2012	73.3%
2013	95.5%
2014	81.3%
2015	71.0%
2016	87.5%
2017	83.3%
2018	67.7%
2019	74.5%
2020	84.8%
2021	94.7%
Total	80.3%

***NHW: Non-Hispanic White; MSRF: Metabolic Syndrome Risk Factor.**

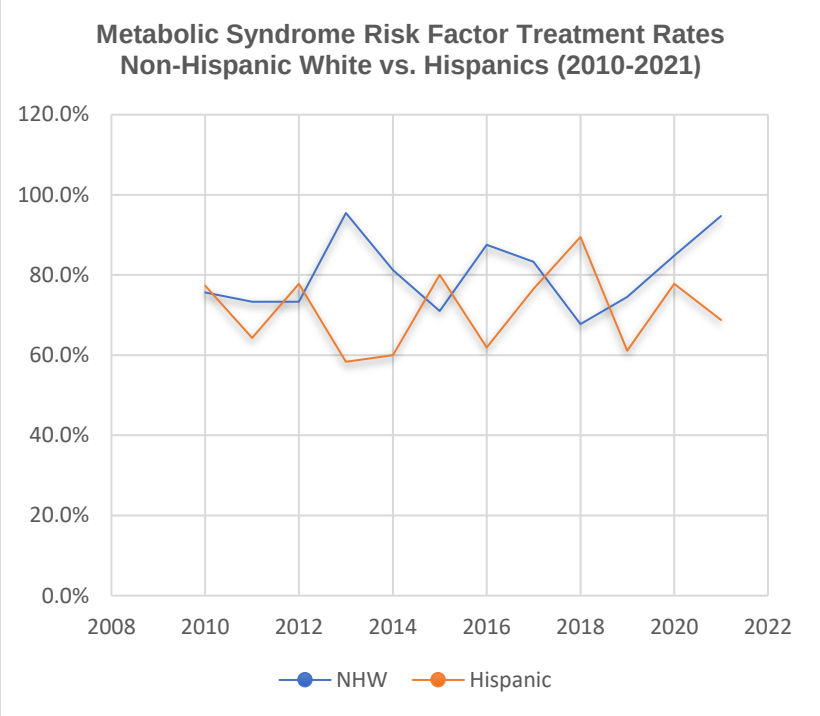
Figure 19. Metabolic Syndrome Risk Factor Treatment Rates among Hispanics (2010-2021)



Year	MSRF* Treatment
2010	77.3%
2011	64.3%
2012	77.8%
2013	58.3%
2014	60.0%
2015	80.0%
2016	61.9%
2017	76.5%
2018	89.5%
2019	61.1%
2020	77.8%
2021	68.8%
Total	71.6%

***MSRF: Metabolic Syndrome Risk Factor.**

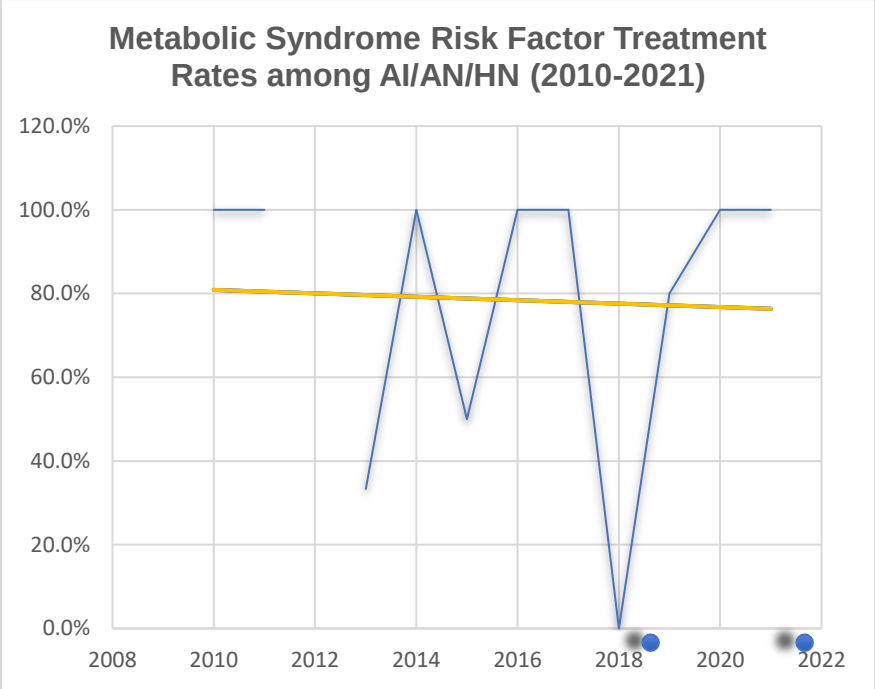
Figure 20. Metabolic Syndrome Risk Factor Treatment Rates (Non-Hispanic White vs. Hispanics) (2010-2021)



MSRF* Treatment		
Year	NHW*	Hispanic
2010	75.6%	77.3%
2011	73.3%	64.3%
2012	73.3%	77.8%
2013	95.5%	58.3%
2014	81.3%	60.0%
2015	71.0%	80.0%
2016	87.5%	61.9%
2017	83.3%	76.5%
2018	67.7%	89.5%
2019	74.5%	61.1%
2020	84.8%	77.8%
2021	94.7%	68.8%

*NHW: Non-Hispanic White; MSRF: Metabolic syndrome Risk Factor.

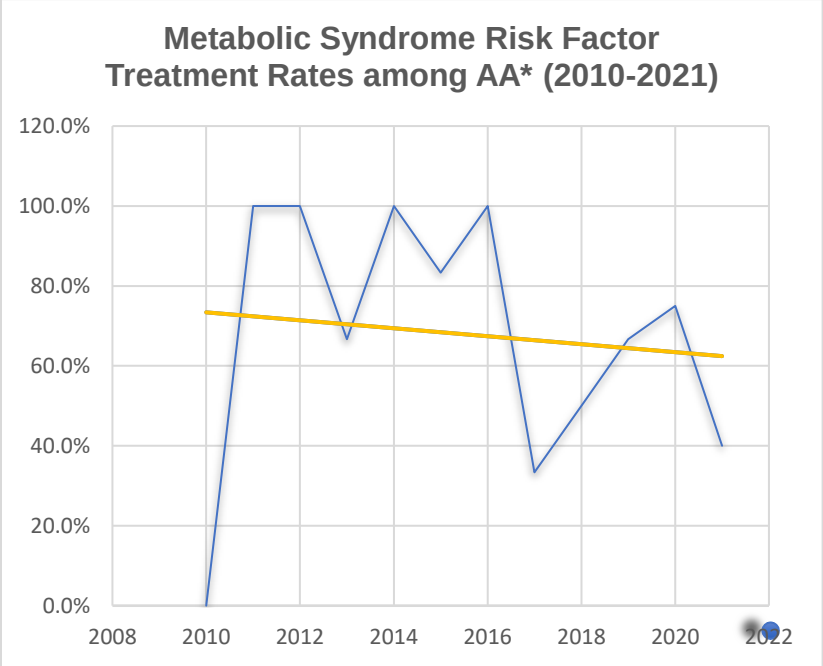
Figure 21. Metabolic Syndrome Risk Factor Treatment Rates Among American Indian/Alaskan Native (2010-2021)



Year	MSRF* Treatment
2010	100.0%
2011	100.0%
2012	Missing/ No patients
2013	33.3%
2014	100.0%
2015	50.0%
2016	100.0%
2017	100.0%
2018	0.0%
2019	80.0%
2020	100.0%
2021	100.0%
Total	83.9%

*** AI/AN/HN: American Indian, Alaskan Native, Hawaiian Native, MSRF: Metabolic Syndrome Risk Factor.**

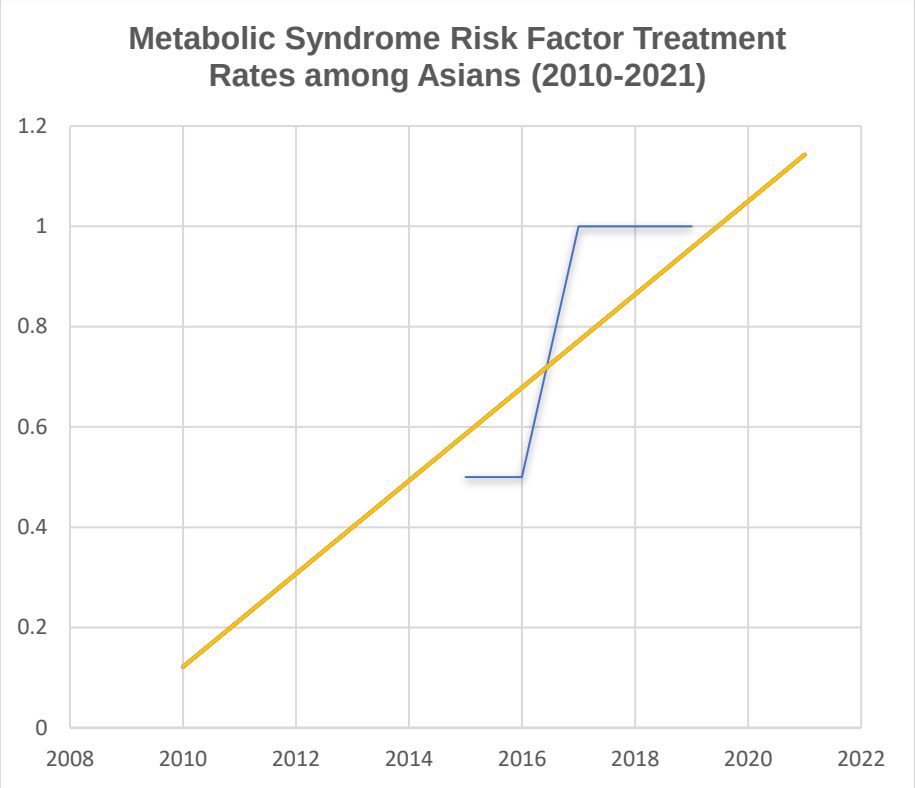
Figure 22. Metabolic Syndrome Risk Factor Treatment Rates Among African American (2010-2021)



Year	MSRF* Treatment
2010	0.0%
2011	100.0%
2012	100.0%
2013	66.7%
2014	100.0%
2015	83.3%
2016	100.0%
2017	33.3%
2018	50.0%
2019	66.7%
2020	75.0%
2021	40.0%
Total	67.5%

***AA: African American; MSRF: Metabolic Syndrome Risk Factor.**

Figure 23. Metabolic Syndrome Risk Factor Treatment Rates Among Asians (2010-2021)



Year	MSRF* Treatment
2010	Missing/ No patients
2011	Missing/ No patients
2012	Missing/ No patients
2013	Missing/ No patients
2014	Missing/ No patients
2015	50.0%
2016	50.0%
2017	100.0%
2018	100.0%
2019	100.0%
2020	Missing/ No patients
2021	100.0%
Total	70.0%

*** MSRF: Metabolic Syndrome Risk Factor.**

Results of Specific Aim 4

Specific Aim 4 was to identify patient and healthcare provider characteristics influencing the receipt of MSRF screening among racial/ethnic groups of PCa patients treated with ADT. Null hypothesis (H_0): There are no differences in patient factors (patient race/ethnicity, age at index date, marital status at index date, insurance coverage status at index date, PCa disease stage at index date, Gleason score at index date, number of co-morbidities at index date, baseline MSRF including "diagnoses of hypertension, diabetes mellitus II, obesity and dyslipidemia before treatment with ADT") or healthcare provider factors (healthcare provider gender, specialty, and years of experience) in the receipt of MSRF screening among PCa patients treated with ADT.

Table 38 provides the results of the unadjusted bivariate logistic regression analysis of the odds of having MSRF screening (n=189) among PCa patients treated with ADT between 2010 and 2021. Results showed that Hispanic men had 0.59 times (95% CI: 0.4-0.087, *p*=0.008) significantly lower odds of having MSRF screening compared to NHW men. Men who were "single" at the index date had 1.63 times (95% CI: 1.08-2.46, *p*=0.02) significantly higher odds of having MSRF screening compared to "married/partnered" men. Men with 5-10 co-morbid disease conditions at baseline had 2.9 times (95%CI: 2.08-4.07, p<0.001) significantly higher odds of having MSRF screening than men with <5 co-morbid disease conditions. Similarly, men with >10 co-morbid disease conditions at baseline had 5.46 times (95% CI: 1.38-22.5, *p*=0.02) significantly higher odds of having MSRF screening than men with <5 co-morbidities.

Table 38. Results of Bivariate Logistic Regression: Unadjusted Predictors of Having Metabolic Syndrome Risk Factor Screening within 6 months Post-index Date

Variable	Odds Ratio	95% Confidence Interval	*P* value	*Include in Multiple Logistic Model* [b]
Race/Ethnicity				
Non-Hispanic White	**Reference**			**Yes**
Hispanic	0.59	0.40-0.87	0.008	
African American	1.20	0.63-2.88	0.57	
AI/AN/HN [a]	0.47	0.19-1.14	0.09	
Asian	0.63	0.18-2.25	0.48	
Age at index date [c]				
≥80	**Reference**			No
65-79	1.53	0.89-2.62	0.15	
45-64	1.53	0.86-2.72	0.12	
Insurance at index date				
Uninsured	**Reference**			**Yes**
Private	2.19	0.64-7.58	0.21	
Public	1.41	0.40-4.94	0.59	
Public + Private	2.96	0.82-10.65	0.09	
Marital Status at index date				
Married/partnered	**Reference**			**Yes**
Never Married/Single	1.63	1.08-2.46	0.02	
Divorced/Separated	1.06	0.60-1.90	0.83	
Widowed	1.18	0.64-2.20	0.59	

TNM [d] Stage at index date				
I	**Reference**			
II	0.88	0.35-2.18	0.78	
III	0.97	0.38-2.50	0.95	No
IV	0.75	0.31-1.85	0.53	
Gleason Score at index date				
<7 (well-differentiated tumor)	**Reference**			
7 (moderately-differentiated tumor)	0.83	0.43-1.61	0.59	**Yes**
>7 (poorly-differentiated tumor)	0.59	0.31-1.13	0.11	
Number of co-morbidities at index date				
<5	**Reference**			
5-10	2.90	2.07-4.07	<0.001	**Yes**
>10	5.46	1.38-22.35	0.02	
Baseline Diabetes Mellitus II				
No	**Reference**			
Yes	1.73	1.21-2.50	0.003	**Yes**
Baseline Hypertension				
No	**Reference**			
Yes	1.97	1.36-2.86	0.0004	**Yes**
Baseline Dyslipidemia				
No	**Reference**			
Yes	3.50	2.50-4.95	<0.0001	**Yes**
Baseline Obesity (BMI≥30) [e]				
No	**Reference**			
Yes	1.39	0.99-1.95	0.054	**Yes**

Table 38. Continuation				
Baseline Metabolic Syndrome				
No	**Reference**			**Yes**
Yes	2.94	2.10-4.13	<0.0001	
Healthcare Provider Gender				**Yes**
Male	**Reference**			
Female	1.34	0.96-1.87	0.084	
Healthcare Provider Experience				**Yes**
<10 years	**Reference**			
10-20 years	1.18	0.73-1.91	0.51	
>20 years	1.58	1.07-2.33	0.02	
Healthcare Provider Specialty				
Oncology	**Reference**			**Yes**
Family Medicine	3.16	(2.8-4.9)	<0.0001	
Internal Medicine	2.55	(2.0-3.2)	<0.0001	
Urology	1.20	(1.1-2.9)	0.02	
Others [f]	2.33	(1.8-3.4)	<0.0001	

Footnote:

- **a.** American Indian/Alaskan Native/Hawaiian Native.
- **b.** "Yes" indicates that the *p-value* for all levels of the variable is significant at <0.20 (i.e., will be included in the adjusted logistic model).
- **c.** Date of first dose of androgen deprivation therapy (ADT) administered during the study period.
- **d.** Tumor Nodes Metastases.
- **e.** Body Mass Index
- **f.** Other specialties included cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician.

Patients with baseline diabetes mellitus II had 1.73 times (95% CI: 1.21-2.50, *p*=0.003) significantly higher odds of having MSRF screening compared to men with no diabetes mellitus II at baseline. Patients with baseline hypertension also had 1.97 times (95% CI: 1.36-2.86, p=0.0004) significantly higher odds of having MSRF screening than men with no hypertension at baseline. Similarly, patients with baseline dyslipidemia had 3.5 times (95% CI: 2.5-4.95, *p*<0.0001) significantly higher odds of having MSRF screening compared to men with no dyslipidemia at baseline. Patients who met the NCEP ATP III diagnostic criteria of metabolic syndrome at baseline had 2.94 times (95% CI: 2.1-4.13, *p*<0.0001) significantly higher odds of having MSRF screening compared to men with no metabolic syndrome at baseline.

Healthcare providers with >20 years of experience had 1.58 times (95% CI: 1.07-2.33, *p*=0.02) significantly higher odds of providing MSRF screening than healthcare providers with <10 years of experience. Family medicine specialists had 3.16 times (95% CI: 2.8-4.9, *p*<0.0001) significantly higher odds of screening for MSRF screening than oncologists. Similarly, Internists had 2.55 times (95% CI: 2.0-3.2, *p*<0.0001) significantly higher odds to provide MSRF screening compared to oncologists. Urologists had 1.2 times (95% CI: 1.1-2.9, *p*=0.02) significantly higher odds of providing MSRF screening than oncologists. Healthcare provides of the following specialties “cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician” had 2.33 times (95% CI: 1.8-3.4, *p*<0.0001) higher odds to provide MSRF screening compared to oncologists.

In summary, the following variables were found significant at $p<0.2$ and were considered in the adjusted multiple logistic regression analyses: patient race/ethnicity, insurance coverage status at index date, marital status at index date, PCa Gleason score at index date, number of co-morbidities at index date, diagnosis of diabetes mellitus II at baseline, diagnosis of hypertension at baseline, diagnosis of metabolic syndrome at baseline, obesity (BMI≥30) at baseline, diagnosis of dyslipidemia at baseline, healthcare provider gender, experience, and specialty.

Multiple Logistic Regression Analyses

Stepwise regression deletion procedure was utilized to select variables to use in our model based on an iterative process of adding or removing variables. Patient race/ethnicity, diagnosis of hyperlipidemia at baseline, healthcare provider specialty, years of experience, and their interaction term were retained in the final model after the stepwise regression deletion procedure.

Table 39 provides the results of the adjusted multiple logistic regression analyses of the odds of having MSRF screening among PCa patients treated with ADT between 2010 and 2021. The overall model was statistically significant ($\chi 2$ (19) = 181.64, $p<0.0001$). The significant impact of race/ethnicity in the unadjusted logistic regression analysis persisted in the multiple logistic regression analysis, after adjusting for other factors. Hispanic men had 0.4 times (95% CI: 0.2-0.6, $p=0.0001$) significantly lower odds of having MSRF screening compared to NHW. AI/AN/HN men had 0.2 times (95% CI: 0.07-0.7, $p=0.007$) significantly lower odds of having MSRF screening compared to NHW.

Table 39. Results of Multiple Logistic Regression: Adjusted Predictors of Having Metabolic Syndrome Risk Factor Screening within 6 months Post-index Date

Variable	Adjusted OR [a]	95% Confidence Interval	*P* value [b]
Race/Ethnicity			
Non-Hispanic White	**Reference**		
Hispanic	0.4	0.2-0.6	**0.0001**
African American	0.8	0.4-1.9	0.62
AI/AN/HN [c]	0.2	0.07-0.7	**0.007**
Asian	0.2	0.04-0.9	**0.04**
Baseline Dyslipidemia			
No	**Reference**		
Yes	3.1	(2.0-4.7)	**<0.0001**
Variables with interactions			
Oncologists & Years of experience			
<10 years	**Reference**		
10-20 years	0.5	(0.1-2.4)	0.40
>20 years	2.9	(1.4-6.3)	**0.006**
Family medicine & Years of experience			
<10 years	**Reference**		
10-20 years	0.9	(0.3-2.4)	0.79
>20 years	0.6	(0.2-1.8)	0.40

Table 39. Continuation **Internal medicine & Years of experience**			
<10 years	**Reference**		
10-20 years	1.1	(0.2-7.1)	0.95
>20 years	4.7	(0.8-27.2)	0.08
Urology & Years of experience			
<10 years	**Reference**		
10-20 years	0.1	(0.01-1.7)	0.10
>20 years	0.3	(0.02-4.9)	0.40
"Other" specialties & Years of experience			
<10 years	**Reference**		
10-20 years	0.1	(0.02-0.8)	**0.03**
>20 years	11.3	(1.04-16.0)	**0.04**

Footnote:

a. Odds Ratio.
b. Bold font indicates that the *p*-value is significant at <0.05
c. American Indian/Alaskan Native/Hawaiian Native.
d. Other specialties included Cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician.
e. The index date is the first dose of androgen deprivation therapy administered during the study period.

This model represents "up to our knowledge" the most parsimonious model. Race/ethnicity, diagnosis of dyslipidemia at baseline, healthcare provider specialty, years of experience, and their interaction were retained in the final model after the step-wise deletion procedure. This model has the lowest AIC value among all tested models. Overall, the model was statistically significant able to predict MSRF screening among PCa patients treated with ADT, p<0.001. More details about model fit statistics were discussed after this section.

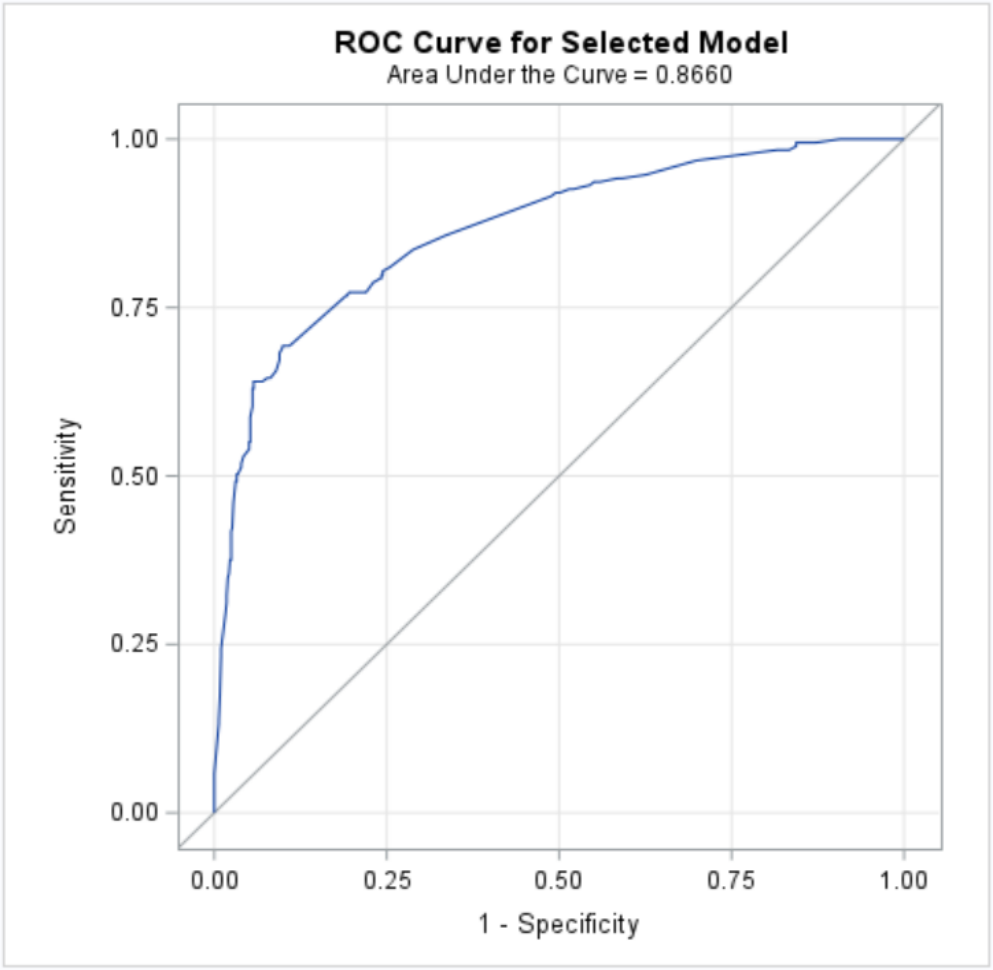
Asian men had 0.2 times (95% CI: 0.04-0.9, p=0.04) significantly lower odds of having MSRF screening compared to NHW. Patients with dyslipidemia at baseline had 3.1 times (95% CI: 2.0-4.7, p<0.0001) significantly higher odds of having MSRF screening compared to patients without a diagnosis of dyslipidemia at baseline.

Among variables with significant interaction terms, oncologists with >20 years of experience had 2.9 times (95% CI: 1.4-6.3, p=0.006) significantly higher odds to provide MSRF screening compared to oncologists with <10 years of experience. Conversely, healthcare providers of “other” specialties (cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician) with 10-20 years of experience had 0.1 times (95% CI: 0.02-0.8, p=0.03) lower odds to provide MSRF screening compared to “other” healthcare providers with <10 years of experience.

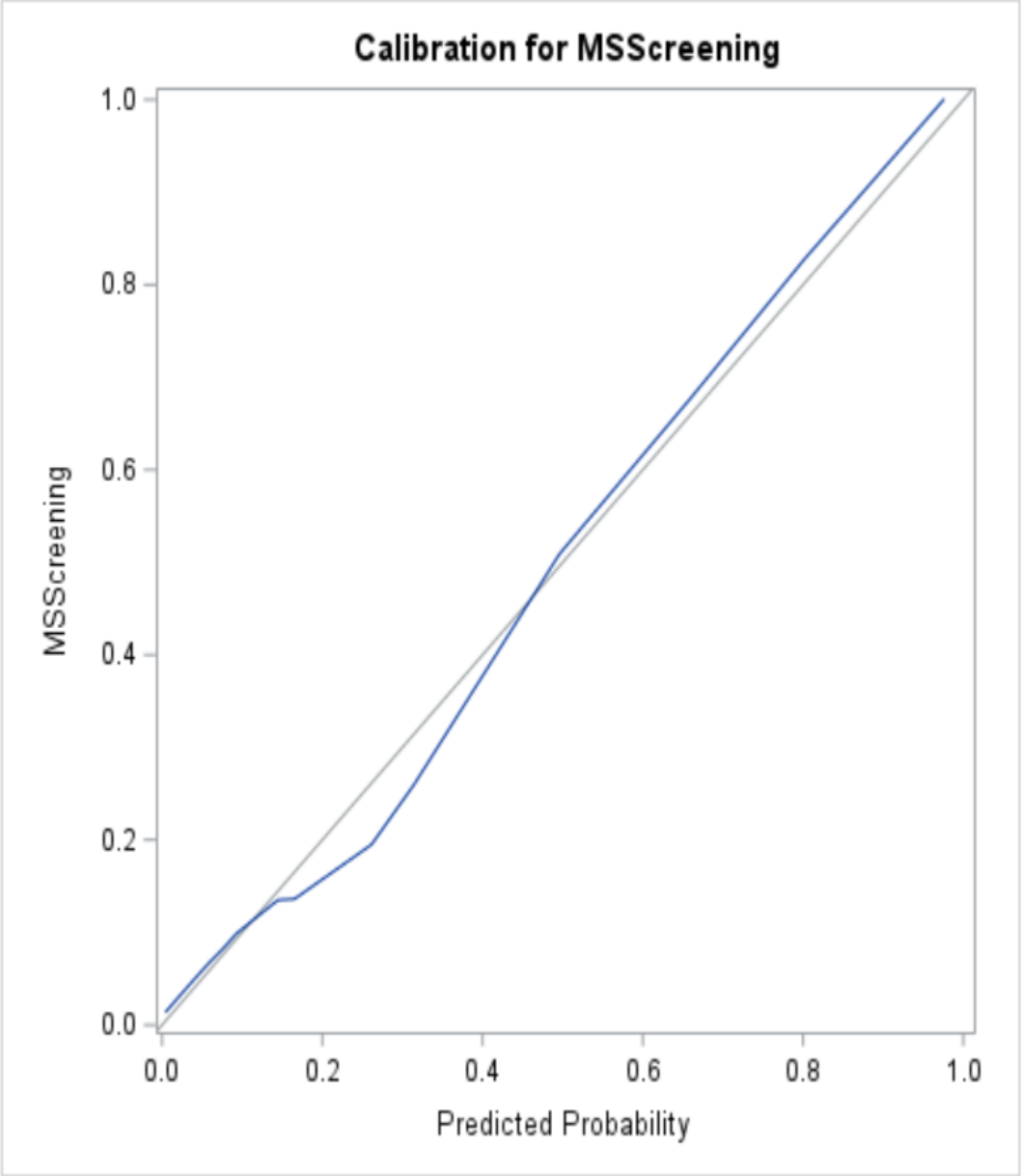
In summary, our adjusted multiple logistic model was statistically significant able to predict MSRF screening among PCa patients treated with ADT, p<0.0001. Up to our knowledge, this model represents the most parsimonious model. It had the lowest Akaike information criterion (AIC) value among all tested models. Since validity of inferences drawn from statistical modeling techniques depends mainly on the assumptions of the statistical model being satisfied[224] and the study research design and other unknown factors in the current study, we determined to evaluate our multiple logistic model appropriateness by examining its fit. This included assessing Hosmer and Lemeshow goodness of fit statistic, ROC and our response variable calibration

curve. We obtained a Hosmer and Lemeshow Goodness of fit statistic of $\chi 2$ (7) = 5.6, p=0.58**,** indicating that our model fit is good. In addition, we obtained an ROC c-statistic value of 0.8660, indicating our prediction model can strongly predict MSRF screening in this population of PCa patients treated ADT. Our response variable "MSRF" screening calibration curve also showed that our prediction model can strongly predict MSRF screening among this patient population of PCa patients treated ADT (diagonal line is close to the reference line). The following SAS output images describe results of ROC and calibration curve.

ROC curve:



MSRF screening (dependent variable) calibration curve:



CHAPTER 5: DISCUSSION

This chapter provides a discussion on the findings of the study. An overall discussion of study results is first presented. This will be followed by discussing study results as per the specific aims. The discussion of the results is followed by the study's limitations and suggestions for how future studies should be conducted based on the strengths and limitations of the current study. Finally, the implications and conclusions of the study are discussed.

Discussion of Study Sample Characteristics Results

Our study included 803 patients treated at the UNMCCC during the period (2010-2021). Almost 6 in 10 patients (56.7%, n=455) were NHW, 30.1% (n=242) were Hispanics, 6.1% (n=49) were AA, 5.1% (n=41) were AI/AN/HN and 2% (n=16) were Asian. These estimates are consistent with the previous literature results. Gilliland et al. (1996) reported higher proportion of PCa diagnosis among NHW (74.1%) compared to Hispanics (20.5%), AI/AN/HN (3.7%), AA (1.3%) and Asian (0.4%) during the period 1983-1992 in the state of NM.[40] Gilliland et al. (1998) also reported that increased PCa screening was a significant determinant of the rising incidence rate of PCa among NHW compared to AI during 1969-1994 in NM.[39] We believe that lower PCa proportions among minority populations compared to NHW in our study could be attributed to lower incidence rate of PCa due to differential access to medical care and underdiagnosis of PCa.[39,40]

As NM state has the largest proportion of AI/AN/HN of any state (~11%)[38], we expected to have larger proportion of AI/AN/AN patient population included in our study. Our study included a total of 41 (5.1%) AI/AN/HN patients who met the

study inclusion criteria and received primary care within the UNM health system during the study period (2010-2021). We believe that low proportion of AI/AN/HN patients included in the current study is influenced by the low proportion of patients receiving primary care within the UNM health system. Most AI/AN/HN individuals receive primary care at the Indian health service and not within the UNM health system which could have limited number of AI/AN/HN patients included in the current study.[225]

We found that our study participants' mean age (69.7, SD=8.8) is consistent with the CDC epidemiological data related to the age of men at PCa diagnosis.[3] Almost 6 in 10 patients (56.7%) of our study participants were 65-79 years old at index date which is consistent with the CDC PCa prevalence data for this age group (~52%).[3] We found a higher proportion of AA (46.9%) who were 45-64 years old at index date compared to NHW (25.5%). AA men suffer disproportionally from PCa, facing a 78% higher incidence rate than NHW men.[2,14] They are more likely to be diagnosed at a younger age and present with more advanced and aggressive PCa disease.[2,14]

Our study sample characteristics included a description of ADT use during the study period. An average of 73 patients received treatment with ADT every year during the study period. Sun et al. (2021) reported 22,700 patients who received treatment with ADT among PCa patients during the period 2010-2017 in the U.S. However, Sun et al. (2021) is a nationwide U.S. study that included additional ADT products not approved as formulary items at the UNMCCC during the period 2010-2021.[7] Specifically, Sun et al. (2021) study included patients who

received treatment with abarelix, flutamide, diethylstilbestrol diphosphate, and medroxyprogesterone acetate in addition to the ADT products approved as formulary items at the UNMCCC.[7]

Our study included more patients (n=101) treated with ADT in 2019 compared to other years (average of 73 patients) during the study period. This could be due to the recruitment of a new oncologist in 2019 by the UNMCCC which might have increased the volume of patients who benefited from the treatment with ADT.

Our study found more AI/AN/HN (19.5%) switched treatment from GnRH antagonist to GnRH agonist compared to NHW (13.4%), Hispanics (12.8%), AA (6.1%) and Asian (6.2%). Previous literature reported that treatment with GnRH antagonists might be warranted initially before switching to GnRH agonists to achieve a rapid state of castration among patients with worse PCa disease stage and poorer prognosis.[226] This might justify higher proportion of patients started on GnRH antagonists among AI/AN/HN patients compared to other racial and ethnic groups in our study. About 63% of AI/AN/HN had metastatic disease stage compared to Asian (50%), AA (49%), Hispanics (45.9%) and NHW (45.1%). In addition, 73.2% of AI/AN/HN had poorly differentiated prostate cancer (i.e., Gleason score >7) compared to AA (59.2%), Hispanics (56.6%) and NHW (56.2%).

Our study collected data on insurance coverage. This included data on private insurance coverage, public insurance coverage, private and public insurance coverage and self-pay or uninsured patients. 99.1% of NHW patients

had insurance coverage (i.e., private, public or both) compared to AI/AN/HN (97.6%), AA (95.9%) and Hispanics (93.8%) during the study period.

Previous literature reported higher percentage of uninsured Hispanics compared to NHW. Velasco-Mondragon et al. (2016) reported that Hispanics in the U.S. have less access to health services and utilize fewer preventive care services compared to other ethnic groups, with 30% reporting no health insurance before the implementation of the Affordable Care Act (ACA) in 2014, compared to 11% for NHW.[227] According to the national health survey of 2014, 7.1% of Hispanics lacked health insurance as compared to 0.5% of near-poor NHWs among persons aged 65 and over.[227,228]

The influence of healthcare insurance coverage status on PCa disease screening, diagnosis and treatment has been studied extensively.[77–79] In a large national observational population-based study that included 85,203 patients diagnosed with PCa, insured individuals were significantly less likely to present with advanced PCa disease stage and more likely to receive definitive treatment (i.e. surgery or radiation) compared with uninsured individuals.[79]

The percentage of unmarried men or men without a partner in the current study was significantly higher among AA (59.2%) compared to AI/AN/HN (46.3%), Hispanics (34.8%), Asian (31.3%) and NHW (30.3%), $p<0.001$. Previous literature showed that marital status is an independent predictor for PCa-specific mortality and overall mortality.[80] Unmarried men have a higher risk of PCa-specific mortality compared to married men of similar age, race, stage, and tumor grade.[80] Huang et al. (2017) also reported that marital status is an

independent prognostic factor for PCa. In addition, unmarried individuals had higher Gleason scores at diagnosis (i.e. poorer disease prognosis) compared to married men.[81] Consistent with the previous literature results, our findings suggest that higher proportion of unmarried AA and AI/AN/HN men was associated with worse PCa disease stage and prognosis compared to other racial and ethnic groups of PCa patients treated with ADT, $p<0.001$.

There was a significant difference in the proportions of patients with MSRF at baseline including diagnoses of diabetes mellitus II ($p<0.001$), obesity ($p=0.008$) and metabolic syndrome ($p<0.001$) across all racial and ethnic groups of PCa patients treated with ADT. The proportion of AI/AN/HN men with diabetes mellitus II (39%) and dyslipidemia (46.3%) was higher compared to other racial and ethnic groups of PCa patients treated with ADT. The prevalence of metabolic syndrome at baseline was also higher among AI/AN/HN and Hispanics (~41%) compared to other racial and ethnic groups. The percentage of Hispanic (43%) individuals with a BMI≥30 was significantly higher compared to AI/AN/HN (39%), AA (36.7%), NHW (29.5%) and Asian (25%), $p=0.008$.

These findings are consistent with prior literature results. Previous population-based studies found that metabolic syndrome is significantly more prevalent in Hispanics compared with NHW due to several environmental and genetic factors.[87–91] Ford et al. (2002) found a higher prevalence of metabolic syndrome among Hispanics (~32%) compared with NHW (~24%) due to high insulin resistance level and obesity.[87] Schumacher et al. (2008) found that the prevalence of metabolic syndrome among AI/AN men from the southwest U.S.

approached nearly 43% due to lifestyle and genetic factors.[92] This included low physical activity, diet rich in saturated fat and clustering of MSRF among this minority population. In a large multi-ethnic cohort study that included 6,751 individuals, the prevalence of metabolic syndrome was highest among Hispanics (29.6%) followed by NHW men (26.7%), AA (23.6%) and Chinese (20.1%) mainly due to high insulin resistance level and obesity.[89]

Discussion of The Proportion of Metabolic Syndrome and CVS Risk Factors Results During 12 months of follow up among PCa Patients Treated with ADT

Our study collected data on the proportion of metabolic syndrome and CVS risk factors during 12 months of follow-up post-ADT initiation. This included data on confirmed diagnoses of diabetes mellitus II, hypertension, dyslipidemia, AMI, coronary heart disease, cardiac arrest, heart failure, cardiac arrhythmias, stroke, and peripheral vascular disease.

Our study found a significant racial and ethnic difference in the prevalence of diabetes mellitus II (p<0.0001) across all racial and ethnic groups of PCa patients treated with ADT during 12 months of follow-up post-index date. Specifically, the proportion of AI/AN/HN (39%) with a documented diagnosis of diabetes mellitus II was higher compared with Hispanics (36.8%), AA (30.6%), NHW (15.6%) and Asian (12.5%) during 12 months of follow-up post-index date, p<0.0001. Consistent with our findings, previous population-based studies reported higher prevalence of diabetes mellitus II among AI/AN/HN and Hispanics compared to other racial and ethnic groups. [91,92,229] However,

compared to baseline data, there were only 9 additional patients of all races/ethnicities diagnosed with diabetes mellitus II following treatment with ADT.

We believe that longer treatment with ADT could increase the prevalence of diabetes mellitus and other MSRF across all races and ethnicities.[7,52–56] Lage et al. (2007) found a higher estimated relative risk for incident diabetes among patients treated with ADT (RR= 1.36, $p<0.001$) compared to patients not on ADT after adjusting for demographic characteristics, general health condition, comorbidities and use of statins.[186]

Similarly, Keating et al. (2006) evaluated risks of incident diabetes among 73,196 Medicare enrollees aged 66 years or older with PCa treated with ADT. Patients had an increased risk of incident diabetes as early as 1-4 months following GnRH agonist treatment initiation.[63]

Among patients with CVS risk factors, there were significant differences in the proportion of patients having heart arrhythmias ($p<0.01$) across racial and ethnic groups of PCa patients treated with ADT. NHW patients had higher proportion (14.7%) of cardiac arrhythmias compared to AI/AN/HN (12.2%), Hispanic (8.7%), Asian (6.3%) and AA (6.1%). These results are consistent with the previous literature findings. Patients of minority populations reported lower incidence and prevalence of cardiac arrhythmias compared to NHW.[230] However, they have a higher prevalence of established risk factors associated with developing cardiac arrhythmias. Lower prevalence of cardiac arrhythmias among minority populations could be attributed to lower level of awareness and detection of cardiac arrhythmias compared to NHW.[230]

Discussion of Overall MSRF Screening Rates Results among PCa Patients Treated with ADT

Among the entire study sample, only 12.3% (n=99) of patients were referred to a healthcare provider to screen for MSRF within 6 months of ADT initiation. 99.1% (n=796) of patients had a documented BP reading within 6 months of ADT initiation. 76.2% (n=612) of patients received HbA1C or blood glucose level assessment within 6 months of ADT initiation. 22.9% (n=184) of patients received a lipid profile screening (i.e., HDL-C and triglyceride level) within 6 months of ADT initiation. This resulted in a total of 189 patients (23.5%) who were either referred to healthcare provider to screen for MSRF and/or received all MSRF screening lab orders/tests within 6 months of ADT. This also indicates a large percentage (76.5%) not receiving guideline-concordant MSRF screening among PCa patients treated with ADT at the UNMCCC between 2010 and 2021.

Sun et al. (2021) reported an overall CVS risk factors screening rate of 68.1% among PCa patients started on ADT.[7] However, Sun et al. (2021) had an extended review period of 18 months (12 months baseline period and 6 months post-ADT initiation). Patients who received CVS risk factors screening during the 18 months review period were considered screened for CVS risk factors.[7] It was unclear why Sun et al. (2021) evaluated CVS risk factors up to 12 months before ADT.[7] The science advisory guideline publication indicated no clear indication for patients for whom ADT is believed to be beneficial to be referred or screened for MSRF or CVS before initiation of ADT.[54]

Sun et al. (2021) also had less stringent assessment criteria than our study, which might have increased the CVS risk factors assessment rate among PCa patients treated with ADT. Specifically, data on all components of metabolic syndrome were not collected (e.g., data on TG and HDL-C were not collected).[7]

Current practice at the UNMCCC mandates only PSA screening for patients receiving ADT. Previous population studies documented increased risk of MSRF with prolonged use of ADT.[60,62,63] Therefore, we believe appropriate interventions should be implemented to mitigate the deleterious long-term effects of ADT. This could include periodic follow-up assessment of MSRF every 3-6 months post-ADT initiation. We also believe that including a MSRF screening panel in the patient care plan for every patient started on ADT would substantially increase MSRF screening rates. Developing a referral system and implementing a MSRF standard order set would also improve MSRF screening and treatment among PCa patients treated with ADT. The patient care plan may also mandate that the attending healthcare provider refer patients with pre-existing MSRF or CVS risk factors to the patients' PCP for proper clinical evaluation of patient co-morbidities. These actions can potentially mitigate toxic metabolic and CVS complications associated with ADT. Prescribing physicians should weigh the benefits of ADT for treating that patient's PCa against the potential risks. In particular, when weighing the risks and benefits of ADT in patients with known metabolic syndrome or CVS disease, it is reasonable to consider carefully whether there is a well-established likely benefit of ADT in the specific clinical setting.

We found that 5.2% did not have any MSRF testing until 7-12 months post-ADT initiation (late MSRF screening). Of those, about 67% (n=28) were of minority populations compared to 33% (n=14) NHW. This indicates that minority populations are more likely to experience MSRF screening delays than NHW. Although we expected that extending MSRF screening window up to 12 months post-index date would substantially increase MSRF screening rate, this was not observed during the follow-up. Previous population-based studies limited their follow-up period up to 6 months post-ADT initiation in accordance with the 2010 science advisory guideline publication.[7,54,82] Sun et al. (2021) determined to use a 6 months follow-up window post-ADT initiation to screen for CVS risk factors.[7] Castro-Alonso et al. (2017) also determined to use a 3 months follow-up duration post-ADT initiation to evaluate CVS risk factors assessment.[82]

Our study also collected baseline metabolic syndrome diagnosis data to evaluate MSRF screening among this sub-group patient population. Our study found that among patients who met the NCEP ATP III criteria of metabolic syndrome at baseline (n=245), 38% (n=93) received guideline-concordant MSRF screening and 24% (n=59) were referred to a PCP to screen for MSRF within 6 months post-index date. These findings suggest higher MSRF screening rates among this subpopulation compared to the entire study population. However, rates of MSRF incomplete assessments in these patients remained high, with more than 60% not receiving guideline-concordant MSRF screening. In summary, we believe that treatment with ADT among patients with baseline

metabolic syndrome was not associated with substantial improvements in MSRF assessment.

Discussion of Overall MSRF Treatment Rates Results among PCa Patients Treated with ADT

Almost 8 in 10 patients (81.3%, n=653) in the study sample had a diagnosis indicating need for MSRF treatment, and among those, 76.9% (n=502) of patients received guideline-concordant MSRF treatment within 6 months of ADT initiation. The gap between MSRF screening and MSRF treatment rates might indicate that having pre-existing MSRF among PCa patients in the current study was associated with closer MSRF treatment regardless of ADT initiation. Despite acceptable treatment rates of MSRF, we believe it is still important to screen for MSRF especially among ADT patients without pre-existing MSRF to mitigate harmful effects of short and long-term ADT treatment. some Our study findings are consistent with previous literature findings. Sun et al. (2021) reported that 70.4% of PCa patients treated with ADT received guideline-concordant CVS risk factors treatment.[7]

About 42% (n=335) of patients in our sample had documented CVDs and a treatment indication for CVDs with no known contraindications. This included patients having at least one of the following diagnoses: AMI, coronary heart disease, peripheral vascular disease, cardiac arrest, cardiac arrhythmias, heart failure and stroke. Of those, 62% (n=208) received aspirin/antiplatelet therapy and statin treatment. The AHA and other expert organizations recommended statin and antiplatelet therapy (unless contraindicated) as secondary preventive measures for PCa patients treated with ADT.[54] This brings to our attention the

importance of enforcing medication reconciliation especially among patients with pre-existing MSRF or CVDs. We believe that medication reconciliation would optimize MSRF treatment among patients with CVDs.[231,232] Medication reconciliation can be enforced by integrating it in the patient care plan at the UNMCCC. We also found that 97.7% of hypertensive patients, 95.7% of diabetic patients and 87.6% of patients with dyslipidemia received treatment for these MSRFs within 6 months of ADT initiation. We believe that these high MSRFs treatment rates were associated with patients' pre-existing MSRF (i.e., patients were already taking medications to treat their MSRF prior treatment with ADT and carried out throughout the study follow-up period).

Discussion for Specific Aim 1

Specific Aim 1 was to determine racial/ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT.

Our study found that 26.8% (n=122) of NHW patients, 17.8% (n=43) of Hispanics, 30.6% (n=15) of AA, 14.6% (n=6) of AI/AN/HN and 18.8% (n=3) of Asian received MSRF screening within 6 months of ADT initiation.

Results found a significant difference in the proportion of patients receiving MSRF screening across all racial and ethnic groups of PCa patients treated with ADT, p=0.032. Compared with NHW patients, Hispanic patients had lower MSRF screening rate, p=0.008. Similarly, AA men had higher MSRF screening rate compared with Hispanic patients, p=0.04. These findings suggest an ethnic health disparity in MSRF screening among PCa patients treated with ADT. This healthcare disparity in MSRF screening could be attributed to higher

proportion of uninsured/self-pay patients among Hispanics (6.2%) compared to NHW (0.9%), $p<0.01$ which could have influenced differential access to MSRF screening or preventive care services. Velasco-Mondragon et al. (2016) reported that Hispanics in the U.S. have less access to health services and utilize fewer preventive care services compared to other ethnic groups.[227] However, we believe other factors reported by other studies *(but not directly related to ADT)* could have contributed to lower MSRF screening among Hispanic individuals compared to NHW men. This includes perceived awareness of MSRF complications among Hispanic individuals compared to NHW and healthcare providers' behavior and attitude toward MSRF screening among Hispanic individuals.[17–19,24,25,27–29,31]

The finding of significant differences in MSRF screening rates between AA and Hispanics is consistent with the previous literature results in other health screenings *(not directly related to ADT). For example,* Brown et al. (2001) found that AA (69.9%) had higher cholesterol screening compared to Hispanic (60%) individuals.[217] Similarly, Wilson et al. (2010) reported that physician-ordered cholesterol screening was lower in Hispanics (30.3%) compared to AA (35.4%).[216] It is unclear why AA received greater MSRF screening than Hispanic men in our study. Perhaps, since AA (69%) had a more aggressive PCa disease stage and poorer prognosis than Hispanic (59%) men; this may have prompted more MSRF screening among AA men.

We expected to find significant differences in the proportion of AI/AN/HN who received guideline-concordant MSRF screening while on ADT as they had

significantly higher proportion of diabetes mellitus II and dyslipidemia diagnoses compared to other racial and ethnic groups. However, the small sample size in this patient population may have contributed to greater variance and therefore less likely to find statistical significance in this group.

In summary, this study is the first to explore racial/ethnic disparities in the receipt of MSRF screening among PCa patients treated with ADT among an ethnically diverse population in a southwestern state (NM) in the US. Previous population-based observational studies have not reported the impact of race/ethnicity on MSRF and treatment in PCa patients treated with ADT.[7,82,83] The previous studies assessed different outcome measures, including risks of AMI, stroke, pulmonary embolism and statin medications, among PCa patients treated with ADT.[7,82,83]

Discussion for Specific Aim 2

Specific Aim 2 was to determine racial/ethnic differences in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT.

Among the study sample, 81.3% (n=653) had a diagnosis indicating need for MSRF treatment. Among those, 80.3% (n=298) NHW patients, 71.6% (n=144) Hispanics, 67.5% (n=27) AA, 83.9% (n=26) AI/AN/HN and 70% (n=7) Asian received MSRF treatment within 6 months of ADT initiation.

Results showed no significant racial/ethnic difference in the proportion of patients receiving MSRF treatment among PCa patients treated with ADT. However, we found a statistically significant difference in MSRF treatment between NHW and Hispanic patients, p=0.0214.

Although Hispanic men had a higher proportion of MSRF (41.3%) and obesity (43%) compared to NHW (23.5% and 29.5% respectively), this was not reflected in higher MSRF treatment rates among Hispanics compared to NHW. We found a larger proportion of NHW (90%) who received guideline-concordant treatment for dyslipidemia compared to Hispanic (79%) individuals. More NHW (65%) also received guideline-concordant treatment for CVDs compared to Hispanics (57%). These differences in treatment rates could be attributed to significant lower MSRF screening rates found in the current study among Hispanics compared to NHW.

The proportion of AI/AN/HN (83.9%) who received guideline-concordant MSRF treatment was higher than other racial and ethnic groups of PCa patients treated with ADT. AI/AN/HN had a significantly higher proportion of patients with diabetes mellitus II and dyslipidemia than other racial and ethnic groups. They also had worse PCa disease stage and prognosis compared to other racial and ethnic groups. However, MSRF treatment rate among AI/AN/HN (n=31) compared with other racial and ethnic groups did not meet the minimum required sample size.

Discussion for Specific Aim 3

Specific Aim 3 was to determine longitudinal changes in MSRF screening and treatment rates between 2010 and 2021 across different racial/ethnic groups of PCa patients treated with ADT.

Discussion of Comprehensive MSRF Screening Trends (2010-2021):

We found that the average rate of MSRF screening between 2010-2021 among PCa patients treated with ADT is 23.5%. Adherence to the 2010 science advisory guideline publication would optimize MSRF screening rate.[54] Sun et al. (2021) reported an overall CVS risk factors screening rate of 68.1% among PCa patients started on ADT.[7] However, Sun et al. (2021) had an extended review period of 18 months (12 months baseline period and 6 months post-ADT initiation). Patients who received CVS risk factors screening during 18 months of follow-up were considered screened for CVS risk factors.[7] Sun et al. (2021) also had less stringent assessment criteria compared to our study which might have increased their overall CVS risk factors screening rate. Specifically, data on all components of metabolic syndrome were not collected (e.g., data on TG and HDL-C were not collected).[7]

Although we expected a steady increase in MSRF screening rates after 2010 and throughout the study period because of anticipated raised awareness about the science advisory guideline publication, this was not reflected in MSRF screening rates trends in the current study. Conversely, MSRF screening rates did not show a clear pattern and varied from 13.9% to 35.6% throughout the study period and did not appear to show an increasing upward trend as the guidelines became more widely distributed. Although the NCCN clinical practice guideline of PCa does provide recommendations or guidance to treating oncologists on how and when MSRF/CVS risk factor should be initiated among PCa patients treated with ADT, the recommendations are limited to one

paragraph and are not prominently highlighted as in the guideline. We believe the way the recommendations are presented in the NCCN guideline could have resulted in reduced level of knowledge and awareness about MSRF screening among treating oncologists. We believe that emphasizing the importance of MSRF screening by the NCCN clinical practice guideline would optimize MSRF screening among PCa patients treated with ADT.

Although our study included more patients (n=101) treated with ADT in 2019 compared to other years (average of 73 patients) during the study period, we noticed a significant drop in MSRF screening in 2019. We believe that this drop could be caused by the lower proportion of patients with confirmed criteria of metabolic syndrome at baseline in 2019 (21%) compared to 2018 (26%) and 2020 (27%). We believe that the sharp rise in the overall MSRF screening rate in 2015 (35.6%) is driven by more Hispanic patients (38.5%) screened for MSRF compared to other years during the study period. We also noticed a significant drop in MSRF screening rate (0%) in 2018 among Hispanic individuals (i.e., none of the 19 Hispanic individuals in 2018 received MSRF screening within 6 months post-ADT initiation). However, of the 19 Hispanic individuals with PCa and treated with ADT in 2018, 4 (~21%) received late MSRF screening (i.e., 7-12 months post-ADT initiation). As per our earlier discussion, among patients who received delayed MSRF screening, nearly 67% were of minority populations, raising concerns about under-detection and underdiagnoses of MSRF compared to NHW.

Our sample included small number of AI/AN/HN, AA and Asian populations (n=106) which influenced MSRF screening patterns throughout the study period. Therefore, the spikes depicted in figures 13-15 should be interpreted cautiously because of the sample size of these patient populations in the current study.

Discussion of MSRF Treatment Trends (2010-2021):

The average rate of MSRF treatment among PCa patients treated with ADT was 76.9% and varied from 71.8% to 82.8% throughout the study period.

Sun et al. (2021) reported comparable overall CVS risk factors treatment rate of 70.4% between 2010 and 2017 among PCa patients treated with ADT.[7] Overall, we noticed that the rate of MSRF treatment in our study dropped to its lowest (71.8%) in 2019. We believe that the sharp drop in MSRF treatment rate in 2019 could be caused by the lower proportion of patients with confirmed diagnostic criteria of metabolic syndrome at baseline in 2019 (21%) compared to 2018 (26%) and 2020 (27%).

Rates of MSRF treatment among NHW men averaged 80% during the study period. Although slight variations were noticed in MSRF treatment rates among NHW men throughout the study, MSRF treatment rates were generally considered consistent. Hispanic men had a significantly lower mean of MSRF treatment rate (71.6%) compared to NHW men (80.3%) throughout the study period, $p<0.05$. Similarly, although slight variations were noticed throughout follow-up, treatment rates were generally considered consistent among Hispanic

individuals. We believe that lower MSRF screening rates among Hispanic individuals contributed to lower MSRF treatment rates compared to NHW.

We believe that small number of AI/AN/HN, AA and Asian populations (n=106) we had in the current study influenced MSRF treatment patterns throughout the study period. Nearly 20% (n=21) of these minority populations received guideline-concordant MSRF treatment between 2010 and 2021. Therefore, spikes illustrated in figures 21-23 should be interpreted with caution because of the small sample size these patient populations had in the current study.

Discussion for Specific Aim 4

Specific Aim 4 was to identify patient and healthcare provider factors influencing the receipt of MSRF screening among racial/ethnic groups of PCa patients treated with ADT.

Our findings revealed that Hispanic men (p=0.0001), AI/AN/HN (p=0.007), and Asian (p=0.04) had significantly lower odds of having MSRF screening compared to NHW. In addition, patients with dyslipidemia at baseline also had significantly higher odds of having MSRF screening than patients without a diagnosis of dyslipidemia at baseline (p<0.0001).

Our study is the first to evaluate patient and healthcare provider factors influencing MSRF screening among PCa patients treated with ADT. We believe this contributes to the current knowledge of PCa health disparities and MSRF screening among PCa patients treated with ADT. Previous population-based studies mainly focused on evaluating racial and ethnic differences in screening

certain metabolic risk factors like cholesterol screening [216,217] and diabetes screening [220,221]. Although Sun et al. (2021) shared many of our study objectives, it evaluated CVS outcomes. It also did not primarily aim to evaluate the impact of race/ethnicity on CVS risk factors assessment or assessed factors influencing MSRF screening among PCa patients treated with ADT.[7] We believe it is of great importance to evaluate patient and healthcare provider factors that predict MSRF screening because it will help us design and implement interventions tailored to optimize MSRF screening. For example, we found that having a diagnosis of dyslipidemia at baseline would significantly predict MSRF screening. Therefore, a lipid profile screening panel in a standard order set for any patient started on ADT would substantially optimize MSRF screening and mitigate some of the toxic cardiometabolic complications associated with short and long-term treatment with ADT.

Our study also found that among variables with significant interaction terms, oncologists with >20 years of experience had significantly higher odds of providing MSRF screening than oncologists with <10 years of experience (p=0.006). We noticed that this was mostly driven by one oncologist with >20 years of experience and a large interest in metabolic syndrome disease screening. We also believe that oncologists with more than 20 years of experience encountered more cases of cardiometabolic complications associated with ADT treatment compared to oncologists with <10 years of experience. Therefore, this could have raised their awareness about MSRF associated with ADT, which could have prompted higher MSRF screening among PCa patients

treated with ADT. Oncologists with <10 years of experience might also not be aware or have lower awareness about the 2010 science advisory guideline publication (i.e., there were not in practice or fresh specialists when the guideline was published) compared to oncologists with >20 years of experience.

Our study is the first to evaluate the impact of healthcare provider specialty and years of experience on MSRF screening among PCa patients treated with ADT. Previous population-based studies evaluated the impact of healthcare provider characteristics on the screening of different measures or health conditions. [73,209] Schrager et al. (2021) evaluated patient and healthcare provider characteristics that predict breast cancer screening in 4 different primary care settings at the University of Wisconsin-Madison. It was reported that of 7 patients seen by clinicians with <10 years of experience, 4 (57%) received mammograms. This is compared to 77.2% (17 of 22), and 80% (8 of 10) of patients visiting clinicians with 10–20, and >30 years of experience, respectively. Authors found that clinicians' years of experience was a significant predictor of breast cancer screening in the adjusted model, $p<0.018$.[209] Edlefsen et al. (1999) also reported that female physicians with ≥20 years of experience were more likely to report ordering PSA screening (22.2%) compared to female physicians with ≤10 years of experience.[73]

Our study also found that healthcare providers of "other" specialties (cardiology, endocrinology, neurology, emergency medicine, physician assistant, nephrology, and pharmacist clinician) with 10-20 years of experience had lower odds to provide MSRF screening compared to "other" healthcare providers with

<10 years of experience, p<0.03. Williams et al. (2018) evaluated incidence and prevalence of metabolic syndrome using ICD-9/ICD-10 diagnostic codes among active members of the armed forces between 2002 and 2017. They reported steady increase in metabolic syndrome annual prevalence counts with slight variations throughout the study period.[233] Increased prevalence counts of metabolic syndrome in recent years might indicate that healthcare providers' level of awareness about metabolic syndrome increased. Therefore, healthcare providers of "other" specialties with <10 years of experience could have been exposed to more advanced knowledge and training level about metabolic syndrome compared to "other" specialties with >10 years of experience.

In summary, our conceptual model "integration of targeted health interventions into health systems" was useful in examining factors associated with MSRF screening at the patient and healthcare provider levels.[71] It allowed us to understand and assess factors that predict the adoption and diffusion of MSRF screening and the extent to which it could be integrated into the UNMCCC healthcare system functions.[71] The model proposes that the adoption system which refers to institutions and key actors of the healthcare system may have different perceptions of the benefits and risks of an innovation and therefore occupy distinct roles and positions in the adoption system.[71]

Using this conceptual framework, we explored, understood and evaluated patient and healthcare providers factors that might influence MSRF screening. Supported by the literature, we determined to evaluate whether healthcare provider gender, specialty and years of experience could predict MSRF

screening among PCa patients treated with ADT. We also evaluated whether patient health insurance coverage status, age, race/ethnicity, marital status, number of co-morbidities, having MSRF at baseline, stage of PCa, and Gleason score influenced the receipt of MSRF screening among PCa patients treated with ADT.

Study Limitations

Our study had several potential limitations. First, our study used a retrospective observational cohort design to answer specific research aims. Although causal inferences cannot be drawn from our study due to study design limitation, our study utilized real-world data to answer our specific aims. Real-world data reflects data collected from clinical practice with high external validity compared to experimental studies.[234,235] Findings of experimental studies cannot be generalized to population at large due to contrived eligibility criteria.[235] Also, retrospective observational study designs are relatively inexpensive compared to experimental or prospective study designs.[235]

Second, although our study collected data from EMRs, the validity of our study results is dependent upon documentation habits of healthcare providers and current workflow at the UNMCCC which may impact EMR-derived data.[236] However, we believe that using both Cerner® millennium and Mosaiq® Oncology EMRs improved internal validity of the study. Data missing or collected on certain variables from Cerner EMR® were verified using Mosaiq® EMR and vice versa.

Third, we believe MSRF screening rates in the current study may have been negatively influenced by the lack of a structured referral system at the UNM

health system. Referral to healthcare providers to screen for MSRF was determined based on clinic visits notes. Current communication system at the UNM HSC would allow sending messages and communicating patient related information between healthcare providers. However, these communications are not documented in patients' charts. Healthcare providers also verbally inform and educate patients about risks of MSRF associated with ADT, and the importance to follow up with PCP to screen for MSRF. We believe that having a structured referral mechanism and system would facilitate routine referral for screening for MSRF.

Fourth, although the UNMCCC Mosaiq® Oncology data analysis team identified patients that met the study inclusion criteria, data extraction of study variables was undertaken by one investigator which may have resulted in possible data extraction errors and subsequently impacted results. However, we believe that extracting data systematically and consistently by one investigator may have minimized potential errors and inconsistencies that could have occurred if more than one investigator was involved in the data extraction process. The primary investigator also conducted a pilot study of 100 patients to evaluate and refine the data extraction process.

Fifth, we believe that our study findings are generalizable to the study population and setting: one cancer center in New Mexico. However, we believe that conducting this study in an ethnically diverse population in the state of NM added a unique value and contribution to the current knowledge of PCa health disparities, MSRF screening and treatment with ADT.

Sixth, our study included small number of AI/AN/HN (5.1%), AA (6.1%) and Asian (2%) populations. However, study participants were identified based on pre-defined inclusion and exclusion criteria. Therefore, future studies could be conducted in other or geographical areas or states where additional high concentrations of minority populations exist.

Seventh, our study excluded patients not treated for primary care within the UNM health system between 2010 and 2021. However, excluding those patients allowed us to properly evaluate MSRF screening and primary care treatment among our patient population. Conversely, patients treated for primary care outside the UNM health system would have been nearly impossible to accomplish and the current study likely would not be able to capture MSRF screening and treatment.

Eighth, our study was restricted to ADT products approved as formulary items at the UNMCCC during 2010-2021. Although the UNMCCC pharmacy formulary included most of ADT products approved by the U.S. FDA to treat patients with PCa, it did not include Relugolix (Orgovyx®), an oral GnRH antagonist therapy that the FDA approved in 2020 to treat patients with advanced PCa.[237] Being an oral treatment, it may have increased the volume of patients who might choose or benefit from this additional therapy.

Finally, since the UNMCCC and UNMHSC websites lacks information about healthcare providers who left the center, our study used publicly available information and LinkedIn to obtain healthcare providers' years of experience post-board certification or board-eligibility. However, we believe that using

multiple sources provided us the with the most reliable estimate for healthcare providers' years of experience.

Study Strengths

Our study had several strengths. First, our study was the first to evaluate MSRF screening and treatment among PCa patients treated with ADT. Assessing racial and ethnic disparities in the receipt of MSRF screening and treatment provided us with information on whether healthcare providers are aware of and following 2010 (AHA, AUA and ACS) science advisory guideline publication [54], and FDA drug safety communication related to GnRH agonist use.[69] Our study also provided valuable information on whether there are racial and ethnic differences in the proportion of patients receiving MSRF screening among PCa patients treated with ADT. Adherence to the science advisory guideline could reduce risks of developing CVDs and mortality among all racial and ethnic groups, specifically among minority populations.

Second, our study is the first to evaluate longitudinal changes in MSRF screening and treatment among PCa patients treated with ADT over 10 years. This provided us with valuable evidence about the rate of physicians' awareness, adoption and adherence to the evidence-based recommendations between 2010 and 2021.[54]

Third, our study is the first to assess patient and healthcare provider factors that predict MSRF screening among PCa patients treated with ADT. This helped us provide recommendations to implement necessary changes to optimize MSRF screening and treatment. Our study findings provided valuable

information and contributed to the current knowledge of MSRF screening and treatment among PCa patients treated with ADT.

Fourth, our study is the first to report racial and ethnic differences in MSRF screening and treatment among an ethnically diverse population in a southwestern state (NM). NM has the highest proportion of AI individuals and Hispanics of any state (~49% Hispanics, ~37% NHW, 11% AI).[38] The Hispanic population grew in NM from 953,403 (46.3% of the entire NM population) in 2010 to 1.043 million (49.3%) in 2021.[84,85] Similarly, the population of AI/AN grew (yet at a lower growth rate) from 193,222 (9.3% of the entire NM population) in 2010 to 232,747 (11%) in 2021.[84,85] This helped us better understand patients' interaction with the healthcare system in the state of NM and provide recommendations to optimize MSRF screening and treatment.

Lastly, our study utilized real-world data from the UNMCCC data analysis team. This allowed us to assess guideline-concordant MSRF screening and treatment among PCa patients treated in regular clinical practice, reflecting current practice and adherence to national guidelines and recommendations.

Implications for Future Research

Future studies can adopt a prospective randomized controlled trial (RCT) to assess racial and ethnic differences in MSRF screening among PCa patients treated with ADT. PCa patients started on ADT can be randomized into two groups or clinics that treat PCa at the UNMCCC. One clinic will adopt a MSRF screening panel (intervention), and one will continue current practice (control). Outcomes related to MSRF can be evaluated at 3, 6 and 12-months post

treatment with ADT. Despite RCTs being expensive compared to observational cohort study designs, causal inferences can be drawn from study findings.[238] Investigators would know whether or not the intervention “MSRF screening panel” improved MSRF screening and identification rates during follow-up period.

Future research can also adopt a prospective observational study design where MSRF are assessed at 3-, 6- and 12-months post-ADT among PCa patients. Prospective observational study designs are less prone to bias compared to retrospective observational studies. They can also provide better quality of data on the primary exposure and also on confounding variables.[239]

Future studies could improve the study findings' generalizability by expanding the scope of the study to include a nationally representative patient population. For example, future research can utilize the U.S. Veterans Health Administration database to assess MSRF risk factor screening and treatment among PCa patients treated with ADT. This would allow the inclusion of more AI/AN/HN, AA and Asian populations.

Future research could also evaluate healthcare providers' MSRF screening behaviors among PCa patients treated with ADT. Guided by the PRECEDE theoretical framework, factors associated with healthcare providers screening behaviors can be analyzed and understood.[240] This framework provides a structure whereby the factors that influence behavior in educational diagnosis such as predisposing factors (e.g., knowledge, beliefs, personal preferences, existing skills, attitude), reinforcing factors (e.g., social support, economic rewards and changing social norms), and enabling factors (e.g.,

availability of resources and skills) are determined. The model starts with the desired outcomes and goes backward to cover seven successive stages of planning, implementation, and advanced assessment to show how social diagnosis, epidemiology, and behaviors lead to a clear understanding of peoples' needs and aspirations.[241]

Understanding healthcare providers' attitudes and behavior would facilitate designing appropriate interventions that optimize MSRF screening and treatment. Interventions could include integrating popup reminders using EMRs that remind healthcare providers to screen for MSRF among patients started on ADT. This could also include implementing a referral system that mandate patients started on ADT to be evaluated periodically by the PCP for MSRF. Patients started on ADT can be provided with educational materials that aim to raise their awareness about risks of metabolic syndrome and CVS complications associated with ADT. This would mitigate some of the harmful effects associated with treatment with ADT. Pharmacists' clinicians can also monitor and order a MSRF screening panel for patients started on ADT. In a recent study that evaluated the role of pharmacists in metabolic syndrome screening, management and prevention, it was reported that pharmacists had a positive role in ordering and communicating metabolic syndrome screening panel results to physicians for further follow-up. Pharmacists' role in screening for metabolic syndrome was effective for early identification and management.[242]

Implications and Recommendations

We believe appropriate interventions should be designed and implemented to optimize MSRF screening, identification and treatment among patients treated with ADT. This could include: (1) developing and integrating MSRF screening panel in the UNMCCC patient care plan, (2) including MSRF screening panel in an electronic standard order set would allow automatic ordering of appropriate metabolic screening tests for patients started on ADT, (3) developing and integrating electronic popup reminders to remind healthcare providers about MSRF screening if the patient was started on ADT, (4) implementing a referral system that mandates periodic follow up of MSRF and CVS complications every 3-6 months by the PCP for patients started on ADT, (5) involving pharmacists in ordering and monitoring of MSRF screening panel and cardiometabolic complications, respectively. This would take off some of the burden healthcare providers have (e.g., time constraints), (6) enforcing the importance of conducting medication reconciliation especially among patients with pre-existing metabolic and CVS complications would optimize MSRF treatment, (7) developing and distributing educational materials about the importance of MSRF screening to patients started on ADT, (8) payers can take role in providing incentives for patients who do periodic MSRF screening. This can include reducing patient premiums or copayments. Although this can create some financial burden to payers, it could be potentially cost-effective on the long-term because risks of hospitalizations, morbidity and mortality among patients treated with ADT would be expected to decline.

These interventions should mitigate the harmful metabolic complications associated with ADT. This may further help control total healthcare costs leading to better allocation of limited healthcare resources among PCa patients. On a broader level, collaborative efforts are needed from the UNMCCC administrators, healthcare professionals, and public health policy makers to promote campaigns that improve MSRF surveillance and management among all patients and particularly among minority populations treated with ADT.

Conclusions

Racial and ethnic health disparities exist in MSRF screening and treatment among PCa patients treated with ADT. Our study found that Hispanics, AI/AN/HN and Asian populations had significantly lower odds of having MSRF screening compared to NHW, after adjusting for several clinical and socio-economic variables. Hispanics had also significantly less MSRF treatment rate compared to NHW. This raises concerns about the lower screening and treatment of MSRF in these minority populations.

Health disparities is a major public health problem and achieving health equity and improving the health of all U.S. population groups should be a top priority to healthcare providers, public health advocates and healthcare decision makers. Implementing effective strategies and public health programs for reducing health disparities would minimize morbidity, mortality and associated costs. Multidisciplinary efforts and public health strategies developed and implemented to reduce health disparities should be tailored to reach more communities. Screening awareness of MSRF and education as well as programs

tailored to changing behavior among minority populations, high-risk patients and healthcare providers for MSRF would optimize MSRF screening rates. Behavioral changes should be supported by structural mechanisms and polices that facilitate them, such as implementing a referral system to screen for MSRF periodically among PCa patients treated with ADT. We believe the proposed recommendations in the current study to optimize MSRF screening along with a system that promotes health equity would reduce the health disparity gap between minority populations and NHW patients.

Our study also found that average rate of MSRF screening among PCa patients treated with ADT was (23.5%). Adherence to the 2010 science advisory guideline publication would optimize MSRF screening rate. This raises concerns about whether healthcare providers are aware of and following the 2010 science advisory guideline publication.[54]

Our study found that 76.9% of patients with a diagnosed MSRF received guideline-concordant MSRF treatment within 6 months of ADT initiation. The gap between MSRF screening and MSRF treatment rates might indicate that having pre-existing MSRF among PCa patients in the current study was associated with closer MSRF treatment regardless of ADT initiation.

Overall, this retrospective observational study of more than 800 PCa patients treated with ADT over the last decade suggests low rate of MSRF screening. Therefore, closer clinical attention and education, as well as developing and implementing innovative tools and interventions to optimize

MSRF screening and treatment would be warranted to mitigate the harmful short and long-term effects of ADT.

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Appendix A. Up-to-date Online Material Permission to Use

Wolters Kluwer

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Signed: 

Name: Yazan K. Barqawi

Company: University of New Mexico, College of Pharmacy

Address: 10001 Coors Bypass NW, # 1512

City Albuquerque State NM Zip 87114

Phone: 505-900-6004 Fax:

PERMISSION GRANTED
(To be completed by UpToDate)
Adelaide Neville, Permissions Associate
Printed Name and Title
Adelaide Neville
Signature
Date: August 13, 2021

Appendix B. PubMed MeSH Database Entry Terms*

Prostate Cancer	**Metabolic Syndrome**	**Ethnic/Ethnology**	**Healthcare Disparities**	**Hispanics**	**African American**	**American Indians**
Prostate Neoplasms Neoplasms, Prostate Neoplasm, Prostate Prostate Neoplasm Neoplasms, Prostatic Neoplasm, Prostatic Prostatic Neoplasm Prostate Cancer Cancer, Prostate Cancers, Prostate Cancer of the Prostate Prostatic Cancer Cancer, Prostatic Cancers, Prostatic Cancer of Prostate	Metabolic Syndromes Syndrome, Metabolic Syndromes, Metabolic Metabolic Syndrome X Insulin Resistance Syndrome X Syndrome X, Metabolic Syndrome X, Insulin Resistance Metabolic X Syndrome Dysmetabolic Syndrome X Metabolic Cardiovascular Syndrome Cardiovascular Syndrome, Metabolic Reaven Syndrome X Syndrome X, Dysmetabolic Syndrome, Metabolic X Syndrome, Metabolic Cardiovascular Syndromes, Metabolic Syndrome, Metabolic Cardiovascular Cardiometabolic Syndrome Cardiometabolic Syndromes Syndrome, Cardiometabolic Cardiometabolic Syndromes Syndrome, Cardiometabolic Syndromes, Obesity Syndromes, Cardiometabolic Cardiovascular Syndrome, Metabolic Syndromes, Obesity Syndrome	Ethnic Group Ethnicity Nationality Nationalities Primitive Societies Primitive Society Societies, Primitive Society, Primitive	Disparity, Healthcare Health Care Inequalities Health Care Inequality Inequalities, Health Care Inequality, Health Care Healthcare Disparity Healthcare Inequalities Healthcare Inequality Inequality, Healthcare Inequalities, Healthcare Disparities, Healthcare Health Care Disparities Disparities, Health Care Disparity, Health Care Health Care Disparity	American, Hispanic Americans, Hispanic Hispanic American Spanish Americans Americans, Spanish Spanish American Puerto Ricans Puerto Rican Latinos Latino Cuban Americans Americans, Cuban Hispanics Latinas Latina	African Americans Afro American Afro-American Afro Americans American, African African American African American Blacks	American Native Native, American Natives, American Indians, American American Indian American Indians Native Americans American, Native Native American

Appendix B. PubMed MeSH Database Entry Terms*

Caucasians	**Cancer Screening**
Whites	Cancer Early Detection
White Caucasoid	Cancer Screening
Caucasoid Races	Screening, Cancer
Caucasoid Race	Cancer Screening Tests
Race, Caucasoid	Screening Tests, Cancer
Races, Caucasoid	Screening Test, Cancer
Caucasian Race	Cancer Early Diagnosis
Caucasian Races	Early Diagnosis of Cancer
Race(s), Caucasian	

* PubMed MeSH Database does not include terms for race, racial group, Alaskan Natives, and androgen deprivation therapy or ADT. Therefore, Only “All” terms were used to identify relevant articles associated with these terms.

Appendix C. G Power Program Output - Sample Size Determination

Small Effect Size (-5%) & Event Rates (70%, 75% & 80% respectively)

z tests - Logistic regression

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.26
	Pr(Y=1|X=1) H0	=	0.65
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**2690**
	Actual power	=	0.8000275

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.56
	Pr(Y=1|X=1) H0	=	0.60
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**707**
	Actual power	=	0.8003442

Options:	Large sample z-Test, Demidenko (2007) with var core		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.90
	Pr(Y=1|X=1) H0	=	0.55
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**333**
	Actual power	=	0.8006319

Medium Effect Size (-10%) & Event Rates (70%, 75% & 80% respectively)

z tests - Logistic regression

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.29
	Pr(Y=1|X=1) H0	=	0.70
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**2443**
	Actual power	=	0.8001549

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.62
	Pr(Y=1|X=1) H0	=	0.65
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**654**
	Actual power	=	0.8005260

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	2.00
	Pr(Y=1|X=1) H0	=	0.60
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**308**
	Actual power	=	0.8010639

Large Effect Size (-15%) & Event Rates (70%, 75% & 80% respectively)

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.33
	Pr(Y=1|X=1) H0	=	0.75
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**2229**
	Actual power	=	0.8000898

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	1.71
	Pr(Y=1|X=1) H0	=	0.70
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**596**
	Actual power	=	0.8004720

Options:	Large sample z-Test, Demidenko (2007) with var corr		
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Odds ratio	=	2.15
	Pr(Y=1|X=1) H0	=	0.65
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	R^2 other X	=	0
	X distribution	=	Binomial
	X parm π	=	0.5
Output:	Critical z	=	1.9599640
	Total sample size	=	**281**
	Actual power	=	0.8002724

Appendix D. IRB Original Approval Letter and Study Extension

HEALTH SCIENCES

Human Research Protections Program

August 16, 2021
Neda Hashemi
NHashemi@salud.unm.edu

Dear Neda Hashemi:

On 8/16/2021, the HRRC reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	INST CR2103: Prognostic Factors in Prostate Cancer Patients of New Mexico
Investigator:	Neda Hashemi
Study ID:	21-282
Submission ID:	21-282
IND, IDE, or HDE:	None
Submission Summary:	Initial Study
Documents Approved:	• INST CR2103 Protocol - PCa v1_08.07.2021.pdf
Review Category:	EXPEDITED: CATEGORIES (5) Data, documents, records, or specimens
Determinations/Waivers:	Waived the requirement for informed Consent. HIPAA Authorization Addendum waived.
Submission Approval Date:	8/16/2021
Approval End Date:	8/15/2022
Effective Date:	8/16/2021

The HRRC approved the study from 8/16/2021 to 8/15/2022 inclusive. If modifications were required to secure approval, the effective date will be later than the approval date. The "Effective Date" 8/16/2021 is the date the HRRC approved your modifications and, in all cases, represents the date study activities may begin.

Before 8/15/2022 or within 45 days of study closure, whichever is earlier, you are required to submit a continuing review. You may submit a continuing review by navigating to the active study and clicking the "Create Modification/CR" button.

If the study meets the definition of an NIH Clinical Trial, the study must be registered in the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database.

This determination applies only to the activities described in this submission and does not apply should you make any changes to these documents. If changes are being considered these must be submitted for review in a study modification to the HRRC for a determination prior to implementation. If there are questions about whether HRRC review is needed, contact the HRPO before implementing changes without approval. A change in the research may disqualify this research from the current review category. You may submit a modification by navigating to the active study and clicking the "Create Modification/CR" button.

If your submission indicates you will translate materials post-approval of English materials, you may not recruit or enroll participants in another language, until all translated materials are reviewed and approved.

In conducting this study, you are required to follow the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library.

Sincerely,

Walter Dehority, M.D.

Walter Dehority, MD
HRRC Chair

Abbreviated Investigator Responsibilities

NOTE: For a full unabbreviated version of the **Investigator Manual**, please visit the HRPO website at https://hsc.unm.edu/research/hrpo/.

What will happen after HRRC review?

The HRPO will provide you with a written decision indicating that the HRRC has approved the Human Research, requires modifications to secure approval, or has disapproved the Human Research.

- If the HRRC has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. HRRC approval is usually good for a limited period of time which is noted in the approval letter.
- If the HRRC requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the HRRC. If all requested modifications are made, the HRRC will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the HRRC.
- If the HRRC defers the Human Research: The HRRC will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give

you an opportunity to respond in writing. In most cases if the HRRC's reasons for the deferral are addressed in a modification, the Human Research can be approved

- If the HRRC disapproves the Human Research: The HRRC will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the HRRC directly at an HRRC meeting.

What are my obligations after HRRC approval?

1. Do not start Human Research activities until you have the final HRRC approval letter.
2. Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
3. Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
    a. Delegate responsibility to the research staff in accordance with the staff's training and qualifications.
    b. Assure that all procedures associated with the research are performed, with the appropriate level of supervision, only by individuals who are licensed or otherwise qualified to perform them under the laws of New Mexico and policies of The University of New Mexico Health Sciences Center.
    c. Monitor the research study and perform quality management activities to ensure the protection of participants and the quality of the research data.
4. Obtain the legally effective informed consent from human participants or their representatives, using only the currently approved informed consent documents, and provide a copy to the participant, if applicable. a) Ensure that only HRRC-approved investigators obtain informed consent from potential participants.
5. If unavailable to conduct the research personally, as when on sabbatical leave or vacation, arrange for another HRRC-approved investigator on the study to assume direct responsibility or notify the HRRC of alternate arrangements.
6. Maintain accurate and complete research records, including but not limited to, original signed informed consent and authorization documents, and retain these records according to HRRC policy and the applicable regulatory retention terms.
7. Fully inform the HRRC of all locations in which human participants will be recruited for this project and obtain and maintain current HRRC approvals/letters of cooperation when applicable.
8. Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
9. Update the HRRC office with any changes to the list of study personnel.

10. Personally conduct or supervise the Human Research.
    a. Conduct the Human Research in accordance with the relevant current protocol as approved by the HRRC.
    b. When required by the HRRC, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the HRRC.
    c. Do not modify the Human Research without prior HRRC review and approval unless necessary to eliminate apparent immediate hazards to participants.
    d. Protect the rights, safety, and welfare of participants involved in the research.
11. Submit to the HRRC:
    a. Proposed modifications as described in this manual. (See "How do I submit a modification?")
    b. A continuing review application as requested in the approval letter. (See "How do I submit continuing review?"
    c. A continuing review application when the Human Research is closed. (See "How Do I Close Out a Study?")
12. Report any of the information items listed in Appendix A-1 to the HRRC within five business days.
13. Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
14. Do not accept or provide payments to professionals in exchange for referrals of potential participants ("finder's fees.")
15. Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
16. See additional requirements of various federal agencies in Appendix A-2 through A-9 of the Investigator Manual. These represent additional requirements and do no override the baseline requirements of this section.

If the HRRC directs or your study is selected for an onsite post-approval review, cooperate with HRPO Quality Improvement program staff to complete it.

Research Data and Study Records

Researchers and staff should have systems or practices for maintaining the essential Research Records that they create in order to be able reasonably to support research findings, justify the uses of research funds and resources, and protect any resulting intellectual property.

During the life of a study and beyond its closure, many information security and storage policies pertain to the maintenance and archival of study documents and research data. These policies and procedures include those of the researcher's department, UNM HSC, the State of New Mexico, Federal privacy laws (such as HIPAA, FERPA, FOIA, New Mexico IPRA), Federal regulations (FDA, OHRP, DHHS, etc) as well as the data confidentiality requirements associated with research funding (e.g. National Institutes of Health, Department of Defense (DOD), etc.).

PI responsibilities for document and data security are particularly critical during times of study transition, as when a PI is leaving UNM HSC, is transferring PI responsibilities or is closing a study. Be prepared ahead of time and discuss transition and/or long-term storage plans with your department Chair/ Research Chair. Assure that information regarding these plans are documented in a standard place and are using an established process, so that an incoming PI and department personnel can find, understand and follow it.

Appendix A-1 Reportable New Information

Report information items that fall into one or more of the following categories to the HRRC within 5 business days. Reference SOP: New Information (HRP-024).

1. Information that indicates a new or increased risk, or a new safety issue, for example:
    a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
    b. Protocol violation that harmed participants or others or that indicates participants or others might be at increased risk of harm.
    c. Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.
    d. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk.
    e. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
    f. Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
2. Harm experienced by a participant or other individual, which in the opinion of the investigator are unexpected and related or possibly related to the research procedures.
    a. A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the HRRC in terms of nature, severity, frequency, and characteristics of the study population.
    b. A harm is "related or possibly related" to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.
3. Non-compliance with the federal regulations governing human research or with the requirements or determinations of the HRRC, or an allegation of such non-compliance.
4. Failure to follow the protocol due to the action or inaction of the investigator or research staff.

5. Change to the protocol taken without prior HRRC review to eliminate an apparent immediate hazard to a participant.
6. Breach of confidentiality.
7. Complaint of a participant that cannot be resolved by the research team.
8. Premature suspension or termination by the sponsor, investigator, or institution.
9. Incarceration of a participant in a study not approved by the HRRC to involve prisoners.
10. Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483).
11. Written reports of study monitors.
12. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants).
13. Unanticipated Problems Involving Risks to Subjects or Others, including any event or problem that is serious, unexpected, and related to the research, where "related" means the event or problem might reasonably be regarded as caused by, or probably caused by, the research.
14. Disciplinary action against the investigator or research staff by federal, state, and local regulatory agencies.

HEALTH SCIENCES

Human Research Protections Program

May 24, 2022
Neda Hashemi
NHashemi@salud.unm.edu

Dear Neda Hashemi:

On 5/24/2022, the HRRC reviewed the following submission:

Type of Review:	Continuing Review
Title of Study:	INST CR2103: Prognostic Factors in Prostate Cancer Patients of New Mexico
Investigator:	Neda Hashemi
Study ID:	21-282
Submission ID:	CR00008517
IND, IDE, or HDE:	None
Submission Summary:	Continuing Review for Study 21-282.
Documents Approved:	All documents remain unchanged and approved as previously determined and stated in the most recent study submission approval letter.
Review Category:	EXPEDITED: CATEGORIES (5) Data, documents, records, or specimens
Determinations/Waivers:	Waived the requirement for informed Consent. HIPAA Authorization Addendum waived.
Submission Approval Date:	5/24/2022
Approval End Date:	5/23/2023
Effective Date:	5/24/2022

The HRRC approved the study from 5/24/2022 to 5/23/2023 inclusive. If modifications were required to secure approval, the effective date will be later than the approval date. The "Effective Date" 5/24/2022 is the date the HRRC approved your modifications and, in all cases, represents the date study activities may begin.

Before 5/23/2023 or within 45 days of study closure, whichever is earlier, you are required to submit a continuing review. You may submit a continuing review by navigating to the active study and clicking the "Create Modification/CR" button.

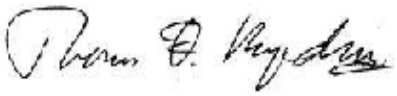
If the study meets the definition of an NIH Clinical Trial, the study must be registered in the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database.

This determination applies only to the activities described in this submission and does not apply should you make any changes to these documents. If changes are being considered these must be submitted for review in a study modification to the HRRC for a determination prior to implementation. If there are questions about whether HRRC review is needed, contact the HRPO before implementing changes without approval. A change in the research may disqualify this research from the current review category. You may submit a modification by navigating to the active study and clicking the "Create Modification/CR" button.

If your submission indicates you will translate materials post-approval of English materials, you may not recruit or enroll participants in another language, until all translated materials are reviewed and approved.

In conducting this study, you are required to follow the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library.

Sincerely,



Thomas F. Byrd, MD
HRRC Executive Chair

Abbreviated Investigator Responsibilities

NOTE: For a full unabbreviated version of the **Investigator Manual**, please visit the HRPO website at https://hsc.unm.edu/research/hrpo/.

What will happen after HRRC review?

The HRPO will provide you with a written decision indicating that the HRRC has approved the Human Research, requires modifications to secure approval, or has disapproved the Human Research.

- If the HRRC has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. HRRC approval is usually good for a limited period of time which is noted in the approval letter.
- If the HRRC requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the HRRC.

If all requested modifications are made, the HRRC will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the HRRC.

- If the HRRC defers the Human Research: The HRRC will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give you an opportunity to respond in writing. In most cases if the HRRC's reasons for the deferral are addressed in a modification, the Human Research can be approved
- If the HRRC disapproves the Human Research: The HRRC will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the HRRC directly at an HRRC meeting.

What are my obligations after HRRC approval?

1. Do not start Human Research activities until you have the final HRRC approval letter.
2. Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
3. Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
    a. Delegate responsibility to the research staff in accordance with the staff's training and qualifications.
    b. Assure that all procedures associated with the research are performed, with the appropriate level of supervision, only by individuals who are licensed or otherwise qualified to perform them under the laws of New Mexico and policies of The University of New Mexico Health Sciences Center.
    c. Monitor the research study and perform quality management activities to ensure the protection of participants and the quality of the research data.
4. Obtain the legally effective informed consent from human participants or their representatives, using only the currently approved informed consent documents, and provide a copy to the participant, if applicable. a) Ensure that only HRRC-approved investigators obtain informed consent from potential participants.
5. If unavailable to conduct the research personally, as when on sabbatical leave or vacation, arrange for another HRRC-approved investigator on the study to assume direct responsibility or notify the HRRC of alternate arrangements.
6. Maintain accurate and complete research records, including but not limited to, original signed informed consent and authorization documents, and retain these records according to HRRC policy and the applicable regulatory retention terms.

7. Fully inform the HRRC of all locations in which human participants will be recruited for this project and obtain and maintain current HRRC approvals/letters of cooperation when applicable.
8. Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
9. Update the HRRC office with any changes to the list of study personnel.
10. Personally conduct or supervise the Human Research.
    a. Conduct the Human Research in accordance with the relevant current protocol as approved by the HRRC.
    b. When required by the HRRC, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the HRRC.
    c. Do not modify the Human Research without prior HRRC review and approval unless necessary to eliminate apparent immediate hazards to participants.
    d. Protect the rights, safety, and welfare of participants involved in the research.
11. Submit to the HRRC:
    a. Proposed modifications as described in this manual. (See "How do I submit a modification?")
    b. A continuing review application as requested in the approval letter. (See "How do I submit continuing review?"
    c. A continuing review application when the Human Research is closed. (See "How Do I Close Out a Study?")
12. Report any of the information items listed in Appendix A-1 to the HRRC within five business days.
13. Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
14. Do not accept or provide payments to professionals in exchange for referrals of potential participants ("finder's fees.")
15. Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
16. See additional requirements of various federal agencies in Appendix A-2 through A-9 of the Investigator Manual. These represent additional requirements and do no override the baseline requirements of this section.

If the HRRC directs or your study is selected for an onsite post-approval review, cooperate with HRPO Quality Improvement program staff to complete it.

Research Data and Study Records

Researchers and staff should have systems or practices for maintaining the essential Research Records that they create in order to be able reasonably to support research findings, justify the uses of research funds and resources, and protect any resulting intellectual property.

During the life of a study and beyond its closure, many information security and storage policies pertain to the maintenance and archival of study documents and research data. These policies and procedures include those of the researcher's department, UNM HSC, the State of New Mexico, Federal privacy laws (such as HIPAA, FERPA, FOIA, New Mexico IPRA), Federal regulations (FDA, OHRP, DHHS, etc) as well as the data confidentiality requirements associated with research funding (e.g. National Institutes of Health, Department of Defense (DOD), etc.).

PI responsibilities for document and data security are particularly critical during times of study transition, as when a PI is leaving UNM HSC, is transferring PI responsibilities or is closing a study. Be prepared ahead of time and discuss transition and/or long-term storage plans with your department Chair/ Research Chair. Assure that information regarding these plans are documented in a standard place and are using an established process, so that an incoming PI and department personnel can find, understand and follow it.

Appendix A-1 Reportable New Information

Report information items that fall into one or more of the following categories to the HRRC within 5 business days. Reference SOP: New Information (HRP-024).

1. Information that indicates a new or increased risk, or a new safety issue, for example:
    a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
    b. Protocol violation that harmed participants or others or that indicates participants or others might be at increased risk of harm.
    c. Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.
    d. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk.
    e. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
    f. Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
2. Harm experienced by a participant or other individual, which in the opinion of the investigator are unexpected and related or possibly related to the research procedures.
    a. A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the HRRC in terms of nature, severity, frequency, and characteristics of the study population.

   b. A harm is "related or possibly related" to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.
3. Non-compliance with the federal regulations governing human research or with the requirements or determinations of the HRRC, or an allegation of such non-compliance.
4. Failure to follow the protocol due to the action or inaction of the investigator or research staff.
5. Change to the protocol taken without prior HRRC review to eliminate an apparent immediate hazard to a participant.
6. Breach of confidentiality.
7. Complaint of a participant that cannot be resolved by the research team.
8. Premature suspension or termination by the sponsor, investigator, or institution.
9. Incarceration of a participant in a study not approved by the HRRC to involve prisoners.
10. Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483).
11. Written reports of study monitors.
12. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants).
13. Unanticipated Problems Involving Risks to Subjects or Others, including any event or problem that is serious, unexpected, and related to the research, where "related" means the event or problem might reasonably be regarded as caused by, or probably caused by, the research.
14. Disciplinary action against the investigator or research staff by federal, state, and local regulatory agencies.