UNIVERSITY OF

CALIFORNIA

IRVINE

Significance of Decipher genomic classifier risk scores for Prostate Cancer: A Systematic Review

THESIS

MASTER OF
SCIENCE

In Biomedical and
Translational Science

by

Mahnoosh Rahimi

Thesis Committee
Dr Sheldon Greenfield, Committee Chair
Dr Sherrie Kaplan
Dr Richard Kelley

2020

DEDICATION

To my family and mentors in recognition of their never-ending support

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

Pca	Prostate Cancer
HR	High Risk
LR	Low Risk
AR	Androgen Receptor
BCR	Biochemical Recurrence
AA	African American
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen
PDGE	Platelet derived Growth Factor
BMP	Bone Morphogenic Proteins
ET-1	Endothelin-1
ADT	Androgen Deprivation Therapy
RP	Radical Prostatectomy
CAPRA-S	Prostate Risk Assessment Postsurgical
GC	Decipher Genomic Classifier
PCSM	Prostate Cancer Specific Mortality
NCCN	National Comprehensive Cancer Network
NCCNG	National Comprehensive Cancer Network Guidelines
AS	Active Surveillance
DCA	Decision Curve Analysis
ART	Adjuvant Radiation Treatment
SRT	Salvage Radiation Treatment
MRD	Minimal Residual Disease
LT-ADT	Long-Term Androgen Deprivation Therapy
MRI	Magnetic Resonance Imaging
PORTOS	Post-Operative Radiotherapy
GLCM	Gray-Level Cooccurrence Matrix
GS	Gleason Score
RM	Rapid Metastasis
LM	Late Metastasis
tPSA	Total PSA
fPSA	Free PSA
MVA	Multivariable Biochemical
BF	Failure Cancer–Specific
CSM	Mortality Conflict Scale
DCS	European-American
EA	

ACKNOWLEDGMENTS

Firstly, I would like to thank the mentors and academic community within the medicine department at UC Irvine (UCI) for their support and collaboration. Their collaborative spirit instilled an open and welcoming environment that encouraged students to discuss all issues openly. This interactive environment fostered equal learning opportunities for all students. There are countless interactions from which I benefitted significantly; however, I would like to highlight a few of them.

The interaction with my committee chair and mentor, Dr. Sheldon Greenfield, is one of the memorable interactions. And I would like to express deep gratitude for his continued guidance and support. His mentorship played a significant role in enhancing my research skills and interests. In addition to this, his vision inspired me to envision myself at a higher position in the future. I would also like to thank him for providing invaluable training on data interpretation and scientific conduct during the previous two years.

Secondly, I would also like to thank Dr. Sherrie Kaplan for being an incredible teacher and mentor. She has consistently encouraged me during the entire course and played a key role in strengthening my passion for clinical research and academics. The increasing emphasis on the purposeful and methodological research skills inculcated due to these mentors' concerted efforts would play an essential role in shaping my future in medicine.

I am also grateful to Dr. Richard Kelley for his continuous support and guidance during the research work. The emphasis on ethics in medicine, policy, and health politics enabled me to learn about ethical frameworks. I would not be able to complete this thesis successfully without his support. Furthermore, I sincerely thank Marissa Saplala, Thuy Pham, and Kaelyn See for their significant contributions and continuous support during my research work.

Last and foremost, I want to express my gratitude to my husband for his love and support over the last two years. There were some difficult times throughout

writing this dissertation, where it was hard to push forward and make progress. However, he always showed patience and helped me to carry on.

ABSTRACT OF THESIS

Significance of Decipher genomic classifier risk scores for Prostate Cancer: Systematic Review

by

Mahnoosh Rahimi

Master of Science

University of California, Irvine, 2020

Dr. Sheldon Greenfield, Committee Chair

Prostate Cancer (PCa) is a non-cutaneous malignancy in men. It is essential to consider the early detection and screening of prostate-specific antigens for decreasing the incidence of death due to this disease. Decipher is a genomic test that has gained increasing attention in estimating the risk of developing a recurrence or metastatic PCa disease in patients. Therefore, this study is focused on evaluating the association of Decipher score risk with recurrence of prostate cancer patients based on their medical, genetic predictors, and demographics (e.g., races) by conducting a systematic review. Moreover, the study would also assess whether Decipher score risk can be a good predictor for prostate patients' metastasis and prostate cancer-specific mortality in men and clinical decision-making regarding Treatment Recommendations for patients. The research study reviewed 120 research articles, and the results of the systematic review have been presented in the form of themes. The studies' review indicated that Decipher acts as a genomic metastasis signature to predict metastatic disease among patients and make better decisions about treating the disease. Moreover, this genomic test can also be used in conjunction with MRI for identifying the lesions that may carry the biological potential for early metastases. Furthermore, the studies also identified that treatment options for PCa might range from ART and SRT to RP; however, the selection of treatment methodology depends upon the GC score and risk stratification. The results further suggested that the occurrence of PCa is two folds greater among AA men as compared to non-AA men. The increasing incidence

of PCa among AA and discrimination within AA's health and socio-economic conditions plays a significant role in treating AA. In this scenario, the Decipher test score plays an essential role in making treatment decisions.

Hence, this research has reviewed the evidence of benefits of the Decipher test, placed the usage into clinical context, made recommendations to help providers and patients know which treatment might be more appropriate based on the GC score, and when they should consider using the Decipher score based on the works of literature. To conclude, further trials are still required for validating the Decipher biomarkers. All of the treatment options should be managed based on the individual risk profile and sensitivity to particular medical treatment. As a future direction, scientists could enhance the decipher test ability to be run on a patient's blood samples instead of tumor tissue, which will help patients use decipher as a screening test at the asymptomatic level. In this way, this test can be routinely done for patients with a family history of prostate cancer, and the biopsy will not be required during the screening stage.

CHAPTER 1:
INTRODUCTION

1.1 Background:

Prostate Cancer (PCa) is a non-cutaneous malignancy in men causing more than 300,000 deaths every year (1). In the United States, approximately 220,800 men are diagnosed with PCa, and 27,000 men die due to this disease per year (2). The statistics have indicated that, on average, one million cases are reported every year across the globe, and risk factors of the disease include ethnicity, family history, age, and environmental risk factors (3, 4).

It is essential to consider the early detection and screening of prostate-specific antigen for decreasing the incidence of death due to this disease. Treatment involves combining histological grading, prostate-specific antigen value, and clinic-radiological staging. However, various studies have emphasized prostate cancer's molecular components and focused on other alterations such as chromatin regulation, androgen/Androgen Receptor (AR) signaling, and gene mutations. Recently, an advanced genomic test known as the Decipher risk score has acquired increasing attention. Therefore, this study would also focus on examining the role of this test in treating PCa.

1.2 Problem Statement:

Decipher is a genomic test that estimates the risk of developing a recurrence or metastatic prostate cancer disease in patients. The technique was co-developed by Mayo Clinic and Genome Biosciences (Vancouver, BC, Canada). The test procedure involves RNA expression of 22 genes in immune system modulation, cell adhesion, cell cycle control, tumor motility, and other genes with code or non-coding function. Thus, Decipher plays a pivotal role in predicting the risk of progression based upon the tumor biology and enables the patients and physicians to optimize the clinical decisions, enabling the patient and physician to optimize clinical decisions. Moreover, it is also useful for determining the

prognosis of the disease after hormonal therapy (5).

Previous literature has examined the likelihood of Decipher in predicting the recurrence of disease after radical prostatectomy (RP). Klein et al. examined 162 patients prone to prostate cancer and patients with positive lymph nodes treated with RP, demonstrating an improvement in predicting patients with metastases over clinic-pathological parameters (6). Similarly, Alshalafa et al. has also studied patients with Biochemical Recurrence (BCR); the result shows that Decipher can be a useful tool for predicting patients with clinical recurrence after biochemical recurrence. Thus the Decipher score could help to determine the best treatment type for PCa. The test can also be used to validate and predict prostate cancer mortality and metastasis after RP (7).

Currently, it is unclear how the genomic test result can be used to treat patients individually. However, studies are presently investigating the predictive approach and timing of postoperative radiation therapy. The emerging prostate cancer molecular biomarkers represent a potential to improve risk assessment and provide selective treatment for patients with PCa. Experimental trials are essential to determine this test's value in treating patients after radical prostatectomy. This can only predict the oncological result, the patient's lifestyle, and health care condition (8). However, most physicians' major challenges while employing Decipher Genomic test or other biomarkers include discussing the disease differently in the case of different patients, possibilities of inadequate diagnosis or suggested treatment, and difficulties in determining the initial strategy sequence of treating patients (9).

This study would focus on reviewing the Decipher genomic classifier risk scores in predicting prostate cancer to embracing the significance of the Decipher Genomic test for treating Prostate cancer and considering challenges associated with it.

1.3 Aims of the study:

This study's primary objectives would be to review the value of Decipher genomic classifier risk scores concerning early detection of prostate cancer, clinical management of prostate cancer, and targeted therapies as precision to prostate cancer.

The aims of this research would be:

- To evaluate the association of Decipher score risk with recurrence of prostate cancer patients based on their medical, genetic predictors, and demographics (e.g., races).
- To assess whether Decipher score risk can be a good predictor for prostate patients' metastasis and prostate cancer-specific mortality in men and clinical decision-making regarding Treatment Recommendations for patients.
- To evaluate the decipher test for prediction of Prostate Cancer Risk in African-American (AA) men Vs. other races.

CHAPTER 2:
LITERATURE
REVIEW

This chapter aims to deliberate the causes and techniques for examining and treating Prostate cancer. Moreover, the literature would also evaluate the Decipher Genomic Classifier tests' prospects in treating Prostate cancer.

2.1 Prostate cancer

PCa is one of the deadliest illnesses that occur in men's prostate glands (10). PCa has different variability, such as malignant causing Prostatic Intraepithelial Neoplasia (PIN), prostate cancer localization, intense prostate adenocarcinoma (local invasion), and increasing rates of metastatic prostate cancer (8). Despite recent progress, prostate cancer still tends to pose a severe threat to men in the United States (2). The initial identification of PCa depends on the biopsy and Prostate-Specific-Antigen (PSA blood test) at the later diagnosis stage. Since the occurrence of PCa is high among AA men as compared to American or European men, and a biomarker can be beneficial for predicting the initial detection, staging, and response to a particular treatment (11).

2.2 Metastatic prostate cancer

It is a developed form of cancer associated with a high prostate cancer-related death rate. It causes damage to lymph nodes adjacent bones, lungs, and liver (12). These cancerous cells may enter the blood after breaking away from tumor cells while traveling across the body attach to various tissues. Once attached with tissues, they started multiplying and for new blood vessels and carrying nutrients for new tumors. This cancer's growth is observed within particular areas like the spine, pelvic bones, ribs, and lymph nodes. The osteoblastic lesions mixed with osteolytic structures results in pain, hypercalcemia, and recurrent fractures (13).

The presence of prostate cancer cells in the bone marrow results in the mutual association of cancer cells and microenvironments, which causes bone transformation (vicious cycle) and obliteration. This affects tumor growth,

discharge, and enhanced cancer cell formation. The end result of growth factors released by prostate cancer includes Platelet-Derived Growth Factor (PDGF), Bone Morphogenetic Proteins (BMPs), and Endothelin 1 (ET-1). They stimulate osteoblast bone formation through paracrine signaling (14-17).

2.3 Etiology

Over the past years, many studies focused on identifying the causes and risks associated with prostate cancer development. Currently, the leading causes of prostate cancer have not been identified by medical researchers. Although a few risk factors have been detected, they are supported by decreasing evidence. Genetic background is one of the most dominant causes of PCa. Hereditary prostate cancer occurs when the prostate cells undergo genetic mutations related to an autosomal dominant trait. This can increase the probability of developing the disease with inadequate penetrance results and a high percentage of early-onset cases, with 9% of prostate cancer cases. Many studies have established genetic factoring in prostate cancer's etiology. This topic has been reviewed in various reputable studies (13, 18-20). Additionally, the occurrences and impacts of prostate cancer vary in men depending upon their race and ethnicity. Studies show that AA men of descent have the highest rates of prevalence and mortality (21), which may be caused by the genetic composition of AA men (22). Identifying prostate cancer's genetic factors has been the first step in managing disease subtypes and related therapeutic approaches (13).

The family background and history are also significant epidemiological factors for causing PCa. This occurs due to familial clustering without noticeable Mendelian traits. There is an increased tendency to get affected with familial prostate cancer because it is more aggressive than the general population. With the high risks associated with a positive family history, it is necessary to screen and undergo early diagnosis tests in men with relatives (brother or father) who have prostate cancer (21). Recent studies have indicated that family history is the cause of prostate cancer in 10% of diagnosed patients (21). The other factors responsible for causing this cancer include age, endogenous hormone balance,

obesity, and environmental factors (23).

2.4 The existing model of care and promising treatments for the prostate Cancer:

Generally, this cancer type treatment is based upon some factors, including phase, grade, age, and varies from active surveillance to intensive surgery, radiation, chemotherapy, and Androgen Deprivation Therapy (ADT) in most cases (24). Gleason Grading System is one of the widely used techniques for estimating prostate cancer aggressiveness (25). A Gleason Score (GS) is given to prostate cancer based upon its pathologic features. Cancers with a higher GS are more aggressive and have a worse prognosis. Pathological scores range from 2 to 10, and the higher score is associated with increased risk and mortality rate (26).

According to the GS, there are three grades of cancers: low, intermediate, and high-risk (27). The cancers with low risk (Gleason 3+ 3) are often addressed through effective surveillance. A large group of random clinical trials shows low mortality disparities between radiotherapy/radical prostatectomy and active surveillance (28, 29). Men diagnosed with what has classically been termed “intermediate-risk” PCa based on GS 7 (4+3 or 3+4), PSA 10−20 ng/mL, and clinical stage T2b or 2c disease—have highly variable clinical behavior and prognosis and are considered a broad, heterogeneous cohort for whom management recommendations cannot be standardized. The literature provides evidence that not all Gleason sums of 7 have equal potential for progression. Men with a post Radical Prostatectomy (RP) Gleason 4 + 3 are more likely to develop metastasis and die from PCa than patients with a Gleason 3 + 4 (30), and outcomes may vary further based on the quantified predominance of pattern 4 diseases (31, 32). As a consequence, contemporary Gleason grading has explicitly assigned a score (4 + 3) to a higher-grade group (unfavorable) than Gleason (3 + 4) (favorable) to address these levels of risk (33). Meanwhile, clinical T staging has been shown frequently inaccurate and less critical than better markers of tumor volume, such as the extent of biopsy core involvement (34).

The principle distinction between Gleason 6 disease vs. Gleason 7 to 10 disease is that the former does not require definitive treatment (35). Nevertheless, GS's implications are less clear in black men because of disparate PCa outcomes, specifically for Gleason 6 disease, in which risk evaluation and management of disease in black men is controversial (35, 36).

On the other hand, the spectrum with high cancer risk (Gleason ≥8) requires innovative treatment such as surgery and radiation-based medication. PCa treatment decisions are planned based on the patient's results, such as disease with intermediate-risk (e.g., Gleason 3 + 4). Numerous classification systems have been developed in grouping cases with intermediate-risk into favorable and unfavorable subgroups (37) base on the clinical categories (38) or clinical features such as the intermediate-risk factors number (one versus more than one) and Gleason pattern(GS of 3+4 ≥ 7 vs. GS of 4+3=7) and the positive biopsy scores percentage (<50% vs. >50%)(39)

As discussed above, the treatment of PCa using the GS of 6 versus the percentage of scored below or equal to 8 is relatively easy (close monitoring vs. surgical treatment and/or radiation therapy, respectively). The disease management having GS of 7 (3 plus 4 or 4 plus 3) is challenging and requires more effort to detect molecular correlations between the disease outcome. Currently, the development of consistent markers has been hindered by intra-tumor heterogeneity disease found in each patient. Regardless of this, prognostic signatures can be used to obtain precise results. Profile assessments in indolent (with GS less than or equal to 6) and tumors (GS less than or equal to 8) provide accurate results related to an intermediate-risk disease (GS 7) such as cancer mortality, recurrence, and metastasis (28, 40-42).

Furthermore, some studies emphasized biomarkers to provide an accurate prediction of disease outcome and aggressiveness. In some cases, patients who do not experience any improvement after receiving localized treatment will receive anti-hormone treatment known as ADT combined with radiation and surgery. During the early stage of metastatic disease, the pre-treatment measures include

ADT and chemotherapy.

2.5 Emerging Role of Molecular Biomarkers in the Context of Clinical Management of Prostate Cancer

Improvement in scientific computing knowledge promotes integrating clinical data in combination with enormous data sets, including genetics, epigenetics, and prostatectomies (43). The current trends in the treatment procedure for prostate cancer in patients has increased due to the consistency of biomarkers in decision-making in a challenging clinical setting (44). In combination with other pathological and clinical variables, genomic biomarkers act as useful tools to reduce irrelevant biopsies, guide personalized treatment actions, and stratify low-risk from high-risk tumors. Genomic biomarkers application has improved the discovery, risk assessment, and prognosis of PCa. Regardless of the progress made in detecting suitable biomarker candidates, only a few have been used in a clinical setting. The new and detailed PCa molecular biomarkers offer increasing potential in overtreatment reduction, risk assessment, and selective medication for patients exposed to high-risk disease.

In the past decade, there has been rapid development and identification of different biomarkers for PCa. These markers pose significant impacts during cancer treatment stages ranging from its identification and initial stage to later stages. The precise category of biomarkers identified by PCa extents from the spectrum based on DNA (45) modifications and epigenetic changes (e.g., methylation of DNA helps regulate gene expression). These changes lead to the expression of the mRNA gene and either single protein markers or multiplexed. The samples for these markers are in the form of blood, urine, or prostate tissues. The patient's biomaterial source of these markers includes urine, blood, and prostate tissue. Moreover, emerging imaging tests, particularly based upon genetic or metabolic changes, function as biomarkers and need to fulfill similar clinical use standards and validity in a broad aspect. There are several types of biomarkers, such as diagnostic, prognostic, and predictive biomarkers. This biomarker offers inclusive information for defining the risk of high-risk prostate

cancer (45).

However, early screening or biomarkers can detect prostate cancer at the asymptomatic level. “Diagnostic” biomarkers predict cancer disease in patients suffering from the symptoms, while “prognostic” biomarkers mainly determine the disease growth. Also, predictive biomarkers can predict early/advanced risk assessment or response to treatment among patients, while surrogate biomarkers measure clinical benefit and endpoint in patients (46).

Firstly, the sources for diagnostic biomarkers include blood, urine, or prostate tissues. Diagnostic biomarkers are used in predicting disease variability. While some diagnostic markers in PCa provide additional information based on the likelihood of patients suffering from a high-risk disease with a GS of 4 or 5. Regardless of this, the cancers that had a GS of less than three are considered to have the decreasing potential of metastasis and generally over-diagnosed (33, 45). Secondly, Prognostic biomarkers provide information about patient aggressiveness based on disease type and determine whether markers are necessary for treatment purposes. Prognostic biomarkers also offer necessary information on patients who are required treated post-surgery (Decipher) (46). Lastly, the Predictive biological markers convey information on potential benefits acquired from a particular medication (personalized medicine), e.g., whether individuals having a specific mutation may take advantage of a new modality treatment or not (47). Furthermore, prognostic biological markers differ from predictive biological markers as the former relate the patient's physiognomies with the outcome. In contrast, the predictive markers identify the influences of treatment on the consequence (45, 48). Thus, future studies and innovative approaches not only focus on effectiveness but also investigate the impact of biomarkers on clinical decision-making and cost-efficacy. Several high-level pieces of evidence are required to provide answers to the rational use of innovative biomarkers, which can drastically reduce biopsy rates and further decreased costs and low morbidity to advocate their extensive usage (44).

2.6 Initial Treatment Decision

Many instruments have been incorporated to examine protein and gene expression changes across cancerous tissues and identify the risk levels based on prostate cancer diagnosis. This information is useful for both patients and providers in making decisions related to definitive therapy (45).

Recent studies have revealed that physicians might alter the treatment decisions according to the genomic data available when hypothetical cases are available (49). The genomic classifier-based models had a significant net result compared to the clinical models using a decision threshold probability (50). However, these studies attempted to show the importance of genomic markers in predicting patient management decisions. Based on the toxicity level with post-operative treatment such as hormonal, radiation, or chemotherapy balanced against the potential therapy, detailed information will support the patient in decision-making. Adjuvant radiation treatment (this includes pathologic T3 and GS 8-10 or more) results show that 18% of men were suffering from the low-risk disease. Due to this, if men with positive margins or pT3 received adjuvant radiation treatment, the genomic classifier will prevent the low-risk population estimated at 37% (51).

Accurate evaluation of disease aggressiveness is vital for managing prostate cancer (PC) in patients. The traditional risk factors include grade, PSA, and stage (52). RP and other clinicopathologic provides risk-stratify measures in patients. The criteria have been combined into different multivariable models, including cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S). However, CAPRA-S is compared to other individual clinicopathologic variables, but there is room for further improvement and innovative approaches. Regardless of this, there has been growing interest in genomics in treating risk-stratified patients (53). Currently, there are three clinical genomic tests used to predict oncological results (e.g., metastasis, adverse pathology, cancer-related death in PC patients such as Prolaris (Myriad Genetics), Oncotype Dx (Genomic Health), and Decipher (Decipher Biosciences) (53).

2.7 Decipher

The Decipher Genomic Classifier (GC) consists of RNA expression of 22 genes markers, which were designated from 1.4 million candidate RNA probes from a complete transcriptome microarray (which includes both non-coding and protein-coding RNA), to predict metastasis and Prostate Cancer-Specific Mortality (PCSM) (45). Decipher is developed and performed by Genome DX Biosciences through a CLIA-certified high-density microarray (42). Decipher genes were selected according to the patterns of differential expression of 192 new metastatic cases (in 5 years of increasing PSA) in comparison with 271 retrospective and a nested case-control study (54). These genes' signature provides biological pathways for aggressive PCa, cell proliferation, cell structure, modulation of the immune system, cell cycle progression, and androgen signaling. Previously, it was designed to predict systemic progression after undergoing specific treatment (55).

Every patient has unique Pca features, and Decipher genomic testing offers independent and meaningful data for assessing the biology and risks of a particular patient’s disease. Decipher is available in two categories; the first one is Decipher Prostate Biopsy, a genomic test performed on tumor tissue that helps match the selection and intensity of treatment with the tumor's metastatic potential. This test was firstly considered by Medicare Coverage for PCa with intermediate risk. It also provides information for predicting metastasis, mortality, and intensity of the disease. The second one is Decipher prostate RP, it is a genomic test performed on tumor tissue and helps determine if a patient can be safely observed following radical prostatectomy or considered for early or salvage radiation. Moreover, this test is also suitable for effective surveillance and definitive therapy. This is suitable for men considering early or salvage radiation after radical prostatectomy (5).

This 22-marker signature, also known as GC, is accessible for both prostate biopsy specimens and RP. According to the National Comprehensive Cancer

Network (NCCN) guidelines, it is highly recommended for patients suffering from adverse pathology after RP (56). Decipher generates a score ranging from 0 to 1, low (0.0 to 0.44), average (0.45–0.59), and high (0.60–1.0), with higher values indicating an increased probability for both RP and downstream oncologic outcomes. Utilization of molecular profiling with Decipher GC can result in improvement in the identification of patients, thus qualifying for Active Surveillance (AS) by identifying the subset of histologically low-risk (LR) PCa at diagnosis with molecular characteristics confirming indolent disease (57).

After initial development and validation, the independent predictor of metastasis was identified by RP. The GC obtained and confirmed to project metastasis among the cohort of 545 patients gone through RP at the Mayo Clinic, indicating more than 213 suffered from metastasis (42). The precise GC report given to patients and clinicians consists of validated 22 markers. Some of the data are used for further research in genomic expression profiles. This provides additional information on predictive and prognostic characteristics with different responses to radiation (58) or hormone therapy (59).

As discussed earlier, the Decipher score plays a significant role in post-PR prognosis and decision- making about further medication. At the moment, the GC can be done on biopsy samples, and obtained results can be employed for preliminary treatment decisions (45). Decipher GC provides detailed analytical information on the risk factor related to disease progression or recurrence and local treatment. It detects patients with low aggressive disease conditions, which can be controlled using medical surveillance. Also, it helps to detect high-risk patients that can benefit from the escalation treatment approach. Currently, the escalated approach has not been confirmed to project effective responses (45).

Currently, the Decipher biopsy test has been validated and includes risk at RP for pathologic grade upgrading (Gleason pattern 4 or 5), a 5 –year development of metastasis as well as 10-year PCSM (60). The post-operative radiotherapy (adjuvant vs. salvage) can be conducted based on the Decipher scores. The decipher test acts as an independent predictor for clinical metastasis among

patients with biochemical recurrence (61). The biopsy Decipher examined the metastasis risk for post radical prostatectomy. While regardless of this, further research is required on pre-operational awareness of Decipher risk and extensive cohorts related to biopsy, which will help support patients with therapeutic problems and advancement in multimodality therapy (62). A Decipher test can be also be used to predict the clinical metastasis with five years of RP and death rate in men associated with high-risk clinical features or pathology prostate cancer after RP (42, 62, 63).

Thus, Decipher testing helps to improve the decision-making approach for adjuvant radiation treatment in men suffering from pathology and prostatectomy. New molecular tests can also be used to enhance men's treatment with localized prostate cancer (53). Presently, decipher is the most CMS-recognized used for post-prostatectomy decision making. Decipher has been studied in post RP cohorts, including receiving and non-receiving other therapy before metastatic progression (64).

CHAPTER 3:
METHODOLOGY

3.1 Methodology

The relevant research papers and journal articles were obtained through four electronic databases: SNPedia, Science Direct, Ensemble, and PubMed. The study focused only on journal articles involving 2000 participants and published between 2000 and 2020. The keywords for searching the relevant research papers include Prostate cancer, “Decipher,” “genomics,” “biomarker,” “race,” “African-American,” “mortality,” “MRI,” or “metastasis.” The preliminary web search identified 2000 articles based on the keywords mentioned above (see figure 1). All of these articles were published in the English language. The articles' list was then filtered that had either “prostatectomy” or “surgery” in the text body. This generated 600 publications. After reviewing these publications' abstracts and selecting only those signatures that had been tested in men with prostate cancer undergoing prostatectomy, 108 Decipher associated with prostate cancer outcomes were identified.

The next step was to remove the duplicates. The duplicates were identified and excluded using EndNote’s (Clarivate Analytics) Author/Title/Year duplicate checker, followed by manual verification. Truncation and wild cards were also used to avoid missing any articles that might include tests of interest. The remaining articles were first gone through the process of screening. The screening of articles was done based upon two factors, i.e., first on the basis of the title of the journal article and then on its abstract. The articles were further screened based upon the application of the Decipher Score relationship with PCa. The elimination criteria were papers having fewer than 50 cases, editorial, comorbidities, and other diseases (see fgure1).

After screening, the inclusion and exclusion criteria for journal articles were defined based on the nature of studies and treatment options adopted for PCa among men. The research articles adopting clinical utility studies were included and preferred over other journal articles. The study has made concerted efforts

to include all possible study types that could consist of clinical utility evidence. While the articles adopting other treatment methods were excluded (see figure 1). Clinical utility studies assess the ability of the test to affect patient outcomes and treatment decisions. The best way to demonstrate the clinical utility of a test is by showing its ability to decrease PCSM or metastasis. Other essential outcomes in contemporary PCa management are overtreatment and overdiagnosis, and showing how testing affects these would be essential. However, because PCa is a long-term disease, present studies might not be able to demonstrate these outcomes within their relatively short follow-up periods. Thus, clinical utility evidence concerning PCa will logically focus on short-term outcomes, such as a change in treatment decision, patient stratification, or a decrease in interventional treatment. These outcomes will clarify the ability of each test to alter treatment decisions at each disease phase. Therefore, based upon the criteria mentioned above, the inclusion of journal articles was confined to 120 articles only and the systematic review of these articles is explained in the next chapter.

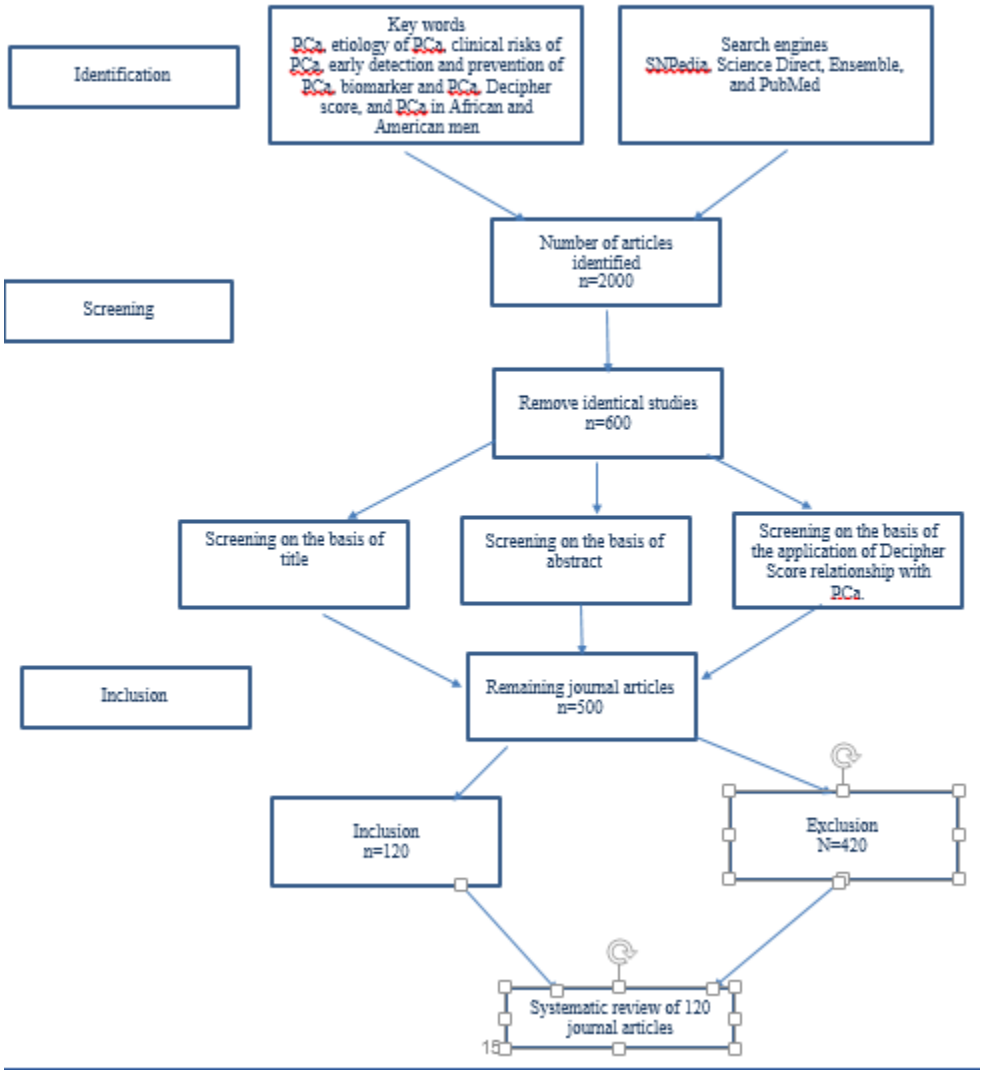

Figure 1: Methodology for conducting systematic review

CHAPTER 4:
RESULTS

The systematic review of identified research papers has identified the following themes, which are discussed in detail below

4.1 Important of Decipher for Prostate Cancer:

In the US and European case-control studies, the average Decipher scores were higher in population cases developed in metastases (65). The multivariable analysis indicated that every 10% increase in Decipher score leads to a high risk in distant metastases during an investigation period of 10-years. This includes a follow-up period with an odds ratio of 1.53 (95% [CI]1.06–2.22; $p<0.025$), and 1.58 (95% [CI]1.31–1.92; $p < 0.001$) for both US and European cohorts respectively. The average follow-up for the European unit was 12 years (interquartile ranging from 8-12). Decipher result shows metastatic recurrence among patients having high-risk and non-metastatic PC within a follow-up of 10-yr. This initial study verified the Decipher predictors in patients who developed cancer recurrence after higher-risk PCa (65).

Another study was done for assessing the approach of Decipher obtained from a biopsy without operation. Also, Klein et al. used the models to calculate the high-grade Gleason at RP and 5-year metastasis after RP. This was assessed employing a decipher GC score on biopsy specimens obtained from 57 men with RP history. The model outcome showed that the AUC for GC was 0.71 (95% CI 0.56–0.86). The 5-year metastasis, the GC's c-index was around 0.87 (95% CI 0.76-0.97), developed metastatic disease indicated that Decipher is associated with aggressive disease and intensified treatment. According to this study, a positive GC was demonstrated by validating the risk of metastasis at 10-yr after RP was measured on prostatectomy tissue, which holds similar predictive protocol when measured on pre-operative treatment biopsies from similar

prostates. Using MVA and C-index, biopsy Decipher overtook NCCN clinical risk grouping, pre-operative PSA, and biopsy Gleason, with a 10% increase in Decipher score and HR increased by 1.72. This was evident when combining Decipher and NCCN risk groups with an increasing index from 0.75 to 0.88. Then, Decipher can be a useful tool to improve local treatment and planning of newly diagnosed PCa patients (62).

In another study the authors investigated the GC based upon the RP specimen for each patient. The results show the GC risk group at three levels(low, intermediate, and high) at 64% concordance (95% [CI] 50-70%) in biopsy and RP GC score. The GC risk concordance rate is similar to a recent study where 75% of 33 patients had both RP specimens and GC biopsy. Furthermore, the GC was examined based on RP and biopsy with $R = 0.7$ ($p < 0.001$) (66).

Some other studies have suggested a strategy characterized by integrating both three and 6-tier medical genomic risk groups. They were acquired through three layers of GC risk scores with four layers of NCCN risk groups. Furthermore, this method is a semi optimal approach because the NCCN risk groups do not accept the analytical information's standard clinical parameters. The authors have also supported multicenter cohorts with 991 patients in the first development process (45, 67).

A study was recently done to improve the prognosticate risk of distant metastasis employing new clinical-genomic risk groups at 10-years interval by combining the NCCN risk classification system and GC score. Furthermore, Spratt et al. demonstrated the effectiveness of combining clinical and genomic data to improve risk stratification compared with NCCN clinical risk grouping. The GC score helps physicians and patients to predict the clinical results based on the treatment and RP results. The novel clinical-genomic risk groups on the clinical data before treatment and GC scores from RP samples were ($N = 756$), while the risk groups validation using biopsy GC scores (N=235) in patients previously undertook RP as the main treatment. The combination of GC risk and NCCN risk improved the prognosis of assessing metastatic disease at ten years after the main

treatment based upon the clinical factors before the treatment and GC score acquired from the biopsy samples. The outcomes provide primary treatment in patients with low clinical-genomic risk using active surveillance. Also, it helps to identify patients with aggressive disease, which requires multimodal treatment and therapy escalations (67).

Furthermore, another study result indicated that in 991 men who previously undertook RP or radiation therapy as the main treatment with NCCN low-, favorable-intermediate, unfavorable- intermediate, and high-risk cancer, the 10-year risk of metastasis was 7.3%, 9.2%, 38.0%, and 39.5%, respectively. Combining clinical risk groupings with GC score, the authors developed a three-tiered clinical-genomic risk stratification in which the risk of metastasis was 0%, 25.9%, and 55.2%, respectively. These findings corroborate previous data validating GC's use in predicting PCSM during long-term follow-up after RP (68).

Moreover, recent studies have shown supporting evidence in the Decipher score among men anticipated with radiation therapy. According to Nguyen et al., the GC score of biopsy tissue assessment is used to predict post-treatment in case of distant metastasis among 100 patients suffering from NCCN intermediate or high-risk diseases that have undertaken primary radiation and ADT after a biopsy. The research discovered that the GC was the main predictor of distant metastasis while investigating different models, including CAPRA, medical variables, or NCCN risk type. To predict the model of metastasis (five years) after radiation, the c-index for CAPRA was 0.84 (95% CI 0.61–0.93) compared to GC 0.76 (95% CI 0.57–0.89) and NCCN 0.63 (95% CI 0.40–0.78). According to the Decision Curve Analysis (DCA), the GC score identified a clear clinical prospect around the threshold probabilities band. This study also showed that the GC score is capable of predicting men with high chances of developing metastatic disease mainly through ADT and radiation impact. Alternatively, it is possible to select lasting ADT chemotherapy, clinical trials, or courses (69).

In another study(50), the Decipher gene signatures were examined retrospectively among 139 men. They were administered salvage or adjuvant radiotherapy for treating pT3-stage and positive margins PCa with RP According to the decipher score, the patients were grouped into three risk categories (high risk >0.6, intermediate risk 0.4-0.6, and low risk <0.4). The clinical trials of 8-years biochemical recurrence incidence ranged from 21% (low risk) to 81% (high risk, p <0.0001). Also, the 8-years cases of distant metastases were estimated at 0% and 17% (p=0.032). Additionally, the GC predicted free metastases (AUC 0.78) and free biochemical recurrence (AUC 0.75). In addition to the genomic classifier, this validated the clinical model (Stephenson model), which leads to a high predictive value (AUC 0.78) for biochemical failure and (AUC 0.80) for distant metastases. The HR score for patients with increased classifier was 8.1 (biochemical recurrence) and 14.3 (distant metastases) (50).

Moreover, the GC was confirmed to predict metastasis among the group of 545 patients that were gone through RP, and consequently, 213 of these patients suffered from metastasis. The multivariable analysis showed that the decipher score was an independent predictor for early metastasis (values includes 1.36, 95% CI 1.16–1.60, p < 0.001) in comparison with biochemical recurrence patients (42).

According to Ross et al., further investigation was carried out based on prognostic value for the genomic classifier. The cohort included 85 patients with a high-risk of PCa and biochemical recurrence after RP. About 8% of the patients with a low-risk profile related to the Decipher classifier developed distant metastases after the follow-up period (compared to 40% with a high-risk profile, p < 0.0001). The results have indicated that GC can be used to predict distant metastasis based on biochemical recurrence (AUC 0.82, 95% CI 0.76–0.86; p= 0.003), compared with the GS (0.64, 0.58–0.70), dtPSA (0.69, 0.58–0.70) and real-time biochemical recurrence (0.52, 0.46–0.59) (61).

More importantly, Badani et al. further investigated clinical decision-making and the Decipher genomic classifier influences. The 10 out of 110 randomly selected

patients with pT3 stage PCa or positive surgical margins after RP received the adjuvant medication recommendation from US board-expert urologists. The authors claimed that without the Decipher test result, the surveillance approach is estimated at 57%, adjuvant radiotherapy at 36%, and additional treatment at 7%. Based on the Decipher test outcome, 31% of the medication decisions changed (95% CI 27–35%). For example, 40% of the previous radiotherapy approvals changed to an observation test when the decipher score was included (95% CI 33–47%). On the other hand, only 13% of the past observational patients were modified to radiotherapy (95% CI 9–17%). The multivariable analysis indicated that GC score was the most important factor for decision making (OR=8.6, 95% Confidence Interval 5.3–14.3, $p < 0.001$). The authors concluded that further GC risk score application might lead to positive clinical decision-making changes in treating high-risk PCa patients (49).

The patients with Rapid Metastasis (RM) generally develop metastasis at an average age of 2.3 yr. Decipher was a significant predictor of RM (OR: 1.48; p= 0.018) after adjusting for clinical risk factors in multivariable analysis. The studies' outcome has thus indicated that Decipher is a confirmed genomic metastasis signature for predicting metastatic disease across 5 yrs after the surgery among high-risk men (70).

Cooperber et al. showed that Decipher reclassification includes 49 out of 185 men suffering from low to intermediate risk and high risk based on a CAPRA-Score less than six. Decipher subgroups of patients with high clinical risk, clinicopathologic features, and prognostic information was included in this study. Both GC and CAPRA-S were significant independent predictors of cancer–specific mortality (CSM). GC was shown to re-stratify many men classified as high-risk based on CAPRA-S ≥6 alone. Patients with both high GC and CAPRA-S risk scores were at markedly elevated post-RP risk for lethal prostate cancer. If validated prospectively, these findings suggest that incorporating a genomic-clinical classifier may allow improved indication of patients with post RP who should be accounted for clinical trials and aggressive secondary therapies. They discovered that the combination of GC and CAPRA-S could predict death due to

PCa at five years after RP among 185 men suffering from high disease risk (71).

Furthermore, a more extensive cohort study of 260 patients suffering from either intermediate or high-risk illness during RP with no adjuvant treatment administered. Another research has also indicated that the decipher score offers extra predictive precision to the CAPRA-S in determining metastatic disease at 10-yr after RP. The c-index of the decipher score was 0.76 (95% CI 0.65– 0.84), and CAPRA-S was 0.77 (95% CI 0.69–0.85). Regardless of this, both CAPRA-S and GC were integrated with an improved c-index of 0.87 (95% CI 0.77–0.94). Thus, the data suggested that cases with a high risk of metastatic progression would benefit less from applying the molecular classifier (72).

Overall, the literature has indicated Decipher as an effective genomic metastasis signature for forecasting metastatic disease among patients and making decisions about treating the disease.

4.2 Association of Decipher score with age categories

Decipher score had a confident Spearman's correlation of 0.09 (95% CI 0.05-0.13, $P<0.001$) compared with the patients' age. This analysis showed that 54% of patients aged less than 50 were grouped as low risk, while only 30% of patients were 70 years or older recognized with low Decipher risk. In addition, after changing from a medical procedure such as PGS, PSA, seminal vesicle invasion, extra-prostatic extension, lymph node invasion, and surgical margin status, the relationship between prostatectomy age and Decipher score was not statistically correlated (51).

4.3 Decipher score and its association with mortality and metastasis:

Decipher displays a predictive approach of metastasis development after primary local treatment (63). Patients with high-risk PCa are more exposed to metastatic development and mortality caused by PC following the initial treatment. Regardless of this, high risk associated with diseases includes only 12% and 22% of patients who develop distant metastases, and 2.8% and 8% of patients from PCa after 5- and 10-year follow-up, respectively (73). Suitable treatment plays an

essential role, especially in distant metastases related to PCa mortality, for maintaining the quality of life (74, 75). A high level of risk involved in metastasis is one of the main factors that influence the decision of active surveillance. This led to extended lymph node dissection and the application of adjuvant medication. Moreover, Decipher is an extensive GC that determines metastasis and PCa mortality after RP (55).

It is vital to predicting the PCa patient's risk of developing metastatic recurrence after a surgical procedure and administers individual follow-up meetings and further treatments. The CAPRA-S score, known as the medical recording system, is the most recognized PCa prognostication. Recent findings indicated a relationship between cancer-related mortality and the Decipher score among patients with unfavorable pathologic properties in the RP specimen (54). These patients are considered to have intermediate to high-risk PCa (60).
For a cohort of mostly low- (40%) and intermediate-risk (47%) patients, Klein et al. determined that biopsy GC score was the only significant predictor of post-RP metastasis (HR 1.72, 95% CI 1.07–2.81; $p = 0.02$) in a model adjusted for age, PSA, and biopsy grade (62). Similarly, Nguyen et al., while conducting a multicenter study on 255 men with intermediate- to high-risk disease treated with RP or RT + ADT, found that biopsy GC score was the only significant predictor of metastasis (HR 1.39, 95% [CI] 1.09–1.80; $p = 0.009$) after adjusting for clinical variables and treatment (60).

Importantly, GC's role may be higher in identifying clear biochemical PSA failures compared to the progressive clinical apparent recurrence. To support these findings, a multicenter study was done by Karnes et al. on a group of 561 patients with severe pathologic characteristics at RP (pT3, pN1, optimistic surgical boundaries, or Gleason score greater than 7. This demonstrates a combined decipher score and CAPRA-S capable of prognosticating10-year PCa death after RP. The reported c-index for GC and CAPRA-S was 0.76 (95% [CI] 0.71–0.82) compared to only CAPRA-S with 0.73 (95% CI 0.68–0.78) and GC along with 0.73 (95% CI 0.67–0.78). According to the authors, DCA shows that

GC's net benefit, with a combination of CAPRA-S, was 10-yr PCa mortality (76).

To sum up, these studies have confirmed that Decipher plays a significant role in predicting metastasis and mortality among PCa patients.

4.4 Magnetic Resonance Imaging (MRI) and Decipher

During the pre-treatment process, prostate MRI tends to offer precise accuracy in identifying clinically significant cases of PCa (for instance. GS $\geq 3 + 4$) (77). Also, MRI does not detect all the significant clinical tumors; this can prevent further evidence on benign and tumors conditions such as benign prostatic hyperplasia and prostatitis. These unobserved tumors are commonly associated with "MRI invisible. The non-invasive prediction of aggressiveness has not been identified. Many approaches are being evaluated, especially multiparametric MRI (78, 79).

Even though the Gleason scoring system is well structured for PCa grading, there are positive measures in evaluating PCa molecular and genomic properties. The usage of advanced radiomics approaches, such as machine learning models, helps to predict the adverse histopathological score and Decipher genomic metastasis risk score. Our results indicate that Decipher is equally prognostic in patients treated or not with postoperative radiotherapy. However, a combination of Decipher and Post-Operative Radiotherapy(PORTOS) could allow for the selection of patients who need to use PORTOS and help decide whether to irradiate in the adjuvant or salvage setting (using Decipher) (58).

In regards to the GC score, a close association was observed among the Gray Level Co-occurrence Matrix (GLCM) texture feature with average T2-weighted imaging (9T2WI) 64 bins (r [<0.40, FDR adjusted $p<0.030$]). Other significant correlations were observed between radiomics features and gene signature PORTOS score with emerging GC to determine post-operative radiotherapy response. On the other hand, patients who received or did not receive post-RP RT were 32 % ($p = 0.76$). In conclusion, the studies investigated that Decipher, CAPRA-S, and the microarray technology of Polaris CCP cannot foresee RT's

response. The hierarchical grouping, coupled with gene signatures and radiomics characteristics, is divided into five categories. The initial group constituted only PORTOS, a signature integrated with both DNA damage and repair genes. While the second category included predictive gene expression signatures expected to foretell PCa and mortality associated with metastasis. The third group consisted of gene signatures associated with metastasis formation, while the fourth and fifth groups have three gene signatures related to Androgen receptor signaling. Machine learning algorithms applied to predict GS and Decipher Genomic Risk Score has the highest diagnostic outcomes with a GS of 8 or more found when using T2-weighted imaging (T2WI) with cross-validated AUC 90.72). In other to predict a GC score of 0.6 or more T2WI, the best scores can be obtained when using a single MRI modality (cross-validated AUC 0.73). Apart from the PCa diagnosis and multiparametric MRI, other parameters focused on radiomics used to identify PCa aggressiveness on the histopathological and genomics levels. This has good potential for PCa management. Their results showed that the multiparametric MRI radiomics features were closely related to the Gleason score and emerging PCa genomic classifiers. Moreover, they found that multiparametric MRI machine learning algorithms are promising for non-invasive prediction for GS and GC risk score. The lesion extent and PI-RADS showed no genomics precision. This illustrates that multiparametric MRI radiomics features performed better than the standard radiological assessment of PCa aggressiveness (80).

Genomic analyses and gene expression signatures, such as Decipher, have the potential to become integral to risk stratification and management. Gleason 7 samples were segregated in both low and high-risk clusters in keeping with the genetic heterogeneity of this subtype. In addition to Gleason Score (GS), the Decipher expression patterns also segregated by risk category have suggested a close correlation between Gleason and Decipher score. Decipher, and GS were also consistent with previous evaluations of tumor specimens from RP. Low Decipher scores were substantially connected with Gleason scores, and all eight samples having GS 6 were categorized as Decipher low risk, based upon the

previously reported cut-points for Decipher risk groups (Decipher score < 0.45). The decipher score was also significantly positively correlated with PSA (p-value = 0.037). The signatures contain over-expressed genes in the case of belligerent PCa and genes that are not expressed adequately in belligerent PCa. There were considerable connections between these genes and quantifiable imaging features, highlighting PCa predictive signs in the radiomic characteristics. The connections have also been detected between radiomic characteristics and substantially expressed genes. Moreover, the genes' ontology analysis indicated that particular radiomic characteristics are connected with metabolism, biological and cell adhesion, and immune response. According to our knowledge, one of the few studies identified the association of radio genomic standards among men with PCa and MRI- biopsy (81). The MRI-visible lesions had GC scores compared to MRI-invisible lesions (95% CI 0.13, 0.32; $p < 0.0001$); while MRI-invisible lesions (82.6%) were at low risk. PT-RADS v2 had slight correlation with Decipher ($r = 0.54$) and high accuracy (AUC 0.863) compared to the prostate cancer grade groups (AUC 0.780) in minor lesions area (95% CI of 0.01, 0.15; $p <0.05$). The MRI phenotypes of prostate cancer can be defined through PI-RADS v2, which is positively related to a genomic classifier estimated by the early risk of metastases. Most of the MRI-invisible lesions had a low risk for early metastases based on the GC classifier. Interestingly, 17.4% of MRI- invisible tumor samples in the study had Decipher scores with intermediate or high-risk range, suggesting that not all MRI-invisible lesions have indolent biological potential. MRI can be used with genomic assays to detect lesions carrying the biological potential for early metastases. Also, the MRI phenotypes of prostate cancer are entirely related to Decipher risk groups. Although the PI-RADS v2 can easily spot the difference between lesions classifier through Decipher in low, intermediate, or high risk, in some cases, the Decipher intermediate/high risk is not visible on MRI. In conclusion, MRI phenotypes of prostate cancer, as defined by PI-RADS v2 positively associated with a genomic classifier that approximates the risk of early metastases. According to genomic classifies, most but not all, MRI-invisible lesions had a

low risk for early metastases. Thus, MRI could be used in conjunction with genomic assays to identify lesions that may carry the biological potential for early metastases (82).

4.5. Clinical decision-making regarding prostate cancer: Treatment approaches with Decipher influences

A recent study has recommended Adjuvant Radiation Treatment (ART) for men with low GC scores. Also, patients with high GC can derive much benefit from ART compared to Salvage Radiation Therapy (SRT). On a large scale, 422 men treated with positive surgical measure at RP were examined by Ross et al. The result shows a mutual relationship between higher GC score patients with metastasis (PSA < 0.2 at RT), no-RT, and minimal residual disease (MRD) SRT (PSA 0.2–0.49), SRT (PSA ≥ 0.50). According to the authors, GC's multivariable analysis had a statistically important predictor of metastasis (p=0.01) with models such as post-op RT and CAPRA-S. Additionally, they highlighted that high decipher scores improve survival without metastasis in the ART and Minimal Residual Disease (MRD). SRT individuals in comparison with non-RT and SRT groups after modifying CAPRA-S. This study also implies that patients having high GC scores might experience more benefits from early RT usage. This decision can facilitate ART through GC scores (83).

Apart from these review studies on patient results, a study on clinician treatments was recommended earlier and later administrated the decipher score among clinicians by managing SRT and ART based on the decipher scores. In the case of patients characterized by ART, 18% of them are recommended to alter their urologist treatment methodologies once knowing the GC scores. Also, the patients having SRT, 37% of them have also suggested a change within their treatment processes. On the other hand, patients having high and risky GC scores are recommended to undergo ART or SRT, and those having low decipher scores are managed through observation. However, whether the patients pursue the suggested therapies or improvement within their conditions is yet to be

ascertained (84). Approximately half of all prostate cancer deaths occur in men diagnosed with localized disease, most of which present with NCCN high-risk cancer (85). Even among the high-risk population, however, clinical outcomes vary widely (38), and the vast majority of men will not develop metastatic disease or die of PCa (86). Thus, accurate, individualized risk stratification is necessary to identify better where treatment intensification or de-escalation can be personalized to optimize patient outcomes. In the United States, the most common treatment for men with high-risk prostate cancer is radiotherapy (RT) with Long-Term Androgen-Deprivation Therapy (LT-ADT) (87). RP is a major treatment method for men having either intermediate or high-risk PCa. Though a large number of men are healed through local treatment; however, these men are entailed with the increasing incidence of developing adverse pathological characteristics and recurrence of the disease. It has been indicated that the decipher test to forecast the metastatic development among groups having adjuvant and salvage treatment after RP (88).

In recent years, RP's employment has enhanced (89), often as part of a multimodality approach, including salvage or adjuvant or RT. These findings are comparable to Nguyen et al., stating that Decipher outcome changes with 45% and 35% of the treatment recommended by urologists and oncologists, respectively. Multivariate analysis showed that GC risk was the largest factor for determining the treatment recommendations, with an adjusted OR of 6.51 (95% [CI], 4.29-9.88) and 4.17 (95% [CI] 2.26-7.70), for radiation oncologists and urologists, respectively. Decipher score results indicates that high metastatic risk leads to intensified treatment, whereas low metastatic risk leads to less aggressive suggestions. The GC results enhanced multidisciplinary agreement regarding treatment recommendations as to the probability of suggesting adjuvant treatment by radiation oncologists and urologists enhanced from 0.27 (95% CI, 0.17-0.44) to 0.46 (95% CI, 0.29-0.75) after results of the GC test were available. The GC test has largely influenced adjuvant postprostatectomy treatment recommendations, decreased disagreement between radiation oncologists and urologists, and has the potential to enhance the personalization

of postprostatectomy care (90). High-risk PCa is clinically-defined to include men harboring biopsy GG 4–5, clinical-stage T3-4, or PSA ≥20 ng/Ml (91). This definition accounts for approximately <20% of men diagnosed with prostate cancer and represents a biologically diverse range of cancers (92). Within this multi-institutional cohort of men with NCCN high-risk prostate cancer, GC scores successfully sub stratified metastatic outcomes during follow-up, while traditional clinicopathologic risk factors had a suboptimal performance. For treatment decisions that are based on prognostic risk stratification, the use of GC has superior performance to clinicopathologic methods. In conclusion, conventional clinicopathologic data had poor discrimination to risk stratifying metastatic disease development among men with high-risk prostate cancer. Decipher classifier score was a significant independent predictor of metastasis and may help distinguish men best suited for treatment intensification/de-escalation (92). Accordingly, patients are offered a wide range of management options, ranging from potential RP monotherapy to multimodal approaches. While traditional clinicopathologic risk strata help stratify localized prostate cancer patients (79, 86), these factors' ability to sub-stratify patients in the high-risk group is limited (67). Given the increasing morbidity and toxicity associated with treatment intensification, improved tools are needed to identify better patients who could be relieved with local therapy alone rather than employing a more aggressive and multimodal approach. Thus, the studies indicated that treatment options for PCa might range from ART and SRT to RP; however, the selection of treatment methodology depends upon the GC score and risk stratification.

4.6 Prostate cancer in African -American

As discussed earlier, PCa is one of the deadliest diseases prevalent among African American(AA) cases. Although the context of prostate cancer varies based on race and ethnicity. Studies have shown that AA men have a higher incidence due to the advanced anatomic stage during diagnosis and high cancer-related mortality. The potential biological claims for these disparities include racial changes in tumor morphology and responsiveness to treatment. Also, other possible extrinsic findings include the mode of screening, differences in access to health care, and treatment received. Also, when these men of diverse races were treated with an equal medical facility, differential results are more likely to reflect variations in underlying biological factors (93). However, PCa inexplicably affects AA compared to the European-American (EA) men. About 70% of the AA are nearly 70% more likely to be diagnosed with prostate cancer and twice more likely to die from the PCa when compared with their EA counterparts (94).

Similarly, another study has identified that AA men have a greater incidence of prostate cancer and more than twice the risk of prostate cancer-specific mortality compared with white men (95). Racial disparities were highest among low-grade Gleason 6 disease, in which the mortality due to PCa among black men is two times greater as compared to nonblack individuals (96). Black men are also more likely to have a comorbid illness such as cardiovascular disease (97) and diabetes (98) diagnoses that are negatively associated with survival outcomes with or without prostate cancer (99).

Novel biomarkers have been identified as a predictive measure for aggressive disease in AA men with PCa, such as Decipher (100). However, AA men experienced more likely to present with metastatic cancer and a high incidence of mortality caused by prostate cancer compared to other ethnicities and races, including the EA (99, 101). As mentioned earlier, this discrepancy is socioeconomic factors, insufficient access to medical facilities (102), and changes in genetic composition (103).

However, there is some controversy about the etiology of disparities in the results. This includes differences in disease aggressiveness, which can lead to a more potential role for biologic changes in prostate carcinogenesis among EA and AA men. Regardless of this, significant PCa biomarkers' comparisons related to PCa aggressiveness based on ethnicity or race are limited. After the validation of biomarkers, a cohort among AA and EA men was tested in gene expression to determine the differences that could predict unfavorable pathology or clinical results (101, 104). The outcome shows that a subset of the validated biomarkers performs in an ethnicity-based approach to predict at least one of the predefined clinicopathologic results. These include a loss-of-function mutation due to tumor suppressors *TP53* and *TP63 as well as* dysregulation of *MKi67*, *MSMB*, and *SRD5A2 (105, 106)*.

However, treatment defined by either radiation or surgery leads to various harms and risks, including urinary failures, irritation of rectum, erectile malfunctioning, and incontinence (107, 108), and some men may eventually regret their treatment choice (109). Black men experienced an increasing level of regret after treatment, especially among men with recurrent prostate cancer after surgery or radiation. The doctors should guarantee that all patients are fully aware of all treatment options' pros and cons to reduce the risk of subsequent regret (109). Other studies claim that black men have poorer outcomes after prostate cancer diagnosis and report greater mistrust levels on the healthcare system than nonblack men (110, 111); therefore, using biomarkers such as Decipher scores might help them have a better treatment plan. As it mentioned before, the Decipher 22 gene GC can improve post RP- decision-making provided there is active prognostic performance over clinicopathologic variables alone. Many studies claimed that assessing the GC had a modest representation among AA. The results of other studies have highlighted that alterations in gene expression affect the Decipher's proactive ability to stratify AA's risks with post RP. The data also supports further studies to improve AA health conditions with a limited number of events and validation treatment (112).

There was an average follow-up of a 9-yr, which caused 37 cases of metastasis

and 20 mortalities from PCa. Commonly, an average of 55% (n=301) of patients belonged to AA origin, and in the case of multivariable analysis, GC was the main indicating sign of metastasis among men (all $p < 0.001$). The CAPRA-S and GC had an increasing c-index for metastasis of five years (0.78 vs. 0.72) and PCSM of ten years (0.85 vs. 0.81). This study indicated GC as an effective predictor of PCa in AA compared to non-AA. Moreover, the risk c-index for PCSM of ten years was 0.9 in AA in comparison to 0.7 in non-AA. The test based upon the GC score and race in the COX model was insignificant for both metastasis and PCSM (both $p \geq 0.3$). The evidence suggests that molecular genetic drivers' prostate cancer cases and carcinogenesis progression affect race-specific mode. The observed differences were consistent with the genes found in different expression focusing on race in other studies. The difference in the level of gene expression was observed for 48% of the genes and found that magnitude of difference in gene expression was slightly small (113).

Reviewing another study, it is evident that caution should be taken when applying genomic predictors developed in predominantly EA to AA with PCa, and emphasizes the importance of conducting de novo genomic studies among samples derived from at-risk AA populations. In general, significant racial differences were observed for individual genes and correlational patterns within panels, albeit relatively small in magnitude. Out of the 60 genes examined, about 48% were differentially expressed between EA and AA. However, these proportions are imprecise because of the small number of genes related to each panel. Furthermore, about half of the genes had different expression levels, while the magnitude of median showed differences were relatively small, with the highest estimated at S1PR4 (encoding Sphingosine 1-Phosphate Receptor-4) in Decipher with 28% higher median expression among EA. The differences were observed based on the consistency with the genes found in a different race in other studies. This study's outcome provides evidence for caution when applying genomic predictors developed in predominantly EA to AA with prostate cancer. It underscores the importance of conducting new genomic studies in samples derived from at-risk AA populations (94).

In conclusion, these studies have confirmed the increasing incidence of PCa among AA, and discrimination within AA's health and socio-economic conditions plays a significant role in their approach towards treating AA. Moreover, other studies claim that Black men have poorer outcomes after PCa diagnosis and report greater mistrust levels_on the healthcare system than nonblack men. Therefore, using biomarkers such as Decipher scores might help them have a better treatment plan.

CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS

The treatment of PCa among men is continuously evolving. In the past few decades, many biomarkers have been developed to detect and treat PCa. These markers currently provide further stratification of risks and diagnosis information about the disease, which may help men with clinical complications. This may not mostly prefer biopsy compared to non-biopsy or therapy surveillance. Consequently, these tests should be done in the case of all patients. Moreover, further trials are still required for validating the markers and their use for evaluating the risks of metastasis and mortality. In addition to this, making a comparison among markers is significant for identifying the superior tests. All of the treatment options should be managed based on the individual risk profile and sensitivity to particular medical treatment. Comparisons between markers are essential to determine whether a superior test exists. Also, treatment must be administered based on cancer's risk individual profile and therapy sensitivity (45). The study following a systematic review has confirmed that Decipher score risk is closely associated with recurrence of prostate cancer patients based on their medical, genetic predictors, and demographics (e.g., races)

Moreover, the study has also confirmed that Decipher score risk can be a good predictor for prostate patients' metastasis and prostate cancer-specific mortality in men and clinical decision-making regarding Treatment Recommendations for patients. Since this research has reviewed the evidence of benefits of the Decipher test, put the usage into clinical context, made recommendations to help providers and patients know which treatment might be more appropriate based on the GC score, and when they should consider using the Decipher score based on the works of literature. However, novel DNA-based genomic assays are important to facilitate patient's treatment and physicians to customize the right treatment (114) as well as post-operative therapy options (6, 42, 115). However, all these approaches offer important prognostic information. However, only the Decipher prostate cancer classifier has been shown to be predictive (63). At the

same time, there are considerations in post RP cases suggested by the National Comprehensive Cancer Network Guidelines (NCCN) (56) requirement and cross-validation, one-on-one comparisons with potential biomarkers, development of marker panels applicable to many clinical contexts, and treatment, accessible, and cheap. The challenges in cancer biomarker developments for prostate cancer are extensive validation (46).

Furthermore, Decipher has been confirmed to predict metastasis among patients with biochemical recurrence and radiotherapy and salvage post RP. The Decipher post RP test is administered to men with severe clinical or pathologic cases (e.g., biochemical recurrence, pT3 disease, and pathologic stage T2 with positive margins). The biopsy GC scores were also predictive in other key results, including the presence of main Gleason pattern 4/5 disease and a major risk of metastasis within five years. Recent results have focused on genomics markers (116, 117), with clinical insight on biological information obtained from routine diagnostic biopsies. The studies also indicated that patients with high Decipher scores in RP specimens many benefitted from adjuvant treatment compared to the salvage radiation treatment (116). The presence of molecular testing, such as Decipher, has shown an improved clinical decision making in localized prostate cancer (118, 119).

However, these studies have not been connected to disease consequences, and thus, the true medical significance of these tests continues to be recognized through potential clinical trials and registries (120). Though molecular tests' signals will possibly be improved with further study and development, these tests are presently accessible and have retrospective evidence of their utility.

The literature has claimed that GC score has an adequate ability to risk-stratify African-American men post-RP. These results claim that Decipher gene expression panels are a better predictor among AA men than other biomarkers. Moreover, Other studies claim that Black men have poorer outcomes after Pca diagnosis and report greater mistrust levels_on the healthcare system than nonblack men. Therefore, using biomarkers such as Decipher scores might help

them have a better treatment plan. Decipher was a very good predictor of poor outcome and performed well in both AA and non-AA. Therefore, the Decipher test can be confidently used in patients regardless of race.

Furthermore, Decipher correlated with baseline tumors has been identified in more than 2,000 patients with tumor specimens and genomic testing. Service providers and patients can also determine their willingness to accept a specific threshold risk related to metastasis and determining whether the genomic testing would be necessary. Based on the wide distribution of risk potential and classification of GC score in regrouping patients, this can alter the management, adjuvant or salvage radiation treatment followed by prostatectomy and genomic testing that can be helpful for postoperative setting (86).

To conclude, further trials are still required for validating the Decipher biomarkers. All of the treatment options should be managed based on the individual risk profile and sensitivity to particular medical treatment. As a future direction, scientists could enhance the decipher score test ability to be run on blood samples of patients instead of tumor tissue which will help patients use decipher as a screening test at the asymptomatic level. In this way, this test can be routinely done for patients with a family history of prostate cancer, and the biopsy will not be required during the screening stage. The other advantages of running decipher test on blood would be reducing the cost to both the patient and health community.

Table 1: Role of Decipher biomarker in treating PCa

Study Design	Sample	Median Follow-up time	Endpoints	Main results
Retrospective study	139 patients with pT3 stage or positive margins at RP undergoing adjuvant RT	8-yrs	Biochemical recurrence, metastatic PCa	Risk stratification based on a GC score/8-yrs incidence of biochemical recurrence: 21% (low-risk) – 81% (high-risk, $p < 0.0001$). 8-yrs incidence of metastatic PCa: 0%-17%/(p-0.032). The GC is able to predict freedom of metastases (AUC 0.78), and freedom of biochemical recurrence (AUC 0.75). The decipher score predicted metastasis and BF after post-RP irradiation. Men with lower GC risk score might benefit from delayed RT in comparison with higher GC score patients (50).
Retrospective study	545 patients after RP	16.9 yrs	Early metastasis (within 5yrs)	Multivariate analysis: Genomic classifier independent predictor of early metastasis (OR 1.36, 95% CI 1.16– 1.60, $p < 0.001$) compared to patients with biochemical recurrence alone. Patients with high GC scores experienced earlier death rate from PCa and reduced total survival rate (42)
Case-Control study	85 patients with high- risk PC and biochemical recurrence after RP	42.6 months	Metastatic PCa	Metastatic PCa in 8% of patients with low-risk profile based on the genomic classifier (vs. 40% with high- risk profile, $p < 0.001$)- Multivariate analysis: GC is able to predict metastatic PCa following biochemical recurrence (AUC 0.82, 95% CI 0.76–0.86; $p = 0.003$), outplays Gleason score alone (0.64, 0.58-0.70), dtPSA (0.69, 0.58–0.70) and time-to-biochemical-recurrence (0.52, 0.46–0.59) (61)
Cohort study	57 patients after prostate biopsy	8yrs	Metastatic PCa	The GC is able to predict a10-years risk of metastatic PCa following RP even at the time of prostate biopsy (HR for 10% score increase 1.75, 95% CI 1.97–2.81, $p = 0.02$). Decipher is associated with aggressive disease and intensified treatment. It can be a useful tool to improve local treatment and planning of newly diagnosed PCa patients (62)

Combined use of case-control & cohort data	561 patients with adverse pathologic features after RP	13.0 yrs	Metastatic PCa/10yrs cancer-specific survival	For high decipher GC score (> 0.6) Vs low-intermediate (≤ 0.6), adjusted OR for CAPRA-S 3.91 (95% CI 2.43–6.29). Decipher established clinically important prediction of PCSM at 10 yrs, independent of CAPRA-S, in patients with adverse pathologic features, BCR2 after RP. GC may improve treatment decision-making for patients with adverse or high-risk pathology after RP (54).
Cohort study	235 patients with intermediate and high- risk disease	6yrs	Metastatic PCa/Cancer-specific survival	Multivariate analysis: genomic classifier is a significant predictor of metastasis (HR 1.37 per 10% increase in score, 95% CI 1.06–1.78, p = 0.018) and CSS (HR 1.57 per 10% increase in score, 95% CI: 1.03–2.48, p = 0.037). Biopsy Decipher GC predicted PCSM and metastasis from diagnostic biopsy specimens of primarily intermediate- and high-risk patients treated with first-line RT or RP (60).
Cohort study	2342 consecutive RP, Median patient age at RP was 66 years (IQR, 60−69)	Not mentioned	consecutive radical prostatectomy (RP) patients	Decipher score had a positive association with pathologic GC (PGS; *r*=0.37, 95% confidence interval [CI] 0.34−0.41), pathologic T-stage (*r*=0.31, 95% [CI] 0.28−0.35), CAPRA-S (*r*=0.32, 95% CI 0.28−0.37) and patients' age (*r*=0.09, 95% [CI] 0.05-0.13). Decipher score reclassified 52%, 76% and 40% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively. They found a 28% incidence of high-risk PCa through the Decipher score in pT2 men and 7% low-risk in pT3b/pT4, PGS 8−10 men. Decipher score had a confident Spearman's correlation of 0.09 (95% CI 0.05-0.13, *P*<0.001) compared with the patients' age. This analysis shows that 54% of patients aged less than 50 were grouped as low risk, while only 30% of patients were 70 or older recognized with low Decipher risk (51).
Case-control cohort study	54 patients with Median age of 64	10-yr & 12-yr for US and European, respectively.	distant metastasis within 5yr	Every time 10% enhancement in Decipher score results in an increase in the risk of distant metastases within 10-yr follow-up, with an odds ratio of 1.53 (95% [CI]1.06–2.22; p=0.025) and 1.58 (95% [CI]1.31–1.92; p < 0.001) for the US and European groups, respectively. This study confirms Decipher as a predictor for metastatic recurrence, even in

				patients with high-risk and nonmetastatic PC (65).
Retrospective study	991 patients (previously undertook RP or radiation therapy as the main treatment)	8-yr	Biochemical Recurrence, Distant Metastasis	During the cohort development process, the 10-year distant metastasis c-index mainly for NCCN 4 tiers was 0.68 (95% CI 0.64–0.72), CAPRA was 0.68 (95% CI 0.62–0.74) while the 6-tier clinical-genomic risk was 0.77 (0.72–0.81). Based on the validation cohort, the c-index for the 6-tier clinical genomic risk was 0.84 (95% CI 0.61–0.93). The integration of GC risk and NCCN risk improved the prognosis in assessing metastatic disease at ten years after the main treatment based upon the preliminary medical factors and GC score of biopsy samples (68).
Retrospective case-control study	260 patients, of whom 99 experienced metastases	9-yr	with an increased cumulative incidence of biochemical recurrence, metastasis, and prostate cancer–specific mortality	The total incidence of metastasis was 47%, and 12% for patients having high and low Decipher scores; decipher was an independent prognosticator of metastasis in multivariable analysis (hazard ratio 1.26 per 10% increase; $p < 0.01$). In patients which have not gone through salvage or adjuvant therapy after prostatectomy until the progression of metastasis, higher Decipher scores associated with clinical events, and inclusion of Decipher scores upgraded the predictive performance of confirmed clinicopathologic risk models (72).

Cohort study	100 patients with intermediate-risk and high-risk	distant metastasis followed radiation therapy and biochemical failure	5.1 years	Every 0.1-unit enhancement in GC score was importantly correlated with time to distant metastasis (HR: 1.40 (1.10–1.84), *P*=0.006) and maintained significant after managing the clinical variables on MVA (adjusted HR: 1.36 (1.04–1.83), *P*=0.024). The c-index for 5-year distant metastasis was 0.76 (95 CI, 0.57–0.89) for the GC score. Using pre-specified GC risk score categories, the cumulative incidence of metastasis for GC>0.6 reached 20% at 5-yr after radiation (*P*=0.02). Men with the highest GC risk (GC>0.6) had increasing metastasis rates despite multi-modal therapy, recommending that they could be candidates for intensifying the treatment or enrolling for clinical trials (69).
Case-control cohort study	169 men were treated with RP	Rapid metastasis (RM), within 5 yr after RP, as shown by positive CT or bone scan.	5-yr	RM patients established metastasis at an average age 2.3 yr (interquartile range: 1.7–3.3). In multivariable analysis, decipher was a prominent prognosticator of RM (odds ratio: 1.48; p= 0.018) after regulating the clinical risk factors. Decipher had the highest c-index, 0.77, in comparison with CAPRA S (c-index: 0.72) and the Stephenson model (c-index: 0.75) as well as with a panel of previously reported PCa biomarkers irrelevant to Decipher. The combination of Decipher score into the Stephenson nomogram enhanced the c- index from 0.75 (95% [CI], 0.65–0.85) to 0.79 (95% [CI], 0.68–0.89). Decipher was confirmed as a genomic metastasis signature for predicting metastatic disease within 5 yr after surgery in a cohort of high- risk patients (70).

Retrospective study	188 patients with pT3 or margin-positive PCa	Metastases in men undergoing post-RP RT	follow-up times after RP and after RT were 10 and 8 years, respectively	The cumulative incidence of metastasis at 5 yr after RT was 0%, 9%, and 29% for low, average, and high GC scores, respectively (*P* = .002). Within the low GC grades (< 0.4), there were no changes in the cumulative occurrence of metastasis in comparison with patients who had done adjuvant or salvage RT (*P* = .79). However, for patients having higher GC scores (≥ 0.4), the total occurrence of metastasis at 5 years was 6% for men treated with adjuvant RT in comparison with 23% for patients treated with salvage RT (*P* < .01). In men treated with post-RP RT, GC is predictive for the establishment of clinical metastasis beyond routine clinical and pathologic features. Although preliminary, patients having low GC scores are best managed with salvage RT, whereas those having high GC scores benefit from adjuvant therapy (63).
Retrospective study	185 patients with high risk	Metastatic PCa, RP	6.9- yr	For patients with both high GC and CAPRA-S scores, CSM's cumulative incidence was 45% at 10 years. Both CAPRA-S and GC were significant prognosticator of CSM. GC was shown to re-stratify many men characterized by high-risk based on CAPRA-S ≥6 alone. Patients characterized by both increasing GC and CAPRA-S risk are at increasing risk of developing lethal PCa. The findings of the studies recommended that integration of GC may enable improved indication of post-RP patients who should be considered for further treatment and therapies (71).
Cohort study	169 patients with metastatic Pca	RM patients established metastasis at an average age of 2.3 yr	7.8-yr	Decipher was an important predictor of RM (OR: 1.48; p = 0.018). Combination of Decipher into the Stephenson nomogram enhanced the c-index from 0.75 (95% [CI] 0.65–0.85) to 0.79 (95% [CI] 0.68–0.89). Decipher was impartially confirmed as a genomic metastasis signature for predicting metastatic disease within 5 yr after operation among groups of high-risk men treated with RP and managed without adjuvant therapy. A combination of Decipher into clinical

				nomograms enhanced the prediction of RM. Decipher may enable at the risk of developing metastasis who should be considered for further clinical trials or therapies based upon multimodal (6).
Cohort study	422 patients with metastatic Pca	Clinical metastasis (regional or distant)	8-yr	During the study follow-up, 37 men established metastasis with an average follow-up of 8 years. Decipher had independent predictive value on multivariable analysis for metastasis (P<0.05). Men with low decipher score value, and low-to-intermediate CAPRA-S have a decreasing rate of metastatic events irrespective of treatment selection. Contrarily, men with high GC and CAPRA-S benefit from ART; however, metastasis's total incidence remains high. The decision regarding the need and timing of extra- local therapy followed by RP is nuanced and needs patients and providers to balance morbidity risks with enhanced oncological outcomes. Post-RP therapy can be safely avoided for men who are at low risk according to clinical–genomic risk, whereas those at high risk should be enrolled for further trials (83).
Cohort study	150 patients (with metastatic disease, high/low risks)	ART and SRT		Before the Decipher test, an observation was recommended for 89% of patients considering ART and 58% of patients considering SRT. After Decipher testing, 18% (95% CI, 12%·25%) of the recommendations regarding treatment transformed in the ART arm, together with 31% among high-risk patients; and 32% (95% [CI], 24%·42%) of management suggestions altered in the salvage arm, including 56% within high-risk patients. Decisional Conflict Scale (DCS) scores were improved after reviewing Decipher test results the PCa related concerns altered after Decipher testing, terror of PCa disease reappearance in the ART arm (P = .02), and PCa-related concerns the SRT arm (P = .05) reduced significantly among patients with low risk. GC results reported per 5% increase in 5-year metastasis possibility were correlated with the verdict to follow ART and SRT in multivariable logistic regression analysis. Decipher test results were associated with making decisions about treatment and improving its

				effectiveness among men with PCa who were seeing ART and SRT (84).
Cohort study	548 men, (55%, n = 301 AA), (43%, n = 235 Caucasian), (2%, n = other races 11)	regional or distant metastasis	9- yrs	In multivariable analyses, GC (high vs. intermediate and intermediate vs. low) was a significant prognosticator of metastasis among all men (all $p < 0.001$). Approving previous studies, relative to CAPRA-S, GC had a higher C-index for 5-year metastasis (0.78 vs. 0.72) and 10-year PCSM (0.85 vs. 0.81). There was a recommendation that GC was more effective predictor in AA as compared to non-AA. Particularly, the 5-year metastasis risk C-index was 0.86 in AA vs. 0.69 in non-AA and the 10-year PCSM risk C-index was 0.91 in AA vs. 0.78 in non-AA. GC is a good predictor of inadequate outcome and did well among both AA and non-AA. Thus, the data confirms the GC's employment for risk stratification in AA post-RP, and it is recommended that GC may actually work better in AA (112).

Reference

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
3. Lee MC. Knowledge, barriers, and motivators related to cervical cancer screening among Korean-American women. A focus group approach. Cancer Nurs. 2000;23(3):168-75.
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
5. Biosciences. Decipher Biosciences 2020 [Available from: https://decipherbio.com/prostate/
6. Klein EA, Yousefi K, Haddad Z, Choeurng V, Buerki C, Stephenson AJ, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol. 2015;67(4):778-86.
7. Alshalalfa M, Crisan A, Vergara IA, Ghadessi M, Buerki C, Erho N, et al. Clinical and genomic analysis of metastatic prostate cancer progression with a background of postoperative biochemical recurrence. BJU Int. 2015;116(4):556-67.
8. Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev. 2010;24(18):1967-2000.
9. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU- AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-92.
10. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
11. Cucchiara V, Cooperberg MR, Dall'Era M, Lin DW, Montorsi F, Schalken JA, et al. Genomic Markers in Prostate Cancer Decision Making. Eur Urol. 2018;73(4):572-82.
12. Datta K, Muders M, Zhang H, Tindall DJ. Mechanism of lymph node metastasis in prostate cancer. Future Oncol. 2010;6(5):823-36.
13. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. Genes Dev. 2018;32(17-18):1105-40.
14. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119(6):1420-8.
15. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014;15(3):178-96.
16. Brabletz T, Kalluri R, Nieto MA, Weinberg RA. EMT in cancer. Nat Rev Cancer. 2018;18(2):128-34.
17. Mittal V. Epithelial Mesenchymal Transition in Tumor Metastasis. Annu Rev Pathol. 2018;13:395-412.
18. Benafif S, Eeles R. Genetic predisposition to prostate cancer. Br Med Bull.

2016;120(1):75-89.
19. Cooney KA. Inherited Predisposition to Prostate Cancer: From Gene Discovery to Clinical Impact. Trans Am Clin Climatol Assoc. 2017;128:14-23.
20. Benafif S, Kote-Jarai Z, Eeles RA. A Review of Prostate Cancer Genome-Wide Association Studies (GWAS). Cancer Epidemiol Biomarkers Prev. 2018;27(8):845-57.
21. Shenoy D, Packianathan S, Chen AM, Vijayakumar S. Do African-American men need separate prostate cancer screening guidelines? BMC Urol. 2016;16(1):19.

22. Huang FW, Mosquera JM, Garofalo A, Oh C, Baco M, Amin-Mansour A, et al. Exome Sequencing of African-American Prostate Cancer Reveals Loss-of-Function ERF Mutations. Cancer Discov. 2017;7(9):973-83.
23. Grozescu T, Popa F. Prostate cancer between prognosis and adequate/proper therapy. J Med Life. 2017;10(1):5-12.
24. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. Jama. 2017;317(24):2532-42.
25. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. 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(2):244-52.
26. Rubin MA, Girelli G, Demichelis F. Genomic Correlates to the Newly Proposed Grading Prognostic Groups for Prostate Cancer. Eur Urol. 2016;69(4):557-60.
27. Rodrigues G, Warde P, Pickles T, Crook J, Brundage M, Souhami L, et al. Pre-treatment risk stratification of prostate cancer patients: A critical review. Can Urol Assoc J. 2012;6(2):121-7.
28. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415- 24.
29. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377(2):132-42.
30. Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, Eisenstein AS, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol. 2009;27(21):3459-64.
31. Sauter G, Steurer S, Clauditz TS, Krech T, Wittmer C, Lutz F, et al. Clinical Utility of Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens. Eur Urol. 2016;69(4):592-8.
32. Reese AC, Cowan JE, Brajtbord JS, Harris CR, Carroll PR, Cooperberg MR. The quantitative Gleason score improves prostate cancer risk assessment. Cancer. 2012;118(24):6046-54.
33. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016;69(3):428- 35.
34. Reese AC, Cooperberg MR, Carroll PR. Minimal impact of clinical stage on prostate cancer prognosis among contemporary patients with clinically localized disease. J Urol. 2010;184(1):114-9.
35. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018;16(5s):620-3.
36. Sundi D, Ross AE, Humphreys EB, Han M, Partin AW, Carter HB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol. 2013;31(24):2991-7.
37. Serrano NA, Anscher MS. Favorable vs Unfavorable Intermediate-Risk Prostate Cancer: A Review of the New Classification System and Its Impact on Treatment Recommendations. Oncology (Williston Park). 2016;30(3):229-36.
38. Reese AC, Pierorazio PM, Han M, Partin AW. Contemporary

evaluation of the National Comprehensive Cancer Network prostate cancer risk classification system. Urology. 2012;80(5):1075-9.
39. Zumsteg ZS, Zelefsky MJ. Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care? Lancet Oncol. 2012;13(6):e259-69.
40. Sinnott JA, Peisch SF, Tyekucheva S, Gerke T, Lis R, Rider JR, et al. Prognostic Utility of a New mRNA Expression Signature of Gleason Score. Clin Cancer Res. 2017;23(1):81-7.
41. Irshad S, Bansal M, Castillo-Martin M, Zheng T, Aytes A, Wenske S, et al. A molecular signature predictive of indolent prostate cancer. Sci Transl Med. 2013;5(202):202ra122.
42. Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One. 2013;8(6):e66855.
43. Wang Y, Navin NE. Advances and applications of single-cell sequencing technologies. Mol Cell. 2015;58(4):598-609.
44. Kretschmer A, Tilki D. Biomarkers in prostate cancer - Current clinical utility and future perspectives. Crit Rev Oncol Hematol. 2017;120:180-93.
45. Gadzinski AJ, Cooperberg MR. Prostate Cancer Markers. Cancer Treat Res. 2018;175:55-86.
46. Kohaar I, Petrovics G, Srivastava S. A Rich Array of Prostate Cancer Molecular Biomarkers: Opportunities and Challenges. Int J Mol Sci. 2019;20(8).
47. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Reporting Recommendations for Tumor Marker Prognostic Studies. Journal of Clinical Oncology. 2005;23(36):9067- 72.
48. Ballman KV. Biomarker: Predictive or Prognostic? J Clin Oncol. 2015;33(33):3968-71.
49. Badani KK, Thompson DJ, Brown G, Holmes D, Kella N, Albala D, et al. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. BJU Int. 2015;115(3):419-29.
50. Den RB, Feng FY, Showalter TN, Mishra MV, Trabulsi EJ, Lallas CD, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int J Radiat Oncol Biol Phys. 2014;89(5):1038-46.
51. Den RB, Santiago-Jimenez M, Alter J, Schliekelman M, Wagner JR, Renzulli Ii JF, et al. Decipher correlation patterns post prostatectomy: initial experience from 2 342 prospective patients. Prostate Cancer Prostatic Dis. 2016;19(4):374-9.
52. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2018;199(3):683-90.
53. Ross AE, D'Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. Prostate Cancer Prostatic Dis. 2016;19(1):1-6.
54. Karnes RJ, Choeurng V, Ross AE, Schaeffer EM, Klein EA, Freedland SJ, et al. Validation of a Genomic Risk Classifier to Predict Prostate Cancer-specific Mortality in Men with Adverse Pathologic

Features. Eur Urol. 2018;73(2):168-75.
55. Nakagawa T, Kollmeyer TM, Morlan BW, Anderson SK, Bergstralh EJ, Davis BJ, et al. A Tissue Biomarker Panel Predicting Systemic Progression after PSA Recurrence Post-Definitive Prostate Cancer Therapy. PLoS ONE. 2008;3(5):1-14.
56. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, et al. Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw. 2016;14(1):19-30.
57. Cooperberg MR, Erho N, Chan JM, Feng FY, Fishbane N, Zhao SG, et al. The Diverse Genomic Landscape of Clinically Low-risk Prostate Cancer. Eur Urol. 2018;74(4):444-52.
58. Zhao SG, Chang SL, Spratt DE, Erho N, Yu M, Ashab HA, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol. 2016;17(11):1612-20.
59. Zhao SG, Chang SL, Erho N, Yu M, Lehrer J, Alshalalfa M, et al. Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy. JAMA Oncol. 2017;3(12):1663-72.
60. Nguyen PL, Haddad Z, Ross AE, Martin NE, Deheshi S, Lam LLC, et al. Ability of a Genomic Classifier to Predict Metastasis and Prostate Cancer-specific Mortality after Radiation or Surgery based on Needle Biopsy Specimens. Eur Urol. 2017;72(5):845-52.
61. Ross AE, Feng FY, Ghadessi M, Erho N, Crisan A, Buerki C, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis. 2014;17(1):64-9.
62. Klein EA, Haddad Z, Yousefi K, Lam LL, Wang Q, Choeurng V, et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. Urology. 2016;90:148-52.
63. Den RB, Yousefi K, Trabulsi EJ, Abdollah F, Choeurng V, Feng FY, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol. 2015;33(8):944-51.
64. Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, Mitra AP, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol. 2013;190(6):2047-53.
65. Van den Broeck T, Moris L, Gevaert T, Tosco L, Smeets E, Fishbane N, et al. Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery. Eur Urol Oncol. 2019;2(5):589-96.
66. Knudsen BS, Kim HL, Erho N, Shin H, Alshalalfa M, Lam LLC, et al. Application of a Clinical Whole- Transcriptome Assay for Staging and Prognosis of Prostate Cancer Diagnosed in Needle Core Biopsy Specimens. J Mol Diagn. 2016;18(3):395-406.
67. Spratt DE, Zhang J, Santiago-Jiménez M, Dess RT, Davis JW, Den RB, et al. Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. J Clin Oncol. 2018;36(6):581-90.
68. Spratt DE, Zhang J, Santiago-Jiménez M, Dess RT, Davis JW, Den

RB, et al. Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. Journal of Clinical Oncology. 2018;36(6):581-90.
69. Nguyen PL, Martin NE, Choeurng V, Palmer-Aronsten B, Kolisnik T, Beard CJ, et al. Utilization of biopsy-based genomic classifier to predict distant metastasis after definitive radiation and short-course ADT for intermediate and high-risk prostate cancer. Prostate Cancer Prostatic Dis. 2017;20(2):186-92.
70. Klein EA, Yousefi K, Haddad Z, Choeurng V, Buerki C, Stephenson AJ, et al. A Genomic Classifier Improves Prediction of Metastatic Disease Within 5 Years After Surgery in Node-negative High-risk Prostate Cancer Patients Managed by Radical Prostatectomy Without Adjuvant Therapy. European Urology. 2015;67(4):778-86.
71. Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high- risk prostatectomy cohort. Eur Urol. 2015;67(2):326-33.
72. Ross AE, Johnson MH, Yousefi K, Davicioni E, Netto GJ, Marchionni L, et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol. 2016;69(1):157-65.
73. Yossepowitch O, Eggener SE, Serio AM, Carver BS, Bianco FJ, Scardino PT, et al. Secondary Therapy, Metastatic Progression, and Cancer-Specific Mortality in Men with Clinically High-Risk Prostate Cancer Treated with Radical Prostatectomy. European Urology. 2008;53(5):950-9.
74. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int. 2013;111(4):543-8.
75. Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Annals of Oncology. 2005;16(4):579-84.
76. Spratt DE, Dai DLY, Den RB, Troncoso P, Yousefi K, Ross AE, et al. Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy. Eur Urol. 2018;74(1):107-14.

77. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. N Engl J Med. 2020;382(10):917-28.
78. Borofsky S, George AK, Gaur S, Bernardo M, Greer MD, Mertan FV, et al. What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate. Radiology. 2018;286(1):186-95.
79. Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgiran AM, Hsu W, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. Eur Urol. 2019;75(5):712-20.
80. Hectors SJ, Cherny M, Yadav KK, Beksaç AT, Thulasidass H, Lewis S, et al. Radiomics Features Measured with Multiparametric Magnetic Resonance Imaging Predict Prostate Cancer Aggressiveness. J Urol. 2019;202(3):498-505.
81. Stoyanova R, Pollack A, Takhar M, Lynne C, Parra N, Lam LL, et al. Association of multiparametric MRI quantitative imaging features with prostate cancer gene expression in MRI-targeted prostate biopsies. Oncotarget. 2016;7(33):53362-76.
82. Purysko AS, Magi-Galluzzi C, Mian OY, Sittenfeld S, Davicioni E, du Plessis M, et al. Correlation between MRI phenotypes and a genomic classifier of prostate cancer: preliminary findings. Eur Radiol. 2019;29(9):4861-70.
83. Ross AE, Den RB, Yousefi K, Trock BJ, Tosoian J, Davicioni E, et al. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk. Prostate Cancer Prostatic Dis. 2016;19(3):277-82.
84. Gore JL, du Plessis M, Santiago-Jiménez M, Yousefi K, Thompson DJS, Karsh L, et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. Cancer. 2017;123(15):2850-9.
85. Patrikidou A, Loriot Y, Eymard JC, Albiges L, Massard C, Ileana E, et al. Who dies from prostate cancer? Prostate Cancer and Prostatic Diseases. 2014;17(4):348-52.
86. Sundi D, Tosoian JJ, Nyame YA, Alam R, Achim M, Reichard CA, et al. Outcomes of very high-risk prostate cancer after radical prostatectomy: Validation study from 3 centers. Cancer. 2019;125(3):391-7.
87. Mahal BA, Butler S, Franco I, Spratt DE, Rebbeck TR, D'Amico AV, et al. Use of Active Surveillance or Watchful Waiting for Low-Risk Prostate Cancer and Management Trends Across Risk Groups in the United States, 2010-2015. Jama. 2019;321(7):704-6.
88. Ross A, Johnson MH, Yousefi K, Davicioni E, Fedor HL, Glavaris S, et al. Tissue-based genomics to augment post-prostatectomy risk stratification in a natural history cohort. Journal of Clinical Oncology. 2015;33(15_suppl):5059-.
89. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990-2013. Jama. 2015;314(1):80-2.
90. Nguyen PL, Shin H, Yousefi K, Thompson DJ, Hornberger J, Hyatt AS, et al. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. Urology. 2015;86(1):35-40.
91. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice

Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(5):479- 505.
92. Cooperberg MR, Lubeck DP, Mehta SS, Carroll PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). J Urol. 2003;170(6 Pt 2):S21-5; discussion S6-7.
93. Uchio E, Meyskens FL, Wang PH. Deciphering the Effect of Metformin on Prostate Cancer Risk by Ethnicity. Cancer Prev Res (Phila). 2016;9(10):777-8.
94. Powell IJ, Bollig-Fischer A. Minireview: the molecular and genomic basis for prostate cancer health disparities. Mol Endocrinol. 2013;27(6):879-91.

95. Mahal BA, Ziehr DR, Aizer AA, Hyatt AS, Sammon JD, Schmid M, et al. Getting back to equal: The influence of insurance status on racial disparities in the treatment of African American men with high- risk prostate cancer. Urol Oncol. 2014;32(8):1285-91.
96. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate Cancer-Specific Mortality Across Gleason Scores in Black vs Nonblack Men. Jama. 2018;320(23):2479-81.
97. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. Circulation. 2005;111(10):1233-41.
98. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. Jama. 2000;283(17):2253-9.
99. Dess RT, Hartman HE, Mahal BA, Soni PD, Jackson WC, Cooperberg MR, et al. Association of Black Race With Prostate Cancer-Specific and Other-Cause Mortality. JAMA Oncol. 2019;5(7):975-83.
100. Yamoah K, Johnson MH, Choeurng V, Faisal FA, Yousefi K, Haddad Z, et al. Novel Biomarker Signature That May Predict Aggressive Disease in African American Men With Prostate Cancer. J Clin Oncol. 2015;33(25):2789-96.
101. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010;19(8):1893-907.
102. Albain KS, Unger JM, Crowley JJ, Coltman CA, Jr., Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. J Natl Cancer Inst. 2009;101(14):984-92.
103. Kerns SL, Ostrer H, Stock R, Li W, Moore J, Pearlman A, et al. Genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2010;78(5):1292-300.
104. Erho N, Buerki C, Triche TJ, Davicioni E, Vergara IA. Transcriptome-wide detection of differentially expressed coding and non-coding transcripts and their clinical significance in prostate cancer. J Oncol. 2012;2012:541353.
105. Zeigler-Johnson CM, Walker AH, Mancke B, Spangler E, Jalloh M, McBride S, et al. Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. Hum Hered. 2002;54(1):13-21.
106. Rahimi M, Ghanbari M, Fazeli Z, Rouzrokh M, Omrani S, Mirfakhraie R, et al. Association of SRD5A2 gene mutations with risk of hypospadias in the Iranian population. J Endocrinol Invest. 2017;40(4):391-6.
107. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436-45.
108. Pardo Y, Guedea F, Aguiló F, Fernández P, Macías V, Mariño A, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol. 2010;28(31):4687-96.
109. Mahal BA, Chen MH, Bennett CL, Kattan MW, Sartor O, Stein K, et al. The association between race and treatment regret among men with recurrent prostate cancer. Prostate Cancer Prostatic Dis. 2015;18(1):38-42.

110. Halbert CH, Weathers B, Delmoor E, Mahler B, Coyne J, Thompson HS, et al. Racial differences in medical mistrust among men diagnosed with prostate cancer. Cancer. 2009;115(11):2553-61.
111. Moore AD, Hamilton JB, Knafl GJ, Godley PA, Carpenter WR, Bensen JT, et al. The influence of mistrust, racism, religious participation, and access to care on patient satisfaction for African American men: the North Carolina-Louisiana Prostate Cancer Project. J Natl Med Assoc. 2013;105(1):59-68.
112. Howard LE, Zhang J, Fishbane N, Hoedt AM, Klaassen Z, Spratt DE, et al. Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting. Prostate Cancer Prostatic Dis. 2019.
113. Creed JH, Berglund AE, Rounbehler RJ, Awasthi S, Cleveland JL, Park JY, et al. Commercial Gene Expression Tests for Prostate Cancer Prognosis Provide Paradoxical Estimates of Race-Specific Risk. Cancer Epidemiol Biomarkers Prev. 2020;29(1):246-53.
114. Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol. 2011;12(3):245-55.
115. Cooperberg MR, Simko JP, Cowan JE, Reid JE, Djalilvand A, Bhatnagar S, et al. Validation of a cell- cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol. 2013;31(11):1428-34.
116. Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzarano SM, Maddala T, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol. 2014;66(3):550-60.
117. Blume-Jensen P, Berman DM, Rimm DL, Shipitsin M, Putzi M, Nifong TP, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. Clin Cancer Res. 2015;21(11):2591-600.
118. Shore N, Concepcion R, Saltzstein D, Lucia MS, van Breda A, Welbourn W, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr Med Res Opin. 2014;30(4):547-53.
119. Crawford ED, Scholz MC, Kar AJ, Fegan JE, Haregewoin A, Kaldate RR, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. Curr Med Res Opin. 2014;30(6):1025-31.
120. Apolo AB, Riches J, Schöder H, Akin O, Trout A, Milowsky MI, et al. Clinical value of fluorine-18 2- fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. J Clin Oncol. 2010;28(25):3973-8.