Analyzing Prostate-Specific Antigen (PSA) Trajectories and the Impact of COVID-19 on Prostate Cancer Screening and Diagnosis in Manitoba

By

Qunfeng Wang

A thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Department of Community Health Sciences

University of Manitoba

Winnipeg

Abstract

Background:

Prostate cancer is the most common cancer among Canadian men. However, screening for this cancer using the Prostate-Specific Antigen (PSA) test is not undertaken on a population-wide base and remains debatable among professional organizations due to potential overdiagnosis. Despite the debate, the PSA testing plays a crucial role in both the early detection and ongoing monitoring of prostate cancer. While numerous studies have revealed strong associations between PSA levels and cancer occurrence, aggressiveness, and recurrence, few have examined the comprehensive PSA trajectories from initial diagnosis through treatment to subsequent recurrences. This study aims to fill this gap by exploring the PSA trajectories in patients with high risk of prostate cancer, alongside investigating the impact of the COVID-19 pandemic on the PSA screening and diagnosis of prostate cancer.

Objectives:

The objectives of this study are as follows: 1) to identify distinct PSA trajectories and their associated factors in patients who underwent prostate biopsy; 2) to examine the relationships between PSA trajectories and the cancer's occurrence, aggressiveness, and recurrence; 3) to assess the impact of COVID-19 on PSA screening and diagnosis of prostate cancer.

Study Population and Method:

The study focuses on men aged 40 and older in Winnipeg who were considered at high risk for prostate cancer and underwent prostate biopsies in 2019. After applying exclusion criteria, 856 patients remained available for PSA trajectory analysis. Crucial data, spanning from 2008 to 2023, include PSA test results, biopsy findings, and post-prostatectomy monitoring

information. To assess the pandemic's impact, the analysis encompasses all Manitoba men who had PSA tests from 2016 and 2023.

Statistical Analysis:

A group-based trajectory modeling approach was used to identify the distinctive trajectories of PSA levels among men who underwent prostate biopsies. Model selection was guided by the Bayesian information criterion (BIC), along with model parsimony, stability, and clinical relevance. Multinomial logistic regression models were used to examine factors linked with trajectory group membership, while the generalized linear models were used to explore how the trajectory groups associated with cancer's occurrence, aggressiveness, and recurrence. To assess the COVID-19 pandemic's impact on prostate cancer screening and diagnosis, a descriptive time-series analysis was performed. The Wilcoxon rank sum test was used to compare monthly screening and diagnosis rates before, during and after the pandemic.

Result:

Five distinct PSA trajectory classes were identified through group-based trajectory modeling, reflecting diverse patterns of PSA progression among high-risk men in Winnipeg, Canada. Classes 1 (18.6%) and 2 (30.8%) showed moderate initial levels, a pre-biopsy increase, and post-biopsy declines to low (Class 1) or very low (Class 2) levels, indicating effective intervention; Class 3 (45.6%), the largest group, demonstrated only a slight post-biopsy decrease followed by a rebound to high PSA, suggesting incomplete treatment response. Class 4 (3.3%) exhibited low initial levels with sharp, sustained increases, reflecting aggressive disease, while Class 5 (1.8%) had persistently high pre-biopsy PSA and a dramatic drop after intervention, indicating prompt management of severe cases. Multinomial logistic regression analysis demonstrated that demographic (age and PSA testing frequency), clinical (cancer diagnosis,

aggressiveness, resection, and recurrence), and socioeconomic factors (ethnocultural composition and situational vulnerability) were significantly associated with trajectory class membership. Classes 1 and 2, characterized by sharp PSA declines post-biopsy, were strongly linked to prostate cancer diagnosis, resection, and recurrence. Ordinal regression analysis further revealed that trajectory class was significantly associated with cancer aggressiveness, even after adjusting for covariates. Additionally, PSA screening volumes dropped by 41% during the first COVID-19 wave, with only partial recovery afterward. This decline was accompanied by an increase in the biopsy positivity rate, suggesting delayed cancer detection during the pandemic.

Conclusion and significance:

PSA trajectory classification provides clinically meaningful insights into prostate cancer diagnosis, aggressiveness, treatment, and recurrence for the high-risk men in Winnipeg. It should be noted that the study population, healthcare delivery systems, and socioeconomic context of Manitoba, and specifically Winnipeg, may differ significantly from those in other provinces or countries. As a result, the identified PSA trajectories and their associated factors may not fully generalize outside this population. This study highlights the utility of longitudinal PSA patterns in augmenting traditional screening measures and improving risk stratification strategies. Moreover, the findings underscore persistent healthcare disparities linked to socioeconomic factors and the significant disruption caused by the COVID-19 pandemic. These results offer valuable guidance for enhancing prostate cancer management, screening policy, and healthcare system resilience in Manitoba.

Keywords:

Prostate-specific antigen (PSA), PSA trajectory, prostate cancer, cancer aggressiveness, Gleason score, prostatectomy, biochemical recurrence, COVID-19 pandemic, cancer screening

disruption, group-based trajectory modeling (GBTM), socioeconomic disparities, ethnocultural composition, situational vulnerability, Manitoba healthcare.

Acknowledgment

Foremost, I would like to express my deepest gratitude to my supervisor, Dr. Depeng Jiang, for his acceptance, patience, and invaluable guidance throughout my Master program. His mentorship has been instrumental in shaping my academic journey and research development.

I extend my sincere thanks to my committee members. I am grateful to Dr. Shuangbo Liu for her willingness to serve on my committee and for providing insightful feedback and guidance. Special appreciation goes to Dr. Abdi Sokoro, whose encouragement, mentorship, and leadership perspective have been a source of continual motivation and inspiration.

I would also like to thank Dr. Amin Kabani, my direct supervisor at work, for his unwavering support, including approval of time and resources that enabled me to pursue this program.

I am thankful to my colleagues at Shared Health Diagnostic Services (SHDS): Alun Carter for his support with data analysis, and Dr. Shuying Ji and Vivian Lu for their continuous assistance in addressing pathology-related questions.

To my university classmates, Chendong Li and Beili Huang, thank you for your help in navigating statistical modeling during the early stages of my thesis.

Finally, I would like to express heartfelt thanks to my family for their long-term support, understanding, and encouragement, which have allowed me the time and space to complete this research.

Table of Contents

List of Tables

List of Figures

1. Introduction and Overview

Prostate cancer is the most common cancer among Canadian men (Brenner et al., 2020). It is estimated that approximately 1 in 9 Canadian men will develop prostate cancer during their lifetime and 1 in 29 will die from it (Smith et al., 2019). Specifically, for Manitoba, prostate cancer is the most commonly diagnosed cancer in the male population, with projected 750 cancers (21% of all male cancers) and 190 deaths (12% of all male cancer death) in 2022 (Smith et al., 2019). Early diagnosis improves cancer outcomes by providing care at the earliest possible stage and is therefore an important public health strategy in all settings (World Health Organization, 2022).

The most common tool to screen prostate cancer is the prostate-specific antigen (PSA) test. According to the American Cancer Society, although there is no set cut-off point, many doctors consider PSA test results greater than or equal to 4.0 ng/mL as the alert level (Wolf et al., 2010). In addition, men with PSA levels between 4 and 10 ng/mL have 1 in 4 chances of having cancer, and the chance is over 50% if PSA is above 10 ng/mL (Wolf et al., 2010). When PSA levels continue for a period, the patient will be referred to a urologist for a further examination. Then, biopsy samples may be collected for cancer diagnosis and aggressiveness (Das et al., 2019). In addition to screening, PSA is used to monitor and evaluate prostate cancer treatment efficacy. Specifically for radical prostatectomy (RP), the PSA level falls to a very low or undetectable level approximately 4 weeks after the surgery (Taplin, 2003), and biochemical recurrence of cancer exists if the PSA level is greater than 0.2 ng/mL on at least two successive tests (Cookson et al., 2007).

Although PSA is the most widely used oncological biomarker (Makarov & Carter, 2006), there are some recent guidelines against using PSA test to screen prostate cancer (Canadian Task

Force on Preventive Health Care, 2014; Moyer, 2012). Therefore, understanding the relationship between PSA levels and the diagnosis of prostate cancer is important to evaluate the utilization of PSA test as the screening tool in Manitoba. In addition, pre-operative PSA level is a significant predictor of biochemical recurrence after prostatectomy (Freedland et al., 2006; Gonzalez et al., 2004; Jones et al., 2006).

COVID-19 pandemic caused broad disruptions in healthcare including cancer screening and diagnosis, and there is a marked decline in cancer screening and early diagnosis of prostate cancer (Davis et al., 2023) . Reports indicate that the decrease in PSA testing during the early pandemic ranged from 36% to 62% (Davis et al., 2023; Ferrari et al., 2021; Kaufman et al., 2021; Siyez, 2022). This reduction in testing may lead to patients being diagnosed at more advanced stages of the disease (Siyez, 2022). Therefore, it is essential to examine the impact of the COVID-19 pandemic on prostate cancer screening and diagnosis in Manitoba, which can inform policymakers in developing effective strategies.

Overall, the purpose of this retrospective cohort study was to examine the PSA trajectories and their associations with prostate cancer, its aggressiveness, and prostatectomy in high risk patients. Additionally, it will investigate the impact of the COVID-19 pandemic on prostate cancer screening and diagnosis. By linking PSA trajectories with socioeconomic factors and cancer characteristics, and highlighting the pandemic's disruption to healthcare access, this study offers crucial insights for clinicians and policymakers. It provides a clearer understanding of how to enhance prostate cancer management and policy responses in the post-pandemic era.

.

2. Literature Review

The literature review consists of five sections. The first section covers the basic knowledge of prostate cancer, including its prevalence, risk factors, detection, diagnosis, aggressiveness, treatment, and recurrence. The second section discusses PSA screening, including its guidelines, socioeconomic factors, and the impact of the COVID-19 pandemic. The third section focuses on the derivatives of PSA measurements and their associations with the diagnosis, aggressiveness, and recurrence of prostate cancer. The fourth section reviews PSA trajectories and their relationships with prostate cancer diagnosis, aggressiveness, treatment, and recurrences, and the statistical models used to study these trajectories. Finally, we conclude the literature review by identifying significant research gaps and outlining the objectives of this thesis project.

2.1 Prostate Cancer

2.1.1 Prostate Cancer Statistics and Risk Factors

Prostate cancer is the third most commonly diagnosed cancer globally, with 1.41million cases reported in 2020 (Ferlay et al., 2021). In Canada, it is the most common cancer among men (Brenner et al., 2020), with approximately 1 in 9 men expected to develop prostate cancer in their lifetime and 1 in 29 likely to die from it (Smith et al., 2019). In Manitoba, prostate cancer is projected to have 750 incidences (21% of all male cancers) and 190 deaths (12% of all male cancer death) in 2022 (Canadian Cancer Society, 2021). Despite the high incidence rate, the prostate cancer survival rate is the highest (91% at 5-year survival) among the five leading causes of cancer death (colorectal, female breast, lung and bronchus, pancreas, and prostate) in Canada (Canadian Cancer Society, 2021).

Risk factors for prostate cancer can be divided into non-modifiable factors, such as genetic mutations or polymorphisms, and modifiable factors, such as lifestyle factors (Cuzick et al., 2014). Older age, black race, and a family history of the disease are the only well-established risk factors for prostate cancer (Rawla, 2019), which are non-modifiable. In addition, diet and physical activity play an important role in prostate cancer development and progression (Gann, 2002), which are considered modifiable. Preventing cancer by controlling modifiable factors is ideal, however, early diagnosis is more important in real life. Early diagnosis improves cancer outcomes by providing care at the earliest stages, making it an important public health strategy (World Health Organization, 2022).

2.1.2 Detection, Diagnosis and Aggressiveness of Prostate Cancer

PSA screening is a well-known method to detect prostate cancer at its early stage, but it has limitations due to its low specificity. As PSA is organ-specific but not cancer-specific, elevated serum PSA levels may indicate changes due to cancer as well as inflammation, trauma, or benign prostate hyperplasia (Gretzer & Partin, 2003). Consequently, a PSA test alone is not diagnostic; a prostate biopsy is required to confirm prostate cancer. In determining whether a biopsy is necessary, physicians typically assess PSA levels and digital rectal exam (DRE) results. According to the Canadian Urological Association, repeat PSA testing is advised before biopsy consideration, and abnormal DRE findings may also warrant biopsy in healthy men(Rendon et al., 2017). Generally, when PSA levels are elevated ($\geqslant$4 ng/mL) and/or DRE results are abnormal, a transrectal ultrasound (TRUS) biopsy may be recommended.

The standard prostate biopsy is a core needle biopsy guided by TRUS imaging, which helps the physician identify sampling areas within the prostate. Typically, an extended 12-core biopsy template is used, supported by the American Urological Association (Bjurlin et al., 2013).

However, the procedure can cause discomfort and, in some cases, complications such as bleeding, infection, urinary retention, and erectile dysfunction (Loeb et al., 2013). Therefore, involving patients in the decision-making process for biopsy is essential to address potential risks.

A biopsy is the gold standard for diagnosing prostate cancer, while the Gleason score is used to determine the cancer's aggressiveness. After a biopsy, tissue samples are examined by a pathologist, who assigns a Gleason score based on the microscopic appearance of cancer cells. This score helps predict cancer behavior and guide treatment options (Humphrey, 2004). A score of 6 indicates slow-growing cancer, 7 indicates intermediate risk, and scores of 8 or higher suggest aggressive cancer (Prostate Condition Education Council, 2023). The College of American Pathologists categorizes Gleason scores into five grade groups: Group 1 = 6, Group 2 = 7 (3+4), Group 3 = 7 (4+3), Group 4 = 8, and Group 5 = 9–10 (College of American Pathologists, 2021; Srigley et al., 2009). This is also the current practice of Manitoba pathologists. Understanding these scores and groups is crucial for organizing data and selecting statistical methods to analyze the relationship between PSA levels and prostate cancer aggressiveness.

2.1.3 Treatment and Recurrence of Prostate Cancer

Most prostate cancers diagnosed are localized, which means that the cancer has not spread to lymph nodes or distant sites, and it is also called the T1 or T2 clinical stage (Brawley et al., 2018). It was reported that the ratio of localized prostate cancer was 77% in the United States during 2013-2017 (Siegel et al., 2020) and 75% in Canada in 2018 (LeBlanc et al., 2019). Therefore, the treatment options reviewed here are focused on localized cancer. The National Comprehensive Cancer Network guidelines use four main factors to determine a recommended

treatment: clinical stage, pathologic grade of cancer (Gleason score), PSA level, and comorbidity-adjusted life expectancy (Mohler et al., 2010). Common treatment options include watchful waiting, active surveillance, radiation therapy, and surgery (Brawley et al., 2018).

Watchful waiting is to monitor prostate cancer without treating it, which is best used for men who do not want or cannot receive treatment therapies, especially those with other life-threatening medical conditions (Makarov Danil, 2017). Active surveillance is a more structured program to track the progression of low-risk prostate cancer, allowing for earlier intervention if the risk increases, which involves periodical PSA testing, digital rectal examination, and prostate biopsy (Adolfsson, 2008). Both radiation therapy and surgery are used to treat intermediate to high-risk prostate cancer. Radiation therapy is either a non-invasive, or minimally invasive treatment for prostate cancer that uses x-rays or gamma-rays to eradicate prostate cancer cells. Prostate surgery, also called prostatectomy, is a procedure to remove the prostate, which is typically used for men with early-stage disease or cancer that is confined to the prostate (CancerCare Manitoba, n.d.). Although there are no recommendations on the choices between radiation therapy and prostatectomy, many have reported that prostatectomy is associated with the decreased mortality rate of prostate cancer in comparison to radiation therapy (Petrelli et al., 2014; Wallis et al., 2016; Guo et al., 2022).

After radiation therapy or prostatectomy, many patients may be completely free of prostate cancer, whereas others may have recurrence after a certain period. The recurrence rate of prostate cancer is reported as 20%-30% (John Hopkins Medicine, 2021). The two main possible reasons are not all cancer cells are treated or the cancer was more advanced than the doctor thought. Recurrent prostate cancer is diagnosed when the prostate-specific antigen (PSA) level starts to rise quickly after the initial treatment but there are no other signs of cancer. This is

called biochemical recurrence or PSA failure. The details of how to use PSA to monitor the recurrence will be discussed in section 2.3.

2.2 Prostate Specific Antigen Test as a Screening Tool

2.2.1 PSA Test

The PSA test measures the level of PSA in the blood. A blood sample is sent to a laboratory for analysis, and the results are usually reported as nanograms of PSA per milliliter (ng/mL) of blood. Although there is no set cut-off point, many doctors consider PSA test results greater than or equal to 4.0 ng/mL as the alert level (Wolf et al., 2010). The blood level of PSA is often elevated in people with prostate cancer, and the PSA test was originally approved by the FDA in 1986 to monitor the progression of prostate cancer in men who had already been diagnosed with the disease. Today, most physicians order PSA tests for three main reasons: to confirm the presence of suspected cancer, to monitor the progression of prostate cancer or the effect of treatment, or to predict the likelihood that prostate cancer will occur in the future (Albertsen, 2006).

2.2.2 PSA Screening and Guidelines

Since the 1980s, the PSA test has been used as the tool for early detection of prostate cancer and was formally approved by the Food and Drug Agency (FDA) in 1994 (Charatan, 1994). Since its approval, PSA test has become the primary screening method for detecting prostate cancer at the early stage. Over the past two decades, since the clinical introduction of PSA, the incidence of metastatic prostate cancer and mortality from prostate cancer has significantly decreased. In the United States, it was reported that PSA screening contributed to an annual decrease of 4.1% in prostate cancer mortality between 1994 and 2006 (Jemal et al., 2010) and a reduction of advanced stage prostate cancer from 25% to 4% during 1980-2002 (Etzioni et

al., 2008). In addition, the European Prostate Cancer Screening Trial (ERSPC) randomized a population of 162,243 men between 55 and 69 years for PSA screening (n = 81,816) or control without PSA (n = 99,184). After monitoring for 11 years, screening reduced the risk of metastases by 41% and the chance of death from prostate cancer by 20% (Schröder et al., 2009).

Despite these benefits, PSA screening remains controversial due to its limited specificity, leading to false positives, overdiagnosis, and potential harm from unnecessary treatment (Loeb et al., 2014). In recent years, medical organizations have issued conflicting guidelines on PSA screening. Some have recommended against routine PSA screening for certain age groups or all men (Canadian Task Force on Preventive Health Care, 2014; US Preventive Services Task Force, 2018), while others advised offering PSA testing to men starting at age 50 or 55, depending on individual life expectancy and risk factors (Braga et al., 2017). These conflicting recommendations reflect an ongoing debate over balancing the benefits of early detection with the risks of overdiagnosis and overtreatment.

2.2.3 PSA Screening and the Socioeconomic Status

Although PSA screening is widely used for prostate cancer detection, its utilization and outcomes often vary across socioeconomic groups. Research has consistently demonstrated that socioeconomic status (SES), including income, education, and access to healthcare, significantly influence PSA screening uptake (Benoit & Naslund, 1997; Järbur et al., 2024; Morgan et al., 2013). For instance, lower-income men are less likely to participate in prostate cancer screening and more likely to be diagnosed with advanced stages of prostate cancer which leads to poorer prognosis (Weinrich et al., 2000). Education also plays a critical role, as individuals with higher education levels tend to have more awareness of PSA screening benefits, contributing to higher screening rates (Lerhmann-Lerche et al., 2019). Geographic location and access disparities

further aggravate these inequalities, as individuals in urban settings or areas with abundant healthcare resources are often more likely to access PSA screening than those in rural or underserved areas (Kohar et al., 2023). Furthermore, racial disparities intertwined with socioeconomic factors reveal that minority men, especially African American men, may face additional barriers, such as lower health literacy or mistrust of the healthcare system, which affect their likelihood of undergoing PSA screening (Moses et al., 2017). Collectively, these studies underscore the importance of addressing socioeconomic inequities to ensure more equitable PSA screening practices and outcomes across diverse populations.

In addition to traditional SES factors, immigration status has been shown to influence PSA screening rates. Studies indicate that immigrants in the U.S. have significantly lower PSA testing rates compared to non-immigrants (43% vs. 60%) (Hansen et al., 2023). Furthermore, about 79% of U.S. immigrants are visible minorities (Moslimani & Passel, 2024). Similarly, in Canada, visible minorities comprise 26.5% of the total population and account for approximately 75% of new immigrants (Statistics Canada, 2023). Given that visible minority status is closely associated with immigration and potential barriers to healthcare access, it is crucial to consider it as an additional factor influencing PSA screening participation.

2.2.4 PSA Screening and COVID-19 Pandemic

In general, the COVID-19 pandemic led to sharp declines in cancer screening and early diagnosis of prostate cancer (Davis et al., 2023). The absolute deficit across the US population in prostate cancer screening associated with the COVID-19 pandemic (during Jan-July 2020) was estimated to be 1.6 million (Chen et al., 2021). In other similar studies conducted in different countries, it was reported that the decrease of PSA test during the early COVID-19 pandemic is dramatic and ranges from 36-62% (Davis et al., 2023; Ferrari et al., 2021; Kaufman et al., 2021;

Siyez, 2022). The significant drop of screening is mostly due to the concern of the COVID-19 exposure. According to a study of cancer screening in older adults, 47% of them stopped the prostate cancer screening during the pandemic (Schoenborn et al., 2022). It should also be noted that the PSA testing decrease differs among patients without cancer (1st time screening) or with cancer (follow-up), and the first-time screening decreased more in comparison to the follow-up groups (Davis et al., 2023).

2.3 Associations of PSA with Cancer Detection, Aggressiveness and Recurrence

2.3.1 Single PSA Cutoff and PSA Derivatives

Early studies suggested that men with serum PSA levels of less than 4.0 ng/mL were at low risk, however, using this single cut-off value for all men of all ages may risk exclusion of a high number of patients with clinically significant early-stage cancer whose PSA values are lower than 4.0 ng/mL (Schröder et al., 2000; Thompson et al., 2004). Although lowering the PSA cutoff can help to detect more cancers, it will further lead to overdiagnosis and hence overtreatment, which may be harmful to patients in many situations. Due to these limitations, methods to enhance the performance of PSA in early detection have been evolved by using the PSA derivatives, such as PSA density, PSA velocity, and age-specific PSA.

PSA density (PSAD) is expressed as the serum PSA divided by the prostate volume, and normalization of PSA by prostate volume is believed to enhance cancer specificity (Beduschi & Oesterling, 1997). The rationale behind PSAD is the observation of a positive relationship between serum PSA level and prostatic volume, and the background is that the majority of prostatic enlargement is due to benign hyperplastic tissue of the transition zone (Ankerst et al., 2009).

PSA velocity (PSAV) has significant advantages over a single-PSA measurement not only in differentiating between men with prostate cancer and those with benign disease, but also in predicting the biological aggressiveness of prostate cancer at presentation (Ankerst et al., 2009). There is no recommended cut point for PSAV, but 0.75 ng/mL/year was reported to identify the cancer well (Carter et al., 1992).

Note that PSA doubling time (PSADT) is also a PSA derivative that has been used for many years. Instead of estimating the speed of PSA increase, it measures the time that the PSA level doubles. PSA doubling time is primarily used for post-treatment monitoring, and its use in cancer prediction is unclear. Some studies indicated that PSAV is more useful than PSADT to identify the risk of localized prostate cancer (Loeb, Kettermann, et al., 2008; Ng et al., 2009).

2.3.2 PSA and Cancer Diagnosis

Many researchers have identified strong associations between the initial single PSA level and the subsequent risk of prostate cancer (Clark TW, 1997; Antenor et al., 2004; Grunkemeier & Vollmer, 2006; Kovac et al., 2020). Although high PSA levels do not always indicate prostate cancer, it was reported that men with PSA levels between 4 and 10 ng/mL have 1 in 4 chances of having cancer, and the chance is over 50% if PSA is above 10 ng/mL (Wolf et al., 2010).

Although some studies have shown that PSAV can be used as an independent predictor of prostate cancer (Eggener et al., 2008; Loeb et al., 2007), many researchers have found that PSAV added little or no predictive value to the level of PSA alone (O'Brien et al., 2011; Ulmert et al., 2008; Vickers et al., 2009).

2.3.3 PSA and Cancer Aggressiveness (Gleason score)

Prostate cancer aggressiveness is measured using the Gleason score. The risk of having prostate cancer increases with PSA level, so it is important to understand if this relationship is

reflected between PSA and cancer aggressiveness. However, not many studies are found on the association of single PSA level with prostate cancer aggressiveness, and they conflicted with each other. Some reported that PSA levels have a strong correlation with prostate cancer aggressiveness (Lojanapiwat et al., 2014; Preston et al., 2019), while others found that PSA level has no benefits in predicting the Gleason score (Cihan Temel et al., 2019).

In another hand, it was found that most studies focused on how PSA derivatives can predict prostate cancer aggressiveness. These PSA derivatives include free PSA, PSA velocity, and PSA density, as discussed previously. The percentage of free PSA is reported to correlate with the potential aggressiveness of early-stage prostate cancer, and the higher Gleason score is related to the decreased free to total PSA ratio (Catalona, 1996; Ceylan et al., 2016). It was reported that a PSAV greater than 2 ng/mL/year was significantly associated with a prostatectomy Gleason score of 7 or greater (Loeb, et al., 2008). Furthermore, the odds of having a Gleason score of 7 or greater were 2.3 folds for men with PSAV values >2 ng/mL/year in comparison to men who had PSAV values <0.5 ng/mL/year (Pinsky et al., 2007). Similar studies have indicated that annual percent changes in PSA accurately predicted aggressive disease (Gleason score >=7) (Wallner et al., 2013). For PSAD, it is mostly used to predict cancer upgrading in patients with low risks (Gleason score of 6) (Kundu et al., 2007; Sfoungaristos et al., 2013; Washington et al., 2020).

2.3.4 PSA and Recurrence

The PSA level is a monitoring tool for cancer treatment effectiveness. For radical prostatectomy, PSA should fall to a very low or even undetectable level within a couple of months after surgery (American Cancer Society, 2019). For radiation therapy, PSA will not drop to an undetectable level because it does not kill all cells in the prostate gland. Due to the

remaining normal prostate cells still produce some PSA, PSA levels after radiation tend to drop slowly and might not reach their lowest level until 2 years or more after treatment (American Cancer Society, 2019).

Despite undergoing definitive local therapy with radical prostatectomy or radiation for prostate cancer, many men develop PSA recurrence with no evidence of disease on conventional imaging. This disease state is defined as biochemical recurrence (BCR), and the estimated risk of developing BCR ranges from 20% to 30% (John Hopkins Medicine, 2021). The Phoenix criteria are used to define BCR post-radiation therapy, which requires an increase in PSA of at least 2 ng/mL above the post-radiation PSA nadir, whereas BCR after radical prostatectomy is defined as at least two PSA values that are 0.2 ng/mL or higher (Cookson et al., 2007). It was reported that the median time to BCR ranges from 20 to 38 months, and BCR occurs most often within 3 years after prostatectomy (Tourinho-Barbosa et al., 2018).

Pre-operative PSA level is reported to predict BCR and the risk increases with the PSA level (Jones et al., 2006), and it is also a significant predictor of the time to BCR (Brassell et al., 2005; Gonzalez et al., 2004). Furthermore, PSA, Gleason score, and clinical stage at the time of diagnosis are listed as the three important predictors of BCR, and the risk increases with the value and classification of these three predictors (Harvard Prostate Knowledge, 2009).

2.3.5 The Impacts of COVID-19 on Cancer Diagnosis and Aggressiveness

The COVID-19 pandemic has led to a significant decrease in PSA screening, which subsequently impacted prostate cancer diagnosis (Bakouny et al., 2021; Chen et al., 2021; Davis et al., 2023; Ferrari et al., 2021; Kaufman et al., 2021; Siyez, 2022). This impact is reflected in changes in prostate biopsy rates, cancer incidence, and cancer aggressiveness. Globally, reductions in prostate biopsies during the pandemic ranged from 10% to 58% (Mostafavi Zadeh

et al., 2023). Although the decline in biopsies resulted in an overall lower number of cancer detection, the cancer incidence rate and the proportion of aggressive (or advanced stage) cancers increased (Purushotham et al., 2021; Siyez, 2022; Vardhanabhuti & Ng, 2021).

In a large-scale study conducted in the United States, which compared the early pandemic period (March-May 2020) with the pre-pandemic period (January 2018-February 2020), over 16 million PSA test results and nearly 50,000 prostate biopsies were analyzed. The study found that the number of biopsies decreased by 37.9%, accompanied by a 36.4% decrease in PSA tests. Despite the decrease in biopsy, the rate of cancer incidence and the proportion of higher aggressiveness (Gleason score $\geqslant 8$) increased by 5.1% and 9.3%, respectively (Kaufman et al., 2021). In Canada, a study based on data from the Canadian Institute for Health Information (CIHI) indicated a 12% decrease in prostate cancer diagnoses and a 5.3% decrease in treatment activities during the COVID-19 period from April 2020 to March 2021. Additionally, the impact was more pronounced in non-metastatic hospital admissions for prostate cancer, with a 19% decrease compared to a 9% decrease in metastatic hospital admissions (Lee et al., 2023).

The increase in the proportion of higher aggressiveness (or higher decrease of non-metastatic patients) during the pandemic period suggests that some patients with lower to intermediate risk may have missed screening and diagnosis, potentially allowing them to develop higher-risk or incurable cancer (Kaufman et al., 2021). Efforts are necessary to bring such patients back for screening and cancer diagnosis and to restore appropriate care.

2.4 PSA Trajectories and Statistical Models

The study of PSA trajectories is critical in understanding prostate cancer dynamics and treatment efficacy. There are many statistical models that have been used to explore PSA trajectory, including linear, piecewise, log-linear, and latent class models. Each of these models

offers unique advantages depending on the specific characteristics of the PSA data and clinical questions of interest.

Initial research utilizing linear mixed-effect model analyzed PSA trajectories among controls, benign prostate hyperplasia (BPH), and prostate cancer, and the results indicated that the rate of change in PSA is significantly higher in men with prostate cancer than those in the control and BPH group (Carter et al., 1992). However, PSA levels often remain stable until cancer nears diagnosis time, a growth pattern that may not be adequately captured by simple linear models. Nonlinear mixed-effects models are optimal for PSA trajectory analysis due to their ability to incorporate random effects, thus accounting for non-independence among repeated measurements within subjects and accommodating unbalanced data structures (Morrell et al., 1995). Piecewise mixed-effects model was proposed for PSA trajectory analysis, and it was further divided into linear-exponential piecewise model and linear-linear piecewise Log PSA model (Shoaibi et al., 2016). The rationale is that PSA change over time is most likely linear a few years before the cancer diagnosis, and the change may be either linear or exponential when very close to the diagnosis.

PSA levels will drop after cancer treatment, but they may relapse if the treatment is not effective. For patients receiving prostatectomy, their PSA levels are expected to drop to a nadir and remain at a very low level. However, PSA levels may increase after prostatectomy, which is defined as recurrence. PSA trajectories after surgery can be predicted by a non-linear exponential decay–exponential growth model (Subtil & Rabilloud, 2010). A recent study used latent class mixture models to analyze post-treatment PSA levels over a 2-year period, identifying three distinct PSA trajectory groups: stable low PSA levels, initially low PSA levels followed by an increase, and persistently elevated PSA levels (Wu et al., 2018). The study found that patients in

the persistently elevated PSA levels group had significantly worse prostate cancer-specific survival compared to those in the stable low PSA levels group.

2.5 Research Gaps and Objectives

Despite ongoing debate over PSA screening, PSA testing remains a key tool for physicians in screening and monitoring patients at risk for prostate cancer and tracking potential recurrences after treatment. Therefore, understanding the associations of PSA trajectories with prostate cancer (i.e., positive biopsy), cancer aggressiveness (i.e., Gleason score), treatment options (i.e., prostatectomy), and biochemical recurrences is essential for informing clinical decision-making and improving patient outcomes.

Numerous studies have identified strong associations between baseline PSA levels and prostate cancer risk (Antenor et al., 2004; Clark TW, 1997; Grunkemeier & Vollmer, 2006; Kovac et al., 2020). Research also demonstrates that PSA dynamics and derivatives, such as PSA velocity, PSA density, and the free-to-total PSA ratio, are valuable for detecting prostate cancer and assessing its risk profile (Catalona, 1996; Loeb et al., 2007; Seaman et al., 1993). . Furthermore, the literature review reveals that some researchers have investigated the relationship between PSA levels and prostate cancer aggressiveness, finding that higher PSA levels are predictive of high-grade prostate cancer (Loeb, Sutherland, et al., 2008; Lojanapiwat et al., 2014; Pinsky et al., 2007; Thompson et al., 2006). However, these studies dichotomized cancer aggressiveness into low- and high-grade diseases using a Gleason score of 7 as the criterion. There is a noticeable research gap in comprehensive analysis of PSA trajectories and their associations with each stratification of Gleason scores (6-10) or the five grade groups by the College of American Pathologists (CAP). By employing Manitoba-specific data, this research

addresses this gap, offering insights that are finely tailored to local population risk profiles and specific cancer severity levels.

In addition to the associations with diagnosis and cancer aggressiveness, the research intends to integrate treatment and recurrence data within the same population, which is often missing in many prior studies. Furthermore, while the bulk of the literature on PSA and prostate cancer is derived from U.S. and European data, studies based on Canadian populations remain scarce. Conducting this research with Manitoba data thus provides a meaningful addition to the existing body of knowledge, offering insights tailored to Canadian patients.

Moreover, the COVID-19 pandemic introduced significant disruptions to prostate cancer screening and diagnostic timelines, potentially resulting in delayed diagnoses and more advanced disease stages at presentation (Davis et al., 2023; Siyez, 2022). Investigating the pandemic's impact on prostate cancer screening and diagnosis trends in Manitoba can help policymakers and healthcare providers develop effective, resilient strategies to mitigate similar risks in the future.

This research aims to classify PSA trajectories among patients into distinct groups based on similar patterns of change over time. After classification, it will investigate the factors associated with each trajectory group and examine the relationships between these groups and patient outcomes, such as cancer occurrence, aggressiveness, and recurrence. Additionally, this study will explore the impact of COVID-19 disruptions on PSA screening and prostate cancer diagnosis during 2019–2022. Specifically, the objectives of this research are: 1) to identify distinct PSA trajectories among high-risk patients and investigate the associated demographic and clinical factors; 2) to examine links between PSA trajectories and occurrence, aggressiveness, and recurrence of prostate cancer, providing a deeper understanding of PSA

dynamics in cancer development and progression; 3) to assess the impact of COVID-19 on PSA screening and diagnosis of prostate cancer.

The proposed research aims to fill critical knowledge gaps and provide actionable insights for clinicians in Manitoba, ultimately improving patient outcomes and guiding healthcare policy.

3. Study Population and Method

3.1 Screening, Diagnosis, and Treatment of Prostate Cancer in Manitoba

Unlike population-based cancer screening organized by CancerCare Manitoba (CCMB) for breast, cervix, and colon cancer, prostate cancer screening in Manitoba is an opportunistic screening, which depends on requests from individuals or their health providers. Despite this, prostate cancer screening rate (represented by PSA testing rate) in Manitoba ranged approximately 40%-50% in 2016 for patients aged 50-69 (Wang et al., 2020), which is recommended by professional associations (Braga et al., 2017; Wolf et al., 2010). The high PSA testing rate ensures adequate data to study the screening, diagnosis, and treatment of prostate cancer. The impact of the COVID-19 pandemic on the PSA testing and cancer diagnosis are also examined in this study.

In Manitoba, PSA tests are performed by public laboratories and cancer diagnoses are made by pathologists using the CAP protocol, and both are completed within Shared Health Diagnostic Services (SHDS). After diagnosis, any required cancer treatments are conducted by CCMB.

3.2 Data Source and Availability

The primary data source for this research is the SHDS database, which contains lab test data and cancer diagnosis records. For PSA trajectory analysis, we select data from Winnipeg patients spanning 2008-2023 for several reasons: (1) Winnipeg represents 56% of Manitoba's population (Statistics Canada, 2024a); (2) Winnipeg PSA testing data is available from as early as 2006; and (3) cancer diagnosis data is accessible from 2008. We set a minimum patient age of 40, as prostate cancer is rare in men under 40 (American Cancer Society, 2020). For the COVID-19 impact analysis, we select data from 2018 to 2023 for all Manitobans, as province-wide PSA

test data have been available only since 2016 with the establishment of the provincial lab information system. The corresponding Manitoba population data during the same period are obtained from Statistics Canada (Statistics Canada, 2024b). Socioeconomic status (SES), such as ethnocultural composition index and situational vulnerability index, are important variables in prostate cancer research. These SES data are obtained from the Statistics Canada census data based on the postal codes of patients, providing further context to the research.

3.3 Study Design

This is a retrospective cohort study. In alignment with the research objectives, there are two primary cohorts in this study. The first is the PSA trajectory cohort, which is subdivided into three sub-cohorts: biopsy, cancer, and prostatectomy cohorts.

- The biopsy cohort includes Winnipeg men aged 40 years and older who underwent a prostate biopsy due to suspected cancer in 2019. This cohort is used to identify PSA trajectory groups and analyze the associations between the groups and cancer.
- The cancer cohort comprises Winnipeg men aged 40 years and older who were diagnosed with prostate cancer (positive biopsy results) in 2019. This cohort is utilized to examine the relationship between PSA trajectories and cancer aggressiveness.
- The prostatectomy cohort consists of Winnipeg patients aged 40 years and older who underwent prostatectomy in 2019. This cohort is used to compare PSA trajectories between patients who had prostatectomy and those who did not.

The second primary cohort is the COVID-19 impact cohort, which is subdivided into two sub-cohorts: the screening and diagnosis cohorts. For both sub-cohorts, the data are divided into three distinct periods: pre-pandemic, pandemic, and post-pandemic.

- The screening cohort consists of all Manitoba patients who received PSA tests 1-2 times annually from 2018 to 2023. This cohort is used to quantify changes in monthly test volumes and screening rate across the pre-pandemic, pandemic, and post-pandemic periods.
- The diagnosis cohort includes patients who underwent prostate biopsy from 2019 to 2023. This cohort is used to examine changes in the cancer incidence and the cancer aggressiveness across the pre-pandemic, pandemic, and post-pandemic periods.

3.4 Sample Size

For PSA trajectory cohort, we considered the 16-year span of PSA data from 2008 to 2023 sufficient for trajectory analysis. However, to fully understand PSA trajectories related to screening, occurrence, aggressiveness, prostatectomy, and recurrence, we focused on 856 patients who underwent a first-time biopsy in 2019. We excluded those who had follow-up biopsies to determine cancer progression or treatment effects, as their PSA trajectories differ significantly from the first-time biopsy patients. The data selection process is illustrated in Figure 1.

For the COVID-19 impact cohort, data from 2018 to 2023 were analyzed to capture the pre-pandemic, pandemic, and post-pandemic periods. The screening sub-cohort comprised 218,305 patients who received one to two PSA tests annually, while the diagnosis sub-cohort included 6,433 patients who underwent prostate biopsy between 2019 and 2023. Data from 2018 were excluded from the diagnosis sub-cohort due to the transition to a new pathology reporting system during that year, which introduced inconsistencies in coding and reporting.

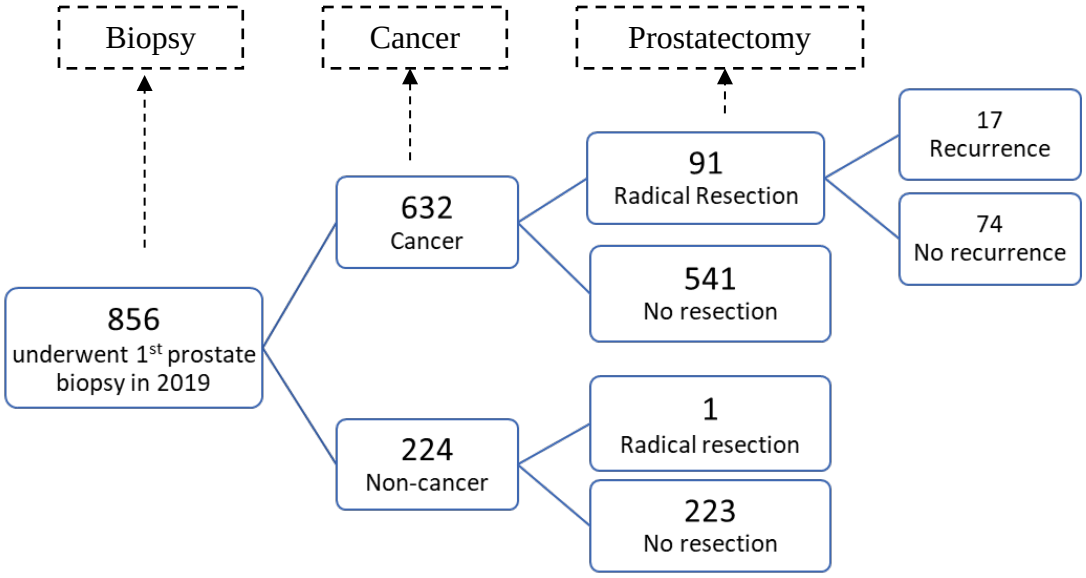

Figure 1 Data selection and three cohorts

3.5 Study Measures

This section summarizes the key variables and confounders to be measured in this study according to the objectives listed in the section 2.5.

3.5.1 PSA Levels

PSA level is the primary biomarker for prostate cancer screening, diagnosis, and treatment monitoring. This study analyzes PSA test results from 856 patients collected between 2008 and 2023, categorizing them into distinct groups based on their PSA trajectory patterns. Since this study is not a controlled clinical trial, the number of test results and the intervals between tests vary randomly among patients. To account for this variability, the PSA level for each patient is represented as the annual average of all PSA test results within a given year.

3.5.2 PSA Test Frequency

For PSA trajectory analysis, the PSA test frequency, coded as *Freq_2008_2019*, refers to the number of years between 2008 and 2019 (i.e., before biopsy) in which a patient received at least one PSA test. It serves as a year-based participation indicator, reflecting the consistency of a patient's engagement in PSA screening over time. Among patients without cancer, higher testing frequency generally indicates better and more consistent access to healthcare services, as well as greater involvement in preventive health practices.

However, for the COVID-19 impact analysis, a different approach was adopted: *annual test frequency*, which measures the number of PSA tests a patient received within a single year. Annual PSA test frequency helps distinguish between populations undergoing routine screening and those undergoing cancer monitoring. Typically, receiving one to two PSA tests per year is consistent with population-based screening practices (Gorday et al., 2014). In contrast, PSA monitoring after cancer diagnosis tends to involve more intensive testing, especially within the first two years after treatment, while patients managed through active surveillance generally undergo regular but less frequent testing.

3.5.3 Cancer Diagnosis, Aggressiveness, Treatment, and Recurrence

Prostate cancer diagnosis, coded as *Diagnosis*, was identified based on pathology-confirmed biopsy results. Individuals were classified as having prostate cancer if a positive biopsy result was recorded during the study period. Cancer diagnosis was treated as a binary variable (1/0) and served as a key clinical outcome linked to PSA screening trajectories and healthcare access disruptions during the COVID-19 pandemic.

Aggressiveness of prostate cancer, coded as *CAP_Aggressiveness*, was categorized using a CAP grade grouping of 1-5. For analytic purposes, a new aggressiveness variable (*New_Agg*)

was recoded as an ordinal categorical variable with four levels: 0 = No cancer; 1 = Low-grade cancer (CAP 1–2); 2 = Intermediate-grade cancer (CAP 3–4); 3 = High-grade cancer (CAP 5). This variable allowed for stratified modeling of prostate cancer severity and its association with PSA trajectory class and healthcare access factors.

Prostate cancer treatment was measured using surgical resection (prostatectomy) status and coded as *Resection*. This binary variable (1/0) captured whether definitive surgical treatment had occurred following cancer diagnosis. Resection status served as an indicator of treatment uptake and progression within the cancer care continuum.

Cancer recurrence (coded as *Recurrence*) was defined as biochemical recurrence, indicated by at least two post-operative PSA test results exceeding 0.2 ng/mL after reaching nadir following resection. Recurrence was treated as a binary variable (1/0) and included in regression models to explore its relationship with PSA trajectory class and related clinical factors.

3.5.4 Socioeconomic Indicators

To examine the role of contextual social determinants of health, two key socioecological indices were included in the analysis: the Ethnocultural Composition Index and the Situational Vulnerability Index. Both indices were derived from the 2021 Canadian Index of Multiple Deprivation (CIMD) and linked at the geographic level based on individuals' area of residence(Statistics Canada, 2024c).

The Ethnocultural Composition Index reflects the degree of cultural and ethnic diversity within a population. It incorporates indicators such as the proportion of visible minorities, the proportion of recent immigrants, and the proportion of population who speak a non-official language at home. Higher scores on this index indicate greater cultural diversity and potential

language or cultural barriers to accessing healthcare services. This variable was included to assess whether ethnocultural differences influenced PSA screening participation and prostate cancer diagnosis patterns.

The Situational Vulnerability Index captures socio-demographic conditions that may increase individuals' vulnerability to adverse outcomes due to limited resources or support structures. This index includes indicators such as the proportion of the population identifying as Indigenous, the prevalence of single-parent households, the proportion of homes requiring major repairs, the percentage of adults aged 25–64 without a high school diploma, the proportion of children under age six, and the median value of dwellings. Higher scores reflect greater vulnerability related to housing, education, and demographic characteristics. This index was used to investigate whether social disadvantage influenced screening behavior and access to cancer-related care during and after the COVID-19 pandemic.

3.6 Ethical Approval

This study involved secondary analysis of de-identified administrative health data to examine PSA testing trends and prostate cancer diagnosis across Manitoba. Ethics approval was obtained from the University of Manitoba Health Research Ethics Board (HS26870; H2025:092), and data access was approved by the Shared Health Diagnostic Services.

All data were de-identified prior to analysis and handled in accordance with the Personal Health Information Act (PHIA) of Manitoba. Data were securely stored, and only authorized personnel had access. Results are presented in aggregate, with cell suppression applied where needed to protect confidentiality. As no direct contact with individuals occurred and no identifiable information was used, the study posed minimal risk. Findings aim to inform equitable prostate cancer care and support evidence-based public health planning.

4. Statistical Analysis

To identify the PSA trajectory groups among those patients who underwent biopsies, we employed a semi-parametric group-based trajectory model (GBTM) (Jones et al., 2001; Nagin, 1999, 2005). This model used PSA levels from tests conducted between 2008 and 2019 as the dependent variables. To examine factors associated with each trajectory group, we conducted multinomial logistic regression analysis. Additionally, we used a generalized linear model (GLM) to examine how each trajectory group links to the patient outcome (i.e., cancer, aggressiveness, prostatectomy, and recurrence). The impacts of COVID-19 on PSA screening and cancer diagnosis were analyzed using the descriptive time-series methods.

4.1 Determine the PSA Trajectory Groups

As the PSA values are not normally distributed and show a positive skewness, logarithm of PSA is used as the outcome variables in the trajectory group analysis. A polynomial relationship was used to link year to the PSA level. The GBTM model can be expressed in the following formula:

$$ln\,(Y_{it}) = \beta_{0k} + \beta_{1k}(t) + \beta_{2k}(t^2) + \cdots + \varepsilon_{it} \quad (1)$$

, where ln (Y_{it}) is the natural logarithm of the observed outcome for individual *i* at time *t*; β_{0k}, β_{1k}, β_{2k} is the class-specific coefficients; *k* is the latent class index; ε_{it} is the residual error term.

Probabilities of membership in each class are modeled using multinomial logistic regression:

$$P(C_i = k) = \frac{exp(\gamma_k)}{\sum_{j=1}^{K} exp(\gamma_j)} \quad (2)$$

, where $P(C_i = k)$ is the probability that an individual belongs to group k; k are the different groups; γ_k is the parameters governing class membership probabilities; $exp(\gamma_k)$ represents the effect of group-specific parameters; $\sum_{j=1}^{K} exp(\gamma_j)$ sums all probability to 1 across groups.

The determination of number of latent trajectory classes remains one of the challenging issues and debates within the trajectory approach. Currently, methods for determining the number of trajectory classes consist of finding the model with the smallest Bayesian information criterion (BIC) (Kass & Raftery, 1995) and a significant likelihood ratio test (LMR-LRT) statistic (Lo et al., 2001). In addition to fit indices, the optimal number of classes were determined by a combination of factors, including parsimony, theoretical justification, and interpretability (Bauer & Curran, 2003; Muthén, 2003; Rindskopf, 2003). The quality of classifications can be assessed using the average posterior probability (APP) for each class, which should ideally exceed 0.7 for well-separated groups (Nagin, 2005).

4.2 Investigate the Factors Associated with Each Trajectory Group

To examine the factors (e.g., age, test frequency, cancer diagnosis, SES factor index, ethno-cultural composition index, etc.) associated with trajectory group membership, multinomial logistic regression was employed. Using the first category as the reference, then, for m = 2 to M, the model expression is the following:

$$z_{mi} = ln\left(\frac{P(Y_i = m)}{P(Y_i = 1)}\right) = \alpha_m + \sum_{k=1}^{K} \beta_{mk} X_{ik} \qquad (3)$$

,where $P(Y_i = m)$ is the probability of being in category m; $P(Y_i = 1)$ is the probability of being in the reference category (category 1); $ln\left(\frac{P(Y_i=m)}{(Y_i=1)}\right)$ is the log odds of being in category m relative to the reference category; $\alpha_m$is the intercept for category m; β_{mk} is the coefficient for predictor X_{ik} in category m; X_{ik} represents the value of the *k*-th predictor for the *i*-th individual,

where k=1,2,…,K; Z_{mi} is the log odds of an individual *i* being in category *m* relative to the reference category.

The probability of each category is calculated as the following:

$$P(Y_i = m) = \frac{exp(\, Z_{mi}\,)}{1 + \sum_{h=2}^{M} exp(\, Z_{hi}\,)} \quad (4)$$

For the reference category,

$$P(Y_i = 1) = \frac{1}{1 + \sum_{h=2}^{M} \exp(Z_{hi})} \quad (5)$$

The model fit was assessed using Akaike Information Criterion (AIC), and the significance of predictors was assessed by the log-likelihood ratio tests (P value < 0.05).

4.3 Examine the Links between Trajectory Groups and Patient Outcomes

To examine the relationships between PSA trajectory groups and cancer occurrence, aggressiveness, and recurrence, generalized linear models (GLMs) were used. GLMs were chosen because they provided a flexible framework that accommodates various types of dependent variables in this study, including binary (e.g., cancer occurrence or recurrence), ordinal (e.g., individual Gleason score ranked from 6-10), or categorical outcomes (e.g., Gleason scores treated as five CAP groups). This flexibility made GLMs an ideal choice for modeling the diverse outcome measures in this study, allowing for the appropriate specification of link functions and distributions to match the nature of each outcome. The general form of the GLM can be expressed as:

$$g(E[Y]) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p + \sum_{k=2}^{K} \alpha_k C_k \quad (6)$$

, where *Y* is the dependent variable (occurrence, aggressiveness, or recurrences), which can be binary, ordinal, categorical, or continuous; *E[Y]* is the expected value (mean) of the dependent

variable; g(·) is the link function, which relates the linear predictor to the mean of the outcome variable; β_0 is the intercept term; $\beta_1, \beta_2, \ldots, \beta_p$ are the regression coefficients corresponding to the predictor variables; $X_1, X_2, \ldots, X_p$ are independent variables or covariates (e.g., latent class membership, SES, age, PSA frequency, etc.); $\sum_{k=2}^{K} \alpha_k C_k$ represents additional effects from a categorical variable (C_k) with K levels (i.e., compare differences across the trajectory groups in occurrence, aggressiveness, or recurrences); α_k are the coefficients corresponding to the levels $C_2, C_3, \ldots, C_K$ of the categorical variable

The model fit was assessed using AIC, pseudo-R^2, and residual deviance, where lower AIC, higher pseudo-R^2, and lower residual deviance values indicate the better fit.

4.4 COVID-19 Impact on PSA Screening and Cancer Diagnosis

To assess the impact of the COVID-19 pandemic on prostate cancer screening and diagnosis, a descriptive time-series analysis was conducted using aggregated monthly PSA test data from 2018 to 2023 and biopsy data from 2019-2023. This timeframe encompasses the pre-pandemic, pandemic, and post-pandemic periods, enabling a comprehensive evaluation of long-term trends and disruptions in healthcare access.

The screening sub-cohort consisted of 218,305 male patients in Manitoba who underwent 1–2 PSA tests per year, thereby representing individuals engaged in routine screening rather than diagnostic or post-treatment surveillance. To estimate expected monthly PSA screening volumes, Excel's FORECAST.ETS() function was used. This function applies Exponential Triple Smoothing, accounting for level, trend, and seasonality based on historical data from the pre-pandemic period (January 2018 to February 2020). Automatic seasonality detection and missing value imputation were enabled. A 95% confidence interval was generated from model residuals,

and the observed PSA screening volumes during the pandemic were compared to these expected forecasts to assess deviations.

To statistically evaluate the significance of screening disruptions across pandemic waves, the Wilcoxon rank sum test was applied to compare monthly PSA screening volumes during each pandemic wave with the pre-pandemic baseline. The Wilcoxon test, a non-parametric alternative to the t-test, was chosen to account for potential non-normality in the distribution of monthly test counts. In Manitoba, the COVID-19 pandemic was characterized by four major waves, defined as follows: Wave 1 (March–May 2020), Wave 2 (October 2020–January 2021), Wave 3 (April–July 2021), and Wave 4 (December 2021–February 2022) (Duong et al., 2023). These periods were used as reference intervals to evaluate the impact of healthcare disruptions and subsequent recovery efforts. These defined intervals allowed for consistent comparison of screening trends across distinct phases of healthcare disruption and recovery. The primary hypothesis was that PSA screening volume significantly declined during the early pandemic phase, particularly Wave 1, due to widespread service suspension and redirection of healthcare resources. Subsequent waves were hypothesized to show partial recovery or adaptation, with screening volumes rebounding toward pre-pandemic norms.

Meanwhile, the diagnosis sub-cohort consists of 6,433 patients who underwent biopsy for potential prostate cancer. This group provides critical insights into the downstream effects of disrupted screening schedules. By analyzing biopsy rates and the corresponding stages of cancer at diagnosis, we aimed to pinpoint any shifts in cancer staging which may suggest delays in diagnosis attributable to reduced screening activity. Additionally, our study investigated any correlations between PSA screening reductions and advanced-stage diagnoses, potentially highlighting gaps in early detection.

5. Results

This chapter presents the results of the statistical analysis, organized into four sections as outlined in Chapter 4. Section 1 identifies distinct PSA trajectory groups before and after biopsy. Section 2 presents the results of patient characteristics associated with PSA trajectory group membership. Section 3 examines the correlation between PSA trajectories and cancer occurrence, cancer aggressiveness, and recurrence. Section 4 compares PSA testing rates during pre-pandemic, pandemic, and post-pandemic periods, and assesses the potential impact of the pandemic on delayed cancer diagnoses and late-stage cancer detection.

5.1 PSA Trajectories Groups and Their Characteristics

As discussed in section 4.1, the GBTM model is used to classify the trajectories into distinct groups based on their patterns of changes over time. To provide a preliminary view of these trajectories before and after biopsy, the PSA trajectories of nine randomly selected patients are shown in Figure 1. Visual inspection of these individual trajectories revealed substantial complexity in PSA progression, including abrupt changes in direction, inflection points, and asymmetrical fluctuations, particularly around the biopsy time. For example, several individuals (e.g., IDs 234, 781, and 170) exhibited rise–fall–rise patterns or steep declines followed by stabilization, which are not adequately captured by simple linear or even quadratic (t^2) term. Incorporating a cubic time term (t^3) allows additional the model to better capture these non-monotonic patterns.

To model individual PSA trajectories over time, three single-class linear mixed-effects models were evaluated with increasing complexity in their polynomial time terms. All models included a random slope for time and treated each individual as a clustering unit. The first model included only a linear time effect (t). The second model added a quadratic term (t^2), while the

third model incorporated both quadratic (t^2) and cubic (t^3) terms, providing greater flexibility to capture non-linear PSA trends. Although keeping on adding higher-order terms of time (e.g., t^4, t^5, …) may generate the better model fit, it becomes less meaningful as it makes the model too complex to interpret. The model incorporating linear, quadratic and cubic terms are used as the base model to determine the PSA trajectory groups.

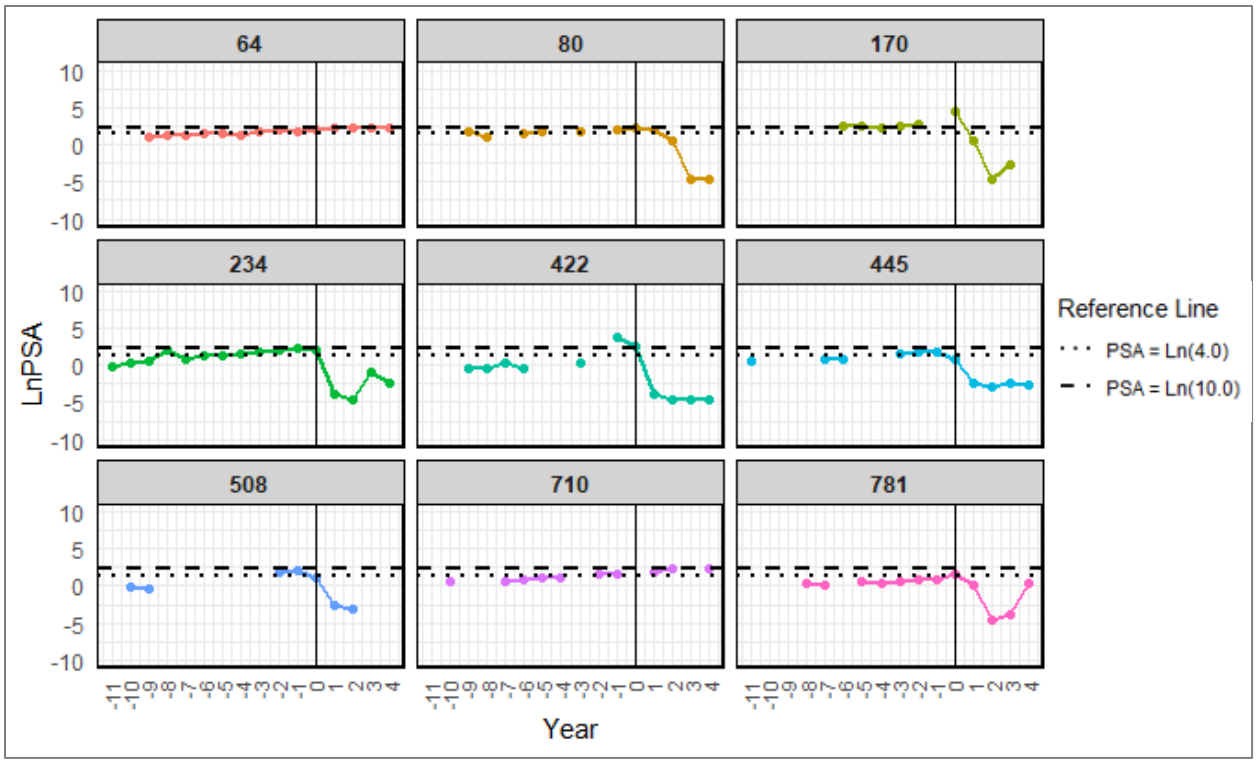

Figure 2 PSA trajectories of 9 randomly selected patients

After selecting the base GBTM model, the next step is to determine the optimum number of latent class (or groups). The determination of number of latent trajectory classes remains one of the challenging issues and debates within the trajectory approach. In addition to fit indices, the optimal number of classes should be determined by a combination of factors, including research question, parsimony, theoretical justification, and interpretability (Bauer & Curran, 2003). Five models with different numbers of groups were compared, and the key fit indices are summarized in Table 1. The model with five groups was considered as the best model, as it had the largest

log-likelihood, lowest BIC, and all five sub-groups has an average posterior probability (APP) greater than 0.70, indicating good quality of classification.

Table 1 Comparison of GBTM Models with 2-6 Groups

Model	Log-likelihood	AIC	BIC	Group	Patient counts	APP
2-group	-14623	29273	29334	1	350	0.95
				2	506	0.95
3-group	-14582	29200	29286	1	159	0.77
				2	412	0.92
				3	285	0.91
4-group	-14538	29122	29234	1	397	0.91
				2	167	0.80
				3	28	0.82
				4	264	0.90
5-group	-14516	29088	29221	1	159	0.82
				2	264	0.91
				3	390	0.91
				4	28	0.82
				5	15	0.78
6-group	-14501	29069	29226	1	89	0.69
				2	368	0.91
				3	33	0.81
				4	141	0.74
				5	212	0.90
				6	13	0.82

Figure 3 displays the mean logarithmic PSA (LnPSA) trajectories for the five distinct latent classes identified through group-based trajectory modeling, covering a period from 11 years before to 4 years after the biopsy year (Year 0). The solid, dashed, and dotted horizontal lines represent clinically significant PSA thresholds: LnPSA = 2.30 (PSA = 10.0 ng/mL), LnPSA = 1.38 (PSA = 4.0 ng/mL), and LnPSA = -1.60 (PSA = 0.2 ng/mL), respectively. The trajectories are summarized by concise pattern-based definitions as follows:

- **Class 1 (Moderate–Increase–Decrease–Low, 18.6%)**: Exhibited moderate initial PSA levels, a gradual increase leading up to biopsy, and followed by a significant decline and

stabilization at low levels after biopsy. This pattern indicates effective clinical intervention and favorable disease management outcomes.

- **Class 2 (Moderate–Increase–Decrease–Very Low, 30.8%)**: Similar to Class 1, but features a sharp decline immediately post-biopsy, stabilizing at very low PSA levels. This trajectory pattern reflects a strong therapeutic response or less aggressive disease.
- **Class 3 (Moderate–Increase–Decrease–High, 45.6%)**: Represented the largest group, demonstrating a consistent moderate increase in PSA levels before biopsy, a slight decrease afterward, but with PSA levels rebounded to relatively high levels. This suggests moderate disease progression or incomplete treatment effectiveness.
- **Class 4 (Low–Increase–Increase–Very High, 3.3%)**: Initially low PSA levels, increase sharply around the time of biopsy and continue to escalate thereafter. This pattern indicates aggressive cancer progression, potentially reflecting late detection or insufficient early intervention.
- **Class 5 (High–Increase–Decrease–Low, 1.8%)**: Consistently elevated PSA levels prior to biopsy, which further increased until the biopsy year. Following biopsy, there was a dramatic reduction, suggesting immediate and aggressive therapeutic intervention, indicative of severe disease promptly managed after diagnosis.

These identified PSA trajectories underscore the heterogeneity in prostate cancer progression and treatment responses among patients. Recognizing these distinct trajectory patterns provides clinically relevant insights that may guide prognosis assessments and inform personalized approaches for patient monitoring, diagnosis, and treatment planning.

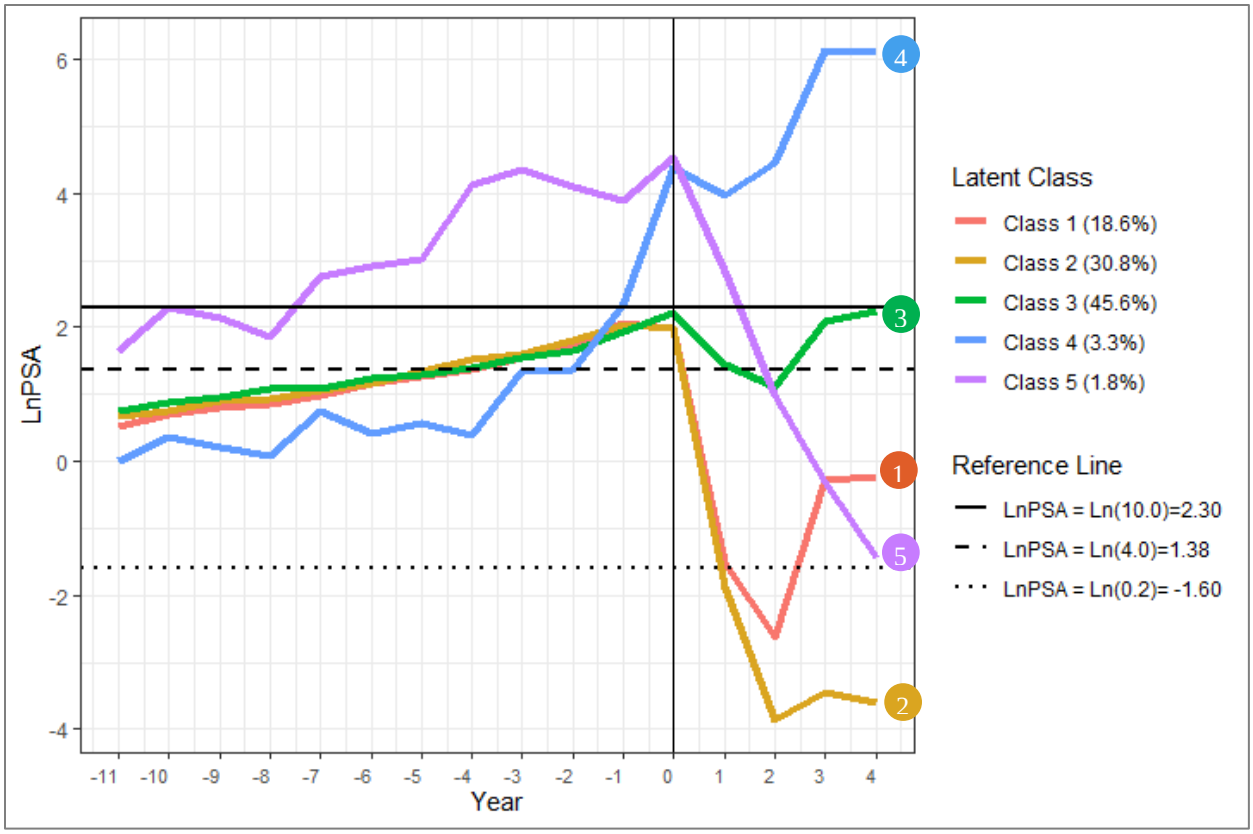

Figure 3 Mean observed Logarithm PSA trajectories by latent class

5.2 Factors Associated with Each Trajectory Group

After identifying the five distinct PSA trajectory groups, the next step was to explore the patient characteristics associated with each group. These characteristics were categorized into three domains: 1) demographic factors, including age, testing frequency; 2) clinical factors, such as cancer diagnosis, aggressiveness, resection (prostatectomy), and recurrence; and 3) socioeconomic status (SES), including ethnocultural composition and situational vulnerability.

Table 2 presents patient characteristics of the PSA trajectory cohort, stratified by latent PSA trajectory class (Classes 1 to 5). A total of 856 men were included, with Class 3 comprising the largest group (n = 390), followed by Class 2 (n = 264), Class 1 (n = 159), Class 4 (n = 28), and Class 5 (n = 15).

There was a statistically significant difference in *age* across classes ($p < 0.001$), with Class 3 having the lowest mean age (68.54 years), and Class 5 having the highest mean age (70.80 years). PSA testing frequency between 2008 and 2019 also varied significantly across trajectory groups, with the highest average in Class 3 (mean = 6.12) and the lowest in Class 4 (mean = 3.46), suggesting differing engagement with prostate monitoring across trajectory patterns.

A significant association was observed between diagnosis status and trajectory class ($p < 0.001$). Over half of individuals in Class 3 had no cancer diagnosis (54.4%), while almost all individuals in Class 1 (96.2%) and Class 2 (99.6%) had been diagnosed with cancer. This suggests that cancer-related PSA changes are more characteristic of Classes 1 and 2.

The distribution of cancer aggressiveness, measured by the *New_Agg* variable, is significantly differed across classes ($p < 0.001$). Class 3 had the highest proportion of men with no cancer (54.4%), while Class 4 and Class 5 were dominated by individuals with high-grade cancer (*New_Agg* = 3), comprising 71.4% and 53.3% of each class respectively. In contrast, Class 1 and Class 2 had a more balanced distribution, though both were still skewed toward aggressive cancer categories.

Prostate resection was most common in Class 2 (22.7%) and least common in Class 3 (1.8%) ($p < 0.001$), reflecting treatment differences aligned with PSA trends. Similarly, recurrence was significantly more frequent in Class 1 (5.7%) and Class 2 (3.0%) compared to zero recurrence in all other classes ($p < 0.001$), indicating a clear trajectory-associated risk of relapse.

There were modest but notable differences in ethnocultural composition across PSA classes. Class 5 had the highest mean score (0.29), indicating greater representation from

ethnoculturally diverse or marginalized populations. Vulnerability scores were also elevated in Class 5 (mean = 0.30), suggesting greatest socioeconomic burden or disparities in access to care within this group.

Table 2 Characteristics of Men (n=856) Receiving the First-Time Biopsy in 2019

Variable	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	***p*-value**
Demographics						
n (%)	159 (18.6%)	264 (30.8%)	390 (45.6%)	28 (3.3%)	15 (1.8%)	
Age (mean ± SD)	69.06 (7.46)	69.46 (8.21)	68.54 (9.14)	70.07 (8.90)	70.80 (11.50)	<0.001
Freq_2008_2019 (mean ± SD)	5.61 (3.16)	5.45 (3.02)	6.12 (3.35)	3.46 (2.86)	4.27 (3.54)	<0.001
Clinical						
Diagnosis						<0.001
No	6 (3.8%)	1 (0.4%)	212 (54.4%)	4 (14.3%)	1 (6.7%)	
Yes	153 (96.2%)	263 (99.6%)	178 (45.6%)	24 (85.7%)	14 (93.3%)	
New_Agg						<0.001
0	6 (3.8%)	1 (0.4%)	212 (54.4%)	4 (14.3%)	1 (6.7%)	
1	27 (17.0%)	41 (15.5%)	61 (15.6%)	2 (7.1%)	1 (6.7%)	
2	66 (41.5%)	110 (41.7%)	56 (14.4%)	2 (7.1%)	5 (33.3%)	
3	60 (37.7%)	112 (42.4%)	61 (15.6%)	20 (71.4%)	8 (53.3%)	
Resection						<0.001
No	136 (85.5%)	204 (77.3%)	383 (98.2%)	27 (96.4%)	14 (93.3%)	
Yes	23 (14.5%)	60 (22.7%)	7 (1.8%)	1 (3.6%)	1 (6.7%)	
Recurrence						<0.001
No	150 (94.3%)	256 (97.0%)	390 (100.0%)	28 (100.0%)	15 (100.0%)	
Yes	9 (5.7%)	8 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Socioeconomic Index						
Ethnocultural (mean ± SD)	0.08 (0.77)	-0.04 (0.69)	0.13 (0.78)	0.01 (0.81)	0.29 (0.79)	<0.001
Vulnerability (mean ± SD)	0.01 (0.54)	0.02 (0.55)	-0.02 (0.46)	0.09 (0.45)	0.30 (0.95)	<0.001

To assess the associations between patient characteristics and latent class membership, a series of multinomial logistic regression was employed. The model development was proceeded by adding factors of demographics, clinical, and socioeconomical groups incrementally to evaluate their individual and combined contributions. Class 3 was selected as the reference group due to its trajectory pattern, prevalence, and clinical neutrality. It follows a Moderate–Increase–Decrease–High pattern, reflecting gradual progression with partial treatment response and PSA rebound, an intermediate and clinically interpretable course. Statistically, Class 3 was the largest subgroup (n = 390), offering a stable and robust comparison point. Conceptually, it represents a middle-ground trajectory, allowing for meaningful contrasts with classes showing better control (e.g., Class 1 or 2) or more aggressive progression (e.g., Class 4 or 5). Using Class 3 as the reference enhances model stability and facilitates clearer interpretation of how demographic, clinical, and socioeconomic factors influence deviations from this common PSA progression pathway.

5.2.1 Multinomial Logistic Regression Model 1 (Demographics Factors)

Model 1 examined the associations between demographic characteristics, i.e., age and PSA testing frequency (Freq_2008_2019), and latent class membership. As shown in Table 3, both factors were significantly associated with the likelihood of being assigned to any of the other PSA trajectory classes. This suggests that demographic characteristics alone, even without incorporating clinical cancer indicators are important factors of PSA trajectory group membership.

Older age was consistently associated with higher odds of membership in more aggressive PSA trajectory groups. Specifically, each one additional year of age was associated with significantly greater odds of being in Class 5 (High–Increase–Plummet-Very Low), Class 4

(Low–Consistent Increase-Very High), and Class 2 (Moderate–Increase–Plummet–Stable Low), compared to the more stable Class 3. This suggests that older individuals were more likely to exhibit atypical or concerning PSA patterns.

Table 3 Multinomial Logistic Regression Results for Model 1

Variable	Class 1	Class 2	Class 4	Class 5
(Intercept)	–1.40 (0.19)***	–1.26 (0.16)***	–3.93 (0.40)***	–5.31 (0.53)***
Age	0.01 (0.00)***	0.02 (0.00)***	0.04 (0.01)***	0.05 (0.01)***
Freq_2008_2019	–0.06 (0.01)***	–0.08 (0.01)***	–0.34 (0.02)***	–0.22 (0.02)***

*Significance codes: *** p < 0.001, ** p < 0.01,* * p < 0.05

Conversely, higher frequency of PSA testing between 2008 and 2019 was associated with lower odds of being in non-stable classes. The strongest negative associations were observed for Class 4 ($\beta = -0.34$, $p < 0.001$) and Class 5 ($\beta = -0.22$, $p < 0.001$), indicating that individuals with fewer PSA tests were more likely to fall into these more concerning PSA trajectory groups. This finding highlights the potential role of reduced PSA surveillance on delayed detection and progression to advanced disease states.

5.2.2 Multinomial Logistic Regression Model 2 (Demographics and Clinical Factors)

Model 2 extended the demographic-only model by incorporating key clinical factors (cancer aggressiveness, resection status, and recurrence) to evaluate their contributions to PSA trajectory class membership. In this model, cancer diagnosis (yes/no) was combined into the cancer aggressiveness variable (*New_Agg*) to create a clinically meaningful and statistically efficient measure of disease severity. This allowed for a single ordinal variable capturing the full spectrum from no cancer (*New_Agg = 0*) to high-grade cancer (*New_Agg = 3*). This approach avoided multicollinearity between diagnosis and aggressiveness, streamlined model interpretation, and ensured that individuals without cancer served as a clear reference group.

As shown in Table 4, across all non-reference classes, cancer aggressiveness (*New_Agg*) was strongly and significantly associated with higher odds of class membership. Notably, patients with intermediate- or high-grade cancer (*New_Agg2* and *New_Agg3*) showed the largest positive coefficients for Class 2 ($\beta = 5.97$ and 6.10, respectively; $p < 0.001$), which was characterized by Moderate–Increase–Decrease–Very Low, indicating no recurrence after the treatment. Similarly, Class 1 (Moderate–Increase–Decrease–Low), which exhibited PSA rebound patterns, had significantly elevated odds for higher cancer aggressiveness grades. These patterns suggest that PSA trajectories in Classes 1 and 2 are strongly indicative of underlying cancer severity.

Resection status, a proxy for surgical treatment, was also positively associated with increased odds of class membership across all non-reference classes, with the largest effect observed for Class 2 ($\beta = 1.98$, $p < 0.001$). This suggests that resection may reflect more aggressive clinical management and may be more common among patients with unstable or concerning PSA trends.

Recurrence emerged as one of the most strongly associated factors in the model. The odds of being in Class 1 or 2 were dramatically elevated for individuals who experienced recurrence ($\beta = 16.93$ and 15.49, respectively; $p < 0.001$), indicating that unstable PSA patterns were closely aligned with cancer progression or return. This pattern persisted, though to a lesser extent, in Classes 4 and 5 as well.

Interestingly, after controlling for clinical factors, the effect of age reversed direction and became negative or non-significant across classes, suggesting that age-related patterns observed in Model 1 may be confounded by cancer status and recurrence. Similarly, PSA test frequency remained negatively associated with membership in the more unstable or severe classes (e.g.,

Class 4 and 5), reinforcing the earlier finding that limited surveillance is linked to worse outcomes.

Table 4 Multinomial Logistic Regression Results for Model 2

Variable	Class 1	Class 2	Class 4	Class 5
(Intercept)	–0.93 (0.24)***	–3.36 (0.32)***	–2.02 (0.40)***	–3.73 (0.58)***
Age	–0.04 (0.00)***	–0.03 (0.00)***	–0.01 (0.01)	–0.01 (0.01)
Freq_2008_2019	–0.00 (0.01)	–0.03 (0.01)**	–0.27 (0.02)***	–0.16 (0.02)***
New_Agg1	2.72 (0.12)***	4.72 (0.26)***	0.63 (0.23)**	1.26 (0.36)***
New_Agg2	3.89 (0.12)***	5.97 (0.26)***	0.66 (0.23)**	2.96 (0.29)***
New_Agg3	3.84 (0.12)***	6.10 (0.26)***	2.80 (0.15)***	3.32 (0.28)***
Resection	0.97 (0.13)***	1.98 (0.12)***	0.97 (0.29)**	1.07 (0.29)***
Recurrence	16.93 (0.07)***	15.49 (0.07)***	3.63 (0.00)***	4.81 (0.00)***

*Significance codes: *** $p < 0.001$, ** $p < 0.01$,* * $p < 0.05$

5.2.3 Multinomial Logistic Regression Model 3 (Demographics, Clinical, and Socioeconomical Factors)

Model 3 extended the previous models by incorporating two additional socioeconomic indicators, ethnocultural composition and situational vulnerability, to examine whether area-level social determinants of health contribute to differences in PSA trajectory group membership, beyond demographic and clinical factors. As shown in Table 5, after adjusting for all prior variables, both ethnocultural composition and situational vulnerability emerged as significant and independent factors of PSA trajectory class.

Specifically, higher ethnocultural composition scores (indicating greater diversity and proportion of racialized populations) were associated with lower odds of being in Class 1 (Moderate–Increase–Decrease–Low) and Class 2 (Moderate–Increase–Decrease–Very Low), but higher odds of membership in Class 5 (High–Increase–Decrease–Low). This suggests that

individuals residing in ethnoculturally diverse communities were more likely to exhibit PSA trajectories characterized by late detection and a sharp post-biopsy decline, potentially reflecting delayed access to early screening or systemic barriers to care.

Table 5 Multinomial Logistic Regression Results for Model 3

Variable	Class 1	Class 2	Class 4	Class 5
(Intercept)	–0.50 (0.25)*	–2.96 (0.33)***	–2.18 (0.42)***	–4.18 (0.61)***
Age	–0.05 (0.00)***	–0.03 (0.00)***	–0.01 (0.01)	–0.01 (0.01)
Freq_2008_2019	–0.01 (0.01)	–0.03 (0.01)**	–0.28 (0.02)***	–0.14 (0.03)***
New_Agg1	2.76 (0.12)***	4.83 (0.26)***	0.62 (0.23)**	1.06 (0.36)***
New_Agg2	3.94 (0.12)***	6.07 (0.26)***	0.63 (0.23)**	2.55 (0.30)***
New_Agg3	3.87 (0.12)***	6.12 (0.26)***	2.66 (0.15)***	3.23 (0.28)***
Resection	0.91 (0.13)***	1.87 (0.12)***	1.01 (0.29)**	1.23 (0.30)***
Recurrence	14.14 (0.07)***	12.73 (0.07)***	–3.24 (0.00)***	1.48 (0.00)***
Ethnocultural	–0.14 (0.04)***	–0.34 (0.04)***	–0.01 (0.07)	0.47 (0.08)***
Vulnerability	–0.25 (0.06)***	–0.32 (0.05)***	0.02 (0.11)	0.72 (0.11)***

*Significance codes: *** p < 0.001, ** p < 0.01,* * p < 0.05

Similarly, situational vulnerability, which captures community-level disadvantage related to housing, education, and Indigenous population density, was significantly associated with PSA trajectory group. Higher vulnerability scores were linked to lower odds of being in Class 1 or 2 and increased odds of belonging to Class 5. These patterns indicate that social disadvantage is associated with more severe PSA profiles, likely due to reduced healthcare access or lower screening participation.

Notably, the inclusion of socioeconomic factors led to modest changes in the coefficients for clinical variables, but the associations remained significant and directionally consistent with Model 2, confirming their robustness.

5.3 Links between PSA Trajectory Groups and Patient Outcomes

5.3.1 Cancer and Latent Class

To identify associated factors of prostate cancer diagnosis, three logistic regression models were estimated using PSA trajectory class as the primary exposure. As shown in Table 6, the unadjusted model (Model_L1) reveals that all trajectory classes were associated with higher odds of diagnosis compared to the stable reference group (Class 3), with Class 2 (Moderate–Increase–Decrease–Very Low) exhibiting the strongest association (OR = 313.48, 95% CI: 190.49–515.88). Results from Model_L2 and Model_L3 indicates that PSA trajectory class remained a strong and consistent variable for cancer diagnosis, even we controlled for the effects of demographics and social economics factors.

Table 6 Odds Ratios (95% CI) of Logistic Regression Models for Cancer Diagnosis

Variable	Model_L1	Model_L2	Model_L3
Class 1	30.38 (24.65–37.44) ***	35.15 (28.31–43.67) ***	36.38 (29.29–45.20) ***
Class 2	313.48 (190.49–515.88) ***	367.53 (222.25–607.70) ***	401.43 (242.89–663.61) ***
Class 4	7.15 (5.45–9.39) ***	6.49 (4.88–8.62) ***	6.36 (4.75–8.51) ***
Class 5	16.68 (10.13–27.47) ***	17.00 (10.14–28.50) ***	15.01 (8.80–25.61) ***
Age	–	1.10 (1.09–1.11) ***	1.11 (1.10–1.12) ***
Freq_2008-2019	–	0.94 (0.93–0.95) ***	0.94 (0.92–0.95) ***
Ethnocultural	–	–	1.37 (1.28–1.47) ***
Vulnerability	–	–	1.68 (1.49–1.89) ***

*Significance codes: *** $p < 0.001$, ** $p < 0.01$,* * $p < 0.05$*

5.3.2 Cancer Aggressiveness (as Ordinal Outcome) and Latent Class

Ordinal logistic regression was used to examine the association between PSA trajectory class and prostate cancer aggressiveness. Model_ord_1 included trajectory class only and revealed that all classes were significantly associated with increased odds of belonging to higher aggressiveness groups, relative to the reference class (Class 3). As shown in Table-7, the strongest association was observed for Class 4 (OR = 22.90, 95% CI: 18.40–28.49), followed by Class 5 (OR = 13.79), Class 2 (OR = 10.24), and Class 1 (OR = 8.31), all statistically significant at $p < 0.001$.

Model_ord_2 extended the model by including age and PSA testing frequency. Age remained strongly associated with cancer aggressiveness (OR = 1.09, 95% CI: 1.09–1.10, $p < 0.001$), indicating increased odds of higher cancer severity with advancing age. PSA testing frequency was inversely associated with aggressiveness (OR = 0.92, 95% CI: 0.91–0.93, $p < 0.001$), suggesting that more frequent screening was protective against more severe diagnoses. The trajectory class effects remained robust and largely unchanged, underscoring the independent contribution of PSA patterns.

Model_ord_3 incorporated two additional socioeconomic measures: ethnocultural composition and situational vulnerability. Controlling class, age, and Freq_2008-2019, vulnerability was positively associated with aggressiveness (OR = 1.07, 95% CI: 1.01–1.14, $p < 0.05$), suggesting that individuals from more socioeconomically disadvantaged areas had greater odds of presenting with more aggressive cancer. Ethnocultural composition was not significantly associated with cancer aggressiveness (OR = 1.04, 95% CI: 0.99–1.08). The class effects persisted and remained statistically significant, reinforcing their central role as explanatory variables of prostate cancer aggressiveness.

Overall, the progression from Model_ord_1 to Model_ord_3 demonstrated that while demographic and socioeconomic variables contribute additional explanatory power, PSA trajectory class remains a dominant and consistent explanatory variable of cancer aggressiveness across models.

Table 7 Odds Ratios (95% CI) of Ordinal Logistic Regression Models for Cancer Aggressiveness

Variable	**Model_ord_1**	**Model_ord_2**	**Model_ord_3**
Class 1	8.31 (7.60–9.10) ***	9.61 (8.77–10.54) ***	9.73 (8.86–10.67) ***
Class 2	10.24 (9.45–11.09) ***	11.82 (10.89–12.83) ***	11.53 (10.64–12.48) ***
Class 4	22.90 (18.40–28.49) ***	23.89 (19.03–29.98) ***	21.05 (16.54–26.81) ***
Class 5	13.79 (10.76–17.67) ***	10.95 (8.47–14.16) ***	12.70 (9.57–16.86) ***
Age	–	1.09 (1.09–1.10) ***	1.10 (1.09–1.10) ***
Freq_2008-2019	–	0.92 (0.91–0.93) ***	0.92 (0.91–0.93) ***
Ethnocultural	–	–	1.04 (0.99–1.08)
Vulnerability	–	–	1.07 (1.01–1.14) *

*Significance codes: *** $p < 0.001$, ** $p < 0.01$,* * $p < 0.05$*

5.3.3 Resection and Latent Class

Binary logistic regression model was used to investigate the relationship of resection and each latent class of PSA trajectory. Results of each model were summarized in Table 8. Model_L1_Res examined the association between class and likelihood of undergoing prostatectomy. Compared to the stable reference class (Class 3), all other trajectory groups showed significantly higher odds of resection, particularly Class 2 (OR = 16.09), indicating a strong treatment response following high PSA peaks. Model_L2_Res incorporated demographic factors and demonstrated that younger age and more frequent PSA testing were significantly associated with increased odds of resection. Class effects remained robust, with Class 2

(Moderate–Increase–Decrease–Very Low) and Class 1 ((Moderate–Increase–Decrease–Low) showing the highest odds (ORs = 28.00 and 14.86, respectively), suggesting these groups were prioritized for surgical intervention. Model_L3_Res extended the model by including socioeconomic indicators. Both ethnocultural composition and situational vulnerability were independently associated with resection, with lower odds observed in more ethnoculturally diverse populations and higher odds among those with greater vulnerability.

Table 8 Odds Ratios (95% CI) of Logistic Regression Models for Resection

Variable	Model_L1_Res	Model_L2_Res	Model_L3_Res
Class 1	9.25 (7.42–11.53) ***	14.86 (11.73–18.81) ***	14.12 (11.13–17.91) ***
Class 2	16.09 (13.29–19.49) ***	28.00 (22.72–34.51) ***	25.68 (20.94–31.48) ***
Class 4	2.03 (1.19–3.45) **	3.36 (1.96–5.75) ***	2.86 (1.65–4.96) ***
Class 5	3.91 (2.30–6.64) ***	6.16 (3.50–10.83) ***	5.01 (2.90–8.65) ***
Age	–	0.87 (0.86–0.88) ***	0.86 (0.85–0.87) ***
Freq_2008_2019	–	1.10 (1.07–1.13) ***	1.14 (1.11–1.17) ***
Ethnocultural	–	–	0.63 (0.57–0.69) ***
Vulnerability	–	–	1.48 (1.34–1.63) ***

Significance codes: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

5.4 COVID-19 Impact on PSA Screening and Cancer Diagnosis

Building on earlier analyses that identified distinct PSA trajectory classes and revealed significant associations between PSA testing frequency and cancer characteristics, this section examines the population-level impact of the COVID-19 pandemic on PSA screening and prostate cancer diagnosis.

5.4.1 COVID-19 Impact on PSA Screening

In Manitoba, four distinct waves were identified: wave 1 (March - May 2020), wave 2 (October 2020 - January 2021), wave 3 (April - July 2021), and wave 4 (December 2021 - February 2022) (Duong et al., 2023). Figure 4 illustrates monthly trends in PSA screening from

2018 to 2023, including forecasted estimates and 95% confidence intervals using methods discussed in Section 4.4. The observed screening volumes (blue line) exhibit strong seasonal patterns, with relatively stable trends prior to the COVID-19 pandemic. However, notable deviations emerged during the pandemic period, corresponding to the four major waves in Manitoba. Table 15 summarizes the statistical comparison of monthly PSA screening volumes before and during each of these four pandemic waves, using the Wilcoxon rank sum test.

During Wave 1 (March–May 2020), a dramatic decline in screening visits was observed, falling well below both the forecasted values and the lower confidence interval. This period represented the sharpest disruption, with screening visits decreasing by approximately 41% compared to the pre-pandemic baseline. The timing aligns with widespread service suspensions and public health restrictions at the onset of the pandemic. Although screening volumes rebounded partially during Waves 2 to 4 (late 2020 to mid-2022), they consistently remained below expected levels. The magnitude of the reduction diminished over time, with screening visits during Wave 4 (early 2022) only 5% below baseline, suggesting a partial recovery of services. Despite this, observed volumes during these waves did not fully return to the pre-pandemic trend or reach the upper bound of forecasted estimates. By 2023, PSA screening volumes approached pre-pandemic levels and closely aligned with the forecast, indicating a recovery in preventive care utilization. However, a small gap remained between observed and expected values, potentially reflecting long-term shifts in patient behavior, clinical prioritization, or systemic backlogs.

Overall, Figure 4 highlights both the acute disruption to prostate cancer screening services during the early pandemic period and the gradual restoration of care in subsequent years. The

observed lag in recovery underscores the importance of monitoring downstream effects on diagnostic delays and cancer outcomes.

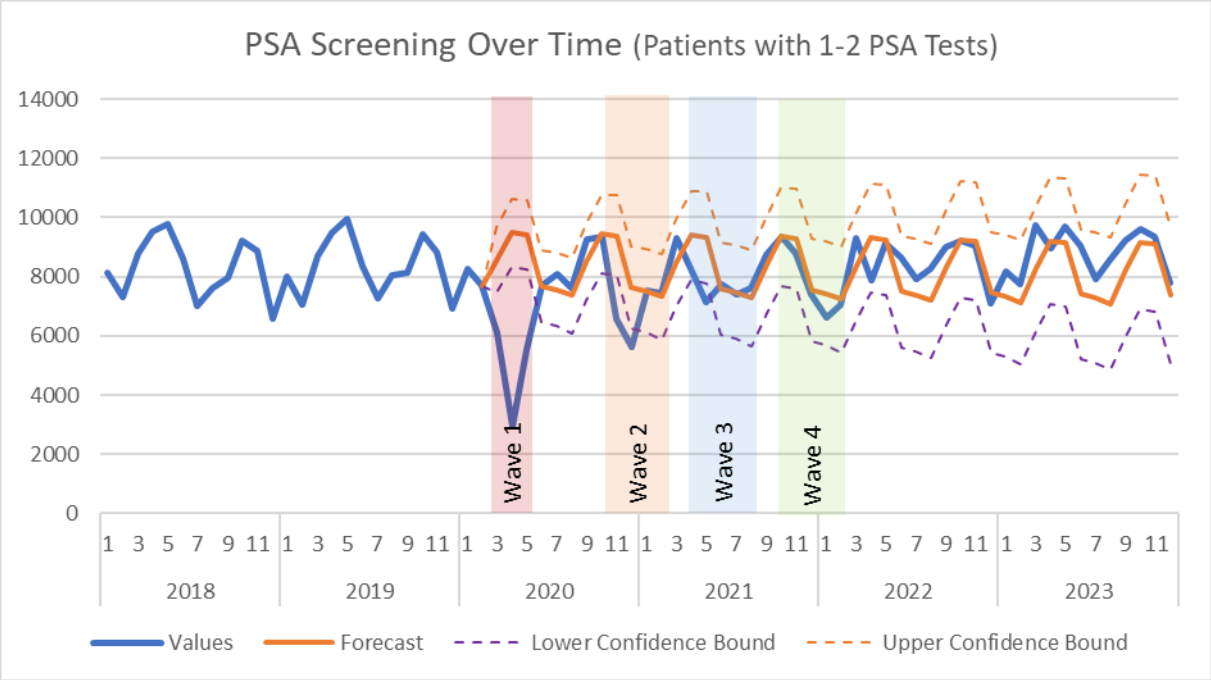

Figure 4 PSA Screening during the pre-pandemic, pandemic, and post pandemic periods

As shown in Table 9, a statistically significant decline in screening volumes was observed during Wave 1, when screening volumes were significantly lower than the pre-pandemic baseline ($p = 0.0052$). Although screening remained below baseline levels during Waves 2 to 4, these differences were not statistically significant, with p-values ranging from 0.0959 to 0.4205. This suggests that, despite modest reductions, screening volumes during later three waves did not deviate meaningfully from expected pre-pandemic levels from a statistical standpoint. The Wilcoxon test, a non-parametric alternative to the t-test, was chosen to account for potential non-normality in monthly visit counts. The results reinforce that the initial wave of the pandemic had the most pronounced and statistically detectable effect on PSA screening uptake, while screening activity during subsequent waves remained relatively resilient or recovered quickly.

Table 9 PSA Screening Comparison Between Pre-Pandemic and Pandemic Waves

Period	Date Range	PSA Test	Change	P-value
Pre-pandemic	Jan 2018-Mar 2020	8293	-	-
Wave 1	Mar-May 2020	4863	-41%	0.0052
Wave 2	Oct 2020-Feb 2021	7299	-12%	0.0959
Wave 3	Apr 2021-Aug 2021	7612	-8%	0.147
Wave 4	Oct 2021-Feb 2022	7844	-5%	0.4205

5.4.2 COVID-19 Impact on Cancer Diagnosis

To simplify the analysis of cancer diagnosis and consider the data availability, this study defines 2019 as the pre-pandemic, 2020-2021 as the pandemic, and 2022-2023 as the post-pandemic period. Monthly aggregated data from 2019 to 2023 were used to capture the trends and disruptions in healthcare services, with a particular focus on prostate cancer screening and diagnosis rates over the years.

Table 10 summarizes yearly prostate-specific antigen (PSA) screening patterns, biopsy rates, and prostate cancer detection among Manitoba men from 2019 to 2023. During the pandemic period (2020–2021), a substantial reduction in PSA screening was observed. The proportion of the population screened decreased from 13.0% in 2019 to 10.9% in 2020, representing the lowest rate across the study period. In 2021, screening remained below baseline at 12.2%, indicating incomplete recovery during the height of pandemic disruptions. Interestingly, the proportion of screened individuals who underwent biopsy slightly increased in 2020 (1.97%) compared to 2019 (1.77%), suggesting a possible triaging effect where only higher-risk cases were referred for biopsy during service restrictions. Despite fewer screenings and stable biopsy volumes, the percentage of biopsies resulting in cancer diagnoses increased,

from 55.9% in 2019 to 60.3% in 2021, potentially reflecting delayed diagnoses or prioritization of symptomatic or higher-risk patients during the pandemic.

In the post-pandemic period (2022–2023), PSA screening rebounded to near pre-pandemic levels (12.7% in 2023), and biopsy volumes also recovered. The proportion of biopsies resulting in cancer diagnoses remained elevated (60.3% in 2023), suggesting that clinical prioritization strategies may have persisted even after the pandemic. Additionally, the cancer detection rate per biopsy in 2022 (63.0%) was the highest observed, further supporting that increased diagnostic yield during the recovery phase.

Overall, these trends highlight the initial disruption and gradual normalization of prostate cancer diagnostic services, with a possible shift toward higher diagnostic efficiency in biopsy selection during and after the COVID-19 pandemic.

Table 10 Statistics of Screening, Biopsy, and Cancer (2019-2023)

Year	Patient	Population	% Screening	Bx	% Bx to Screening	Cancer	% Cancer to Bx
2019	89327	688532	13.0%	1578	1.77%	882	55.9%
2020	75430	694373	10.9%	1484	1.97%	842	56.7%
2021	85380	701972	12.2%	1477	1.73%	890	60.3%
2022	87885	712741	12.3%	1394	1.59%	878	63.0%
2023	93193	734944	12.7%	1527	1.64%	921	60.3%

6. Discussion

This chapter provides an in-depth interpretation of the key results, contextualizes them within existing literature, and outlines their clinical and public health implications. It also discusses the strength and limitations of the study and how they may influence the conclusions. Finally, directions for future research are proposed, with the goal of enhancing prostate cancer risk stratification and addressing disparities in early detection and treatment.

6.1 Summary of Study Findings and Implications

This study examined the clinical, demographic, and socioeconomic factors influencing prostate-specific antigen (PSA) progression among high-risk men in Manitoba. Group-based trajectory modeling (GBTM) was used to identify distinct PSA trajectory classes, followed by multivariable regression analyses to explore associations with clinical outcomes. Additionally, the study investigated the impact of the COVID-19 pandemic on PSA screening practices and prostate cancer diagnosis in the province.

Through GBTM, five distinct PSA trajectory groups were identified, representing a continuum from relatively stable patterns to aggressive disease progression. These groups were: Classes 1 (18.6%) and 2 (30.8%) showed moderate initial levels, a pre-biopsy increase, and post-biopsy declines to low (Class 1) or very low (Class 2) levels, indicating effective intervention; Class 3 (45.6%), the largest group, demonstrated only a slight post-biopsy decrease followed by a rebound to high PSA, suggesting incomplete treatment response. Class 4 (3.3%) exhibited low initial levels with sharp, sustained increases, reflecting aggressive disease, while Class 5 (1.8%) had persistently high pre-biopsy PSA and a dramatic drop after intervention, indicating prompt management of severe cases. Class 3 was selected as the reference group due to its prevalence and clinical neutrality.

Patients in the five PSA trajectory groups showed significant differences in demographic factors (age, PSA testing frequency), clinical characteristics (cancer aggressiveness, surgical resection, recurrence), and socioeconomic indicators (ethnocultural composition and situational vulnerability). Those in Classes 1 and 2, characterized by moderate initial PSA, a steady increase before biopsy, and sharp declines post-biopsy, exhibited the highest likelihood of prostate cancer diagnosis, surgical resection, and biochemical recurrence. These associations remained significant even after adjusting for potential confounders, reinforcing the prognostic value of PSA trajectory patterns for identifying individuals at higher risk for clinically significant disease.

Class 4, though smaller, displayed a delayed but sharp increase in PSA levels and was most associated with severe cancer aggressiveness (highest Gleason scores). Class 5, marked by high initial PSA levels and a continuous increase before biopsy, followed by a sharp decline post-biopsy, was associated with a higher prevalence of high-grade cancer and greater socioeconomic vulnerability, but no recurrence events were observed during follow-up . This suggests that while Class 5 patients experienced aggressive disease initially, treatment response or follow-up dynamics may have differed compared to other high-risk groups.

Ordinal logistic regression models confirmed that PSA trajectory classes were strongly associated with cancer aggressiveness. Patients in Classes 1, 2, 4, and 5 had significantly higher odds of aggressive prostate cancer compared to Class 3, even after controlling for covariates such as age, PSA testing frequency, and socioeconomic factors. Similarly, those in Classes 1, 2, and 5 were more likely to undergo prostatectomy, reflecting their unstable or elevated PSA patterns.

The study also documented the profound impact of the COVID-19 pandemic on prostate cancer screening across Manitoba. A 41% decline in monthly PSA testing volumes was observed

during the first pandemic wave (March–May 2020), representing a major disruption in preventive care. Although screening rates showed partial recovery in subsequent pandemic waves and nearly returned to pre-pandemic levels by 2023, the pattern of cancer diagnosis shifted significantly. The proportion of positive biopsies increased from 55.9% in 2019 to 63.0% in 2022, suggesting that service interruptions may have led to delayed cancer detection and diagnosis at more advanced stages.

Overall, this study shows that PSA trajectory classification provides critical insight into cancer occurrence, aggressiveness, treatment, and recurrence. It also demonstrates that COVID-19 introduced additional disparity, particularly among individuals with limited access to routine screening and healthcare services. Although prostate cancer diagnostic services gradually returned to normal after the initial disruption, there appears to have been a shift toward higher diagnostic efficiency in biopsy selection during and after the pandemic.

Based on these findings, it is recommended that PSA screening strategies in Manitoba incorporate longitudinal PSA trajectory monitoring, rather than relying on isolated PSA measurements, to better identify individuals at elevated risk for clinically significant and aggressive prostate cancers. Integrating PSA trajectory analysis into clinical decision-making could improve patient risk stratification, guide timely referrals for biopsy or specialist consultation, and personalize surveillance plans based on evolving PSA patterns. Furthermore, to address the disparities highlighted in this study, targeted efforts to improve healthcare access - especially among socioeconomically vulnerable and ethnoculturally diverse populations - are critical. Outreach and education programs should be expanded to ensure equitable access to PSA testing and follow-up care.

The disruptions during the COVID-19 pandemic underscore the need for resilient, adaptable screening infrastructure to maintain continuity of preventive services during future public health emergencies. Regular audit of biopsy positivity rates and screening intervals should be implemented to monitor the effectiveness of post-pandemic cancer detection strategies.

Finally, clinicians should be guided by both PSA trajectory patterns and traditional risk factors when making decisions about biopsy, treatment, and post-surgical surveillance, as this approach offers a more nuanced understanding of tumor biology and progression, ultimately supporting more precise and timely interventions for high-risk patients.

6.2 Strengths of the Study

This study demonstrates several important methodological and contextual strengths that enhance the robustness and relevance of its findings. First, the extended temporal scope of the dataset represents a key strength. By analyzing PSA test results across a 16-year period (2008–2023), the study captured both pre-biopsy trends and post-treatment PSA dynamics. This longitudinal design enabled the detection of nuanced PSA trajectory patterns, reflective of real-world disease progression and clinical responses.

In addition, the integration of both clinical and socioeconomic factors allowed for a multidimensional assessment of cancer risk. Specifically, cancer aggressiveness was classified using the College of American Pathologists (CAP) grade groupings, which are consistent with pathology standards used in Manitoba. These clinical indicators were complemented by area-level measures of ethnocultural composition and situational vulnerability, thereby capturing broader social determinants of health that may influence screening behavior, diagnosis, and treatment access.

Another notable strength is the timely assessment of the impact of the COVID-19 pandemic on prostate cancer screening in Manitoba. By incorporating province-wide PSA testing and biopsy data from 2018 to 2023, the study was able to document the extent and duration of service disruptions during pandemic waves. The use of time-series forecasting and non-parametric Wilcoxon rank sum testing contributed additional statistical rigor to the evaluation of changes in monthly test volumes, allowing for clearer inference about the magnitude of pandemic-related screening reductions.

Finally, the use of locally sourced data enhances the clinical relevance and applicability of the study findings. All laboratory and pathology data were obtained from Shared Health Diagnostic Services, ensuring alignment with provincial practice standards. This local context increases the value of the research for informing regional healthcare planning, cancer control policies, and ongoing public health surveillance efforts. Overall, the methodological design, analytical framework, and contextual specificity of this study collectively strengthen the validity and practical utility of its conclusions.

6.3 Limitations of the Study

Despite the strengths of this study, several limitations must be acknowledged. One notable constraint was the absence of individual-level data on race and family history of prostate cancer, both of which are known to influence screening behavior, disease risk, and outcomes. While area-based proxies such as the ethnocultural composition index were employed to approximate the race characteristics, this measure may not fully capture the variability and complexity of individual-level disparities. Consequently, interpretations related to social determinants of health should be viewed with some caution.

Another limitation lies in the incomplete capture of treatment modalities. The study focused solely on surgical resection (prostatectomy) due to data availability. Other commonly used treatments, including radiation therapy, hormone therapy, and active surveillance, were not included in the dataset. This restriction limited the ability to compare PSA trajectories across different treatment pathways and may have omitted important variation in post-treatment PSA responses.

The study also faced limited sample sizes for the recurrence events, particularly in Classes 3, 4, and 5, where no recurrence events were observed. This lack of variation reduced the stability and interpretability of regression analyses for recurrence, constraining the conclusions that could be drawn about factors associated with this outcome.

Moreover, to approximate PSA screening behavior, annual PSA test frequency of 1-2 times was used as a proxy indicator. Although this method aligns with practices reported in previous literature, it may have led to misclassification in certain cases, particularly among individuals undergoing active surveillance or treatment monitoring, whose testing patterns differ from those of the general screening population. This introduces a potential source of bias when interpreting class membership and its implications for early detection. In addition, the study did not account for short-term increases in test intensity, such as multiple PSA tests within one or two years before biopsy. This limitation may have overlooked clinically meaningful testing patterns related to diagnostic workup or disease monitoring.

Additionally, caution should be exercised when applying these findings to other regions. The PSA trajectory analysis was based on a specific high-risk population, i.e., men residing in Winnipeg who underwent first time prostate biopsy in 2019. The study population, healthcare delivery systems, and socioeconomic context of Manitoba, and specifically Winnipeg, may differ

significantly from those in other provinces or countries. As a result, the identified PSA trajectories and their associated factors may not fully generalize outside this population. Further research is warranted to assess whether similar patterns and impacts are observed in different geographical and demographic settings before drawing broader conclusions or implementing changes in clinical practice elsewhere.

Lastly, the observed declines in PSA screening volume during the COVID-19 pandemic were interpreted as indicative of pandemic-related disruptions. However, the attribution of these trends solely to COVID-19 is inherently limited by the observational design of the study. Other contemporaneous influences, such as changes in public health messaging, patient health-seeking behavior, or laboratory capacity constraints, may also have contributed to the observed patterns. As such, causal inferences related to the pandemic should be interpreted cautiously.

Taken together, these limitations underscore the need for continued data refinement and methodological development in future studies aimed at understanding PSA dynamics and prostate cancer care delivery.

6.4 Future Research Directions

Building on the findings of this study, several avenues for future research are warranted to further enhance the understanding of PSA dynamics and their implications for prostate cancer management.

First, future investigations should aim to incorporate a broader range of treatment data, including radiation therapy, hormone therapy, and active surveillance. The inclusion of these modalities would allow for a more nuanced evaluation of treatment-specific PSA trajectories and associated risks of biochemical recurrence, thereby supporting more personalized clinical decision-making.

Additionally, future studies would benefit from linking PSA trajectory classifications to long-term survival outcomes. Examining both cancer-specific and all-cause mortality across trajectory groups would provide critical insight into the prognostic utility of these classifications and their potential value in guiding early intervention strategies.

To improve the precision of disparity modeling and the identification of at-risk populations, future research should also seek access to individual-level data on socioeconomic indicators such as income, education, race, and immigration status. These variables would allow for a more detailed assessment of health inequities and inform targeted interventions aimed at improving screening uptake and cancer outcomes among marginalized populations.

Furthermore, the application of advanced statistical and computational techniques should be considered. Machine learning approaches and time-varying coefficient models may be particularly useful in capturing nonlinear interactions between clinical and social factors that influence PSA patterns over time. These models offer the potential to uncover previously unrecognized risk pathways and enhance predictive accuracy.

Finally, given the documented disruption to prostate cancer screening during the COVID-19 pandemic, there is a clear need for ongoing post-pandemic surveillance. Future work should monitor the trajectory of missed screenings, delayed diagnoses, and shifts in cancer staging, with particular attention to whether recovery efforts have equitably reached socioeconomically disadvantaged groups. Such research would be instrumental in evaluating the effectiveness of policy responses and identifying persistent gaps in care that may require corrective action.

Together, these directions offer a roadmap for building on the current study's contributions and advancing prostate cancer screening, diagnosis, and care in both clinical and population health contexts.

7. Impact and Significance

This study offers meaningful contributions to the understanding of PSA dynamics and their clinical implications in the context of prostate cancer screening, diagnosis, and treatment in Manitoba. By employing a longitudinal data analysis and the GBTM method, this research examined the complete course of PSA trajectories in high-risk men, spanning from screening to diagnosis, treatment, and recurrence monitoring.

The identification of five distinct PSA trajectory classes offers a meaningful way to categorize patients beyond traditional PSA thresholds or static measures. These trajectories captured varying disease behaviors and responses to clinical intervention, offering a valuable prognostic tool. Particularly, the finding that Classes 1 and 2 (moderate initial PSA values and steady increase before biopsy) were strongly associated with prostate cancer diagnosis, surgical treatment (prostatectomy), and recurrence highlights the clinical utility of PSA trajectory patterns for early identification of aggressive disease and for guiding therapeutic decision-making. Moreover, the demonstration of significant associations between testing frequency and cancer outcomes underscores the importance of regular PSA screening in at-risk populations.

Beyond clinical applications, this study emphasizes the critical role of structural determinants of health in shaping cancer risks and outcomes. The associations between PSA trajectories and socioeconomic indicators, including ethnocultural composition and situational vulnerability, highlight how social inequities permeate cancer detection and care, even within a publicly funded healthcare system. These findings reinforce the need for targeted outreach initiatives, culturally sensitive interventions, and equitable resource allocation to ensure that marginalized populations receive appropriate prostate cancer care.

Another important contribution lies in the empirical assessment of the COVID-19 pandemic's impact on prostate cancer screening and diagnosis in Manitoba. The documented decline in PSA testing during the initial wave of the pandemic, along with persistently elevated diagnostic yields post-pandemic, provides critical evidence of the lasting effects of healthcare disruptions. This analysis offers valuable insights for public health planning and resilience building in future health emergencies.

Overall, this thesis advances the understanding of PSA behavior over time, supports trajectory-informed approaches in prostate cancer management, and offers evidence to guide both clinical practice and public health strategy in Manitoba and similar healthcare settings.

REFERENCES

Adolfsson, J. (2008). Watchful waiting and active surveillance: The current position. In *BJU International* (Vol. 102, Issue 1, pp. 10–14). https://doi.org/10.1111/j.1464-410X.2008.07585.x

Albertsen, P. C. (2006). PSA Testing - Public Policy or Private Penchant. *JAMA*, *296*(19), 23712373. https://doi.org/10.1001/jama.296.19.2371

American Cancer Society. (2019). *Following PSA Levels During and After Prostate Cancer Treatment*. https://www.cancer.org/cancer/types/prostate-cancer/treating/psa-levels-after-treatment.html

American Cancer Society. (2020, June 9). *Prostate Cancer Risk Factors* . https://www.cancer.org/cancer/types/prostate-cancer/causes-risks-prevention/risk-factors.html

Ankerst, D. P., Tangen, C. M., & Thompson, I. M. (2009). *Prostate Cancer Screening* (Second). Humana Press.

Antenor, J. A. V., Han, M., Roehl, K. A., Nadler, R. B., & Catalona, W. J. (2004). Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. *Journal of Urology*, *172*(1), 90–93. https://doi.org/10.1097/01.ju.0000132133.10470.bb

Bakouny, Z., Paciotti, M., Schmidt, A. L., Lipsitz, S. R., Choueiri, T. K., & Trinh, Q. D. (2021). Cancer Screening Tests and Cancer Diagnoses during the COVID-19 Pandemic. In *JAMA Oncology* (Vol. 7, Issue 3, pp. 458–460). American Medical Association. https://doi.org/10.1001/jamaoncol.2020.7600

Bauer, D., & Curran, J. (2003). Distributional Assumptions of Growth Mixture Models: Implications for Overextraction of Latent Trajectory Classes. *Psychological Methods*, *8*(3), 338–363. https://psycnet.apa.org/doi/10.1037/1082-989X.8.3.338

Beduschi, M. C., & Oesterling, J. E. (1997). PROSTATE-SPECIFIC ANTIGEN DENSITY. *Urologic Clinics of North America*, *24*(2), 323–332. https://doi.org/10.1016/S0094-0143(05)70379-7

Benoit, R. M., & Naslund, M. J. (1997). THE SOCIOECONOMIC IMPLICATIONS OF PROSTATE-SPECIFIC ANTIGEN SCREENING. *Urologic Clinics of North America*, *24*(2), 451–458. https://doi.org/10.1016/S0094-0143(05)70392-X

Bjurlin, M. A., Carter, H. B., Schellhammer, P., Cookson, M. S., Gomella, L. G., Troyer, D., Wheeler, T. M., Schlossberg, S., Penson, D. F., & Taneja, S. S. (2013). Optimization of Initial Prostate Biopsy in Clinical Practice: Sampling, Labeling and Specimen Processing. *The Journal of Urology*, *189*(6), 2039–2046. https://doi.org/10.1016/J.JURO.2013.02.072

Braga, L. H., Lorenzo, A. J., & Romao, R. L. P. (2017). Canadian Urological Association-Pediatric Urologists of Canada (CUA-PUC) guideline for the diagnosis, management, and followup of cryptorchidism. *Canadian Urological Association Journal*, *11*(7), E251–E260. https://doi.org/10.5489/cuaj.4585

Brassell, S. A., Kao, T. C., Sun, L., & Moul, J. W. (2005). Prostate-specific antigen versus prostate-specific antigen density as predictor of tumor volume, margin status, pathologic stage, and biochemical recurrence of prostate cancer. *Urology*, *66*(6), 1229–1233. https://doi.org/10.1016/J.UROLOGY.2005.06.106

Brawley, S., Mohan, R., & Nein, C. D. (2018). Localized Prostate Cancer: Treatment Options. *American Family Physician*, *97*(12), 798–805. https://www.aafp.org/pubs/afp/issues/2018/0615/p798.html

Brenner, D., Poirier, A., Woods, R., & Ellison, L. (2020). Projected estimates of cancer in Canada in 2022. *Canadian Medical Association Journal*. https://doi.org/10.1503/cmaj.212097/tab-related-content

Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, S. C. and the P. H. A. of C. (2021). *Canadian Cancer Statistics 2021*.

Canadian Task Force on Preventive Health Care. (2014). Recommendations on screening for prostate cancer with the prostate-specific antigen test. *CMAJ*, *186*(16), 1225–1234. https://doi.org/10.1503/cmaj.140703

CancerCare Manitoba. (n.d.). *Manitoba Prostate Centre - Treatment Options*. Retrieved September 27, 2023, from https://www.cancercare.mb.ca/Treatments/treatments/manitoba-prostate-centre

Carter, H. B., Pearson, J. D., Metter, E. J., Brant, L. J., Chan, D. W., Andres, R., Fozard, J. L., & Walsh, P. C. (1992). Longitudinal Evaluation of Prostate-Specific Antigen Levels in Men With and Without Prostate Disease. *The Journal of the American Medical Association*, *267*(16), 2215–2220.

Catalona, W. J. (1996). Clinical utility of measurement free and total prostate-specific antigen (PSA): A review. *The Prostate*, *29*(S7).

Ceylan, C., Gazel, E., Kele, B., Doluolu, Ö., & Yman, M. (2016). Can the Free/Total PSA Ratio Predict the Gleason Score Before Prostate Biopsy? *Current Urology*, *9*(1), 24. https://doi.org/10.1159/000442846

Charatan, F. B. (1994). FDA approves test for prostatic cancer. *BMJ*, *309*(6955), 628–629. https://doi.org/10.1136/BMJ.309.6955.628A

Chen, R. C., Haynes, K., Du, S., Barron, J., & Katz, A. J. (2021). Association of Cancer Screening Deficit in the United States with the COVID-19 Pandemic. *JAMA Oncology*, *7*(6), 878–884. https://doi.org/10.1001/jamaoncol.2021.0884

Cihan Temel, M., Ediz, C., Akan, S., Ozer, E., & Yilmaz, O. (2019). Association of Gleason score with PSA Values and Serum Testosterone Levels Measured Prior To Prostate Biopsy. *Journal of the College of Physicians and Surgeons Pakistan*, *2020*(04), 399–402. https://doi.org/10.29271/jcp

Clark TW, G. L. C. P. W. A. S. J. (1997). Stratification of prostate-specific antigen level and results of transrectal ultrasonography and digital rectal examination as predictors of positive prostate biopsy. *Canadian Association of Radiologists Journal*, *48*(4), 252–258.

College of American Pathologists. (2021, June). *Protocol for the Examination of Prostate Needle Biopsies From Patients With Carcinoma of the Prostate Gland: Case Level Reporting*. https://documents.cap.org/protocols/Prostate.Needle.Case.Bx_1.0.0.0.REL_CAPCP.pdf

Cookson, M. S., Aus, G., Burnett, A. L., Canby-Hagino, E. D., D'Amico, A. V., Dmochowski, R. R., Eton, D. T., Forman, J. D., Goldenberg, S. L., Hernandez, J., Higano, C. S., Kraus, S. R., Moul, J. W., Tangen, C., Thrasher, J. B., & Thompson, I. (2007). Variation in the Definition of Biochemical Recurrence in Patients Treated for Localized Prostate Cancer: The American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel Report and Recommendations for a Standard in the Reporting of Surgical Outcomes. *Journal of Urology*, *177*(2), 540–545. https://doi.org/10.1016/j.juro.2006.10.097

Cuzick, J., Thorat, M. A., Andriole, G., Brawley, O. W., Brown, P. H., Culig, Z., Eeles, R. A., Ford, L. G., Hamdy, F. C., Holmberg, L., Ilic, D., Key, T. J., Vecchia, C. La, Lilja, H., Marberger, M., Meyskens, F. L., Minasian, L. M., Parker, C., Parnes, H. L., … Wolk, A. (2014). Prevention and early detection of prostate cancer. *The Lancet Oncology*, *15*(11), e484–e492. https://doi.org/10.1016/S1470-2045(14)70211-6

Das, C. J., Razik, A., Sharma, S., & Verma, S. (2019). Prostate biopsy: when and how to perform. In *Clinical Radiology* (Vol. 74, Issue 11, pp. 853–864). W.B. Saunders Ltd. https://doi.org/10.1016/j.crad.2019.03.016

Davis, M., Stephens, A., Butaney, M., Morrison, C., Corsi, N., Sood, A., Levin, A. M., Cole, A., Trinh, Q. D., Rogers, C., & Abdollah, F. (2023). Trends in Prostate Cancer Screening in the Pre- and Peri-COVID-19 Pandemic Period. *Urology Practice*, *10*(6), 631–637. https://doi.org/10.1097/UPJ.0000000000000452

Duong, S., Burtniak, J., Gretchen, A., Mai, A., Klassen, P., Wei, Y., Loeppky, C., Shaw, S. Y., Bullard, J., Van Caeseele, P., & Stein, D. R. (2023). Riding high: seroprevalence of SARS-CoV-2 after 4 pandemic waves in Manitoba, Canada, April 2020–February 2022. *BMC Public Health*, *23*(1). https://doi.org/10.1186/s12889-023-17239-6

Eggener, S. E., Yossepowitch, O., Roehl, K. A., Loeb, S., Yu, X., & Catalona, W. J. (2008). Relationship of Prostate-Specific Antigen Velocity to Histologic Findings in a Prostate Cancer Screening Program. *Urology*, *71*(6), 1016–1019. https://doi.org/10.1016/j.urology.2007.12.008

Etzioni, R., Tsodikov, A., Mariotto, A., Szabo, A., Falcon, S., Wegelin, J., Ditommaso, D., Karnofski, K., Gulati, R., Penson, D. F., & Feuer, E. (2008). Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes and Control*, *19*(2), 175–181. https://doi.org/10.1007/s10552-007-9083-8

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International Journal of Cancer*, *149*(4), 778–789. https://doi.org/10.1002/ijc.33588

Ferrari, A., Sanchis-Gomar, F., Mattiuzzi, C., Henry, B. M., & Lippi, G. (2021). Is COVID-19 impacting prostate cancer screening? A survey of prostate-specific antigen test requests during a local outbreak. *International Federation of Clinical Chemistry and Laboratory Medicine*, 69–77.

Freedland, S. J., Humphreys, E. B., Mangold, L. A., Eisenberger, M., & Partin, A. W. (2006). Time to Prostate Specific Antigen Recurrence After Radical Prostatectomy and Risk of Prostate Cancer Specific Mortality. *Journal of Urology*, *176*(4), 1404–1408. https://doi.org/10.1016/j.juro.2006.06.017

Gann, P. H. (2002). Risk factors for prostate cancer. *Rev Urol*, *4*(Suppl 5), S3–S10.

Gonzalez, C. M., Roehl, K. A., Antenor, J. V., Blunt, L. W., Han, M., & Catalona, W. J. (2004). Preoperative PSA level significantly associated with interval to biochemical progression after radical retropubic prostatectomy. *Urology*, *64*(4), 723–728. https://doi.org/10.1016/J.UROLOGY.2004.05.019

Gretzer, M. B., & Partin, A. W. (2003). PSA markers in prostate cancer detection. *Urologic Clinics of North America*, *30*(4), 677–686. https://doi.org/10.1016/S0094-0143(03)00057-0

Grunkemeier, M. N., & Vollmer, R. T. (2006). Predicting prostate biopsy results: The importance of PSA, age, and race. *American Journal of Clinical Pathology*, *126*(1), 110–112. https://doi.org/10.1309/PXV2VMB32EC789DA

Guo, Q., Hu, S., Ye, J., Su, L., Wang, S., Zhang, D., Zhang, Y., Qiu, S., Zhu, L., Ruan, L., Wan, B., Zou, S., Zhang, W., Yu, D., Xu, J., Zhang, H., & Wei, Y. (2022). Surgery offers survival advantage over radiotherapy in patients who are 80 years and older with Stage I and II NSCLC: A retrospective cohort study of 7,045 patients. *Frontiers in Surgery*, *9*. https://doi.org/10.3389/FSURG.2022.1018320

Hansen, N. F., Linscott, J. A., Hayn, M. H., Ryan, S. T., & Sammon, J. D. (2023). Prostate Specific Antigen Testing Behaviors for Prostate Cancer Screening among U.S. Immigrants: A Cross-sectional Analysis Using the National Health Interview Survey. *Journal of Urology*, *209*(1), 161–169. https://doi.org/10.1097/JU.0000000000002993

Harvard Prostate Knowledge. (2009, April 22). *How to handle a relapse after treatment for prostate cancer*. Harvard Health Publishing. https://www.health.harvard.edu/blog/how-to-handle-a-relapse-after-treatment-for-prostate-cancer-2009031122

Humphrey, P. A. (2004). Gleason grading and prognostic factors in carcinoma of the prostate. In *Modern Pathology* (Vol. 17, Issue 3, pp. 292–306). https://doi.org/10.1038/modpathol.3800054

Järbur, E., Holmberg, E., Björk-Eriksson, T., Bratt, O., & Arnsrud Godtman, R. (2024). Associations between socioeconomic factors and PSA testing in a population-based organised testing programme and routine healthcare: a register-based study of 50-year-old men. *BMJ Oncology*, *3*(1), e000400. https://doi.org/10.1136/bmjonc-2024-000400

Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer Statistics, 2010. *CA Cancer J Clin*, *60*, 277–300. https://doi.org/10.1002/caac.20073

John Hopkins Medicine. (2021). *Prostate Cancer Prognosis | Johns Hopkins Medicine*. https://www.hopkinsmedicine.org/health/conditions-and-diseases/prostate-cancer/prostate-cancer-prognosis

Jones, Nagin, D. S., & Roeder, K. (2001). A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Methods & Research*, *29*(3), 374–393.

Jones, T. D., Koch, M. O., Bunde, P. J., & Cheng, L. (2006). Is prostate-specific antigen (PSA) density better than the preoperative PSA level in predicting early biochemical recurrence of prostate cancer after radical prostatectomy? *BJU International*, *97*(3), 480–484. https://doi.org/10.1111/J.1464-410X.2006.06022.X

Kass, R., & Raftery, A. E. (1995). Bayes Factors. *Journal of the American Statistical Association*, *90*(430), 773–795. https://doi.org/10.1080/01621459.1995.10476572

Kaufman, H. W., Chen, Z., Niles, J. K., Radcliff, J., & Fesko, Y. (2021). Patterns of Prostate-Specific Antigen Testing and Prostate Biopsies During the COVID-19 Pandemic. *JCO Clin Cancer Inform*, *5*, 1028–1033. https://doi.org/10.1200/CCI.21

Kohar, A., Cramb, S. M., Pickles, K., Smith, D. P., & Baade, P. D. (2023). Changes in prostate specific antigen (PSA) "screening" patterns by geographic region and socio-economic status in Australia: Analysis of medicare data in 50–69 year old men. *Cancer Epidemiology*, *83*, 102338. https://doi.org/10.1016/j.canep.2023.102338

Kovac, E., Carlsson, S. V., Lilja, H., Hugosson, J., Kattan, M. W., Holmberg, E., & Stephenson, A. J. (2020). Association of Baseline Prostate-Specific Antigen Level with Long-term Diagnosis of Clinically Significant Prostate Cancer among Patients Aged 55 to 60 Years: A Secondary Analysis of a Cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *JAMA Network Open*, *3*(1). https://doi.org/10.1001/jamanetworkopen.2019.19284

Kundu, S. D., Roehl, K. A., Yu, X., Antenor, J. A. V., Suarez, B. K., & Catalona, W. J. (2007). Prostate Specific Antigen Density Correlates With Features of Prostate Cancer Aggressiveness. *The Journal of Urology*, *177*(2), 505–509. https://doi.org/10.1016/J.JURO.2006.09.039

LeBlanc, A. G., Demers, A., & Shaw, A. (2019). Recent trends in prostate cancer in Canada. *Statistics Canada Health Reports*, *30*(4), 12–17. https://doi.org/10.25318/82-003-X201900400002-ENG

Lee, S. H., Ojo, A. T., Halat, M., Bleibdrey, N., Zhang, S., Chalmers, R., & Zimskind, D. (2023). Impact of COVID-19 on hospital screening, diagnosis and treatment activities among prostate and colorectal cancer patients in Canada. *International Journal of Health Economics and Management*, *23*(3), 345–360. https://doi.org/10.1007/s10754-023-09342-3

Lerhmann-Lerche, C. S., Larsen, S. B., Andersen, I., Thygesen, L. C., Kaae Andersen, K., Duun-Henriksen, A. K., Johansen, C., Røder, M. A., Brasso, K., & Dalton, S. O. (2019). Educational level and first-time PSA testing in general practice. *Scandinavian Journal of Urology*, *53*(5), 275–281. https://doi.org/10.1080/21681805.2019.1681503

Lo, Y., Mendell, N. R., & Rubin, D. B. (2001). Testing the number of components in a normal mixture. *Biometrika*, *88*(3), 767–778. https://doi.org/10.1093/biomet/88.3.767

Loeb, S., Kettermann, A., Ferrucci, L., Landis, P., Metter, E. J., & Carter, H. B. (2008). PSA Doubling Time Versus PSA Velocity to Predict High-Risk Prostate Cancer: Data from the Baltimore Longitudinal Study of Aging. *European Urology*, *54*(5), 1073–1080. https://doi.org/10.1016/j.eururo.2008.06.076

Loeb, S., Roehl, K. A., Catalona, W. J., & Nadler, R. B. (2007). Prostate Specific Antigen Velocity Threshold for Predicting Prostate Cancer in Young Men. *The Journal of Urology*, *177*(3), 899–902. https://doi.org/10.1016/J.JURO.2006.10.028

Loeb, S., Sutherland, D. E., D'Amico, A. V, Roehl, K. A., & Catalona, W. J. (2008). PSA Velocity Is Associated With Gleason Score in Radical Prostatectomy Specimen: Marker for Prostate Cancer Aggressiveness. *Urology*, *72*(5), 1116–1120. https://doi.org/10.1016/J.UROLOGY.2008.01.082

Loeb, S., Vellekoop, A., Ahmed, H. U., Catto, J., Emberton, M., Nam, R., Rosario, D. J., Scattoni, V., & Lotan, Y. (2013). Systematic Review of Complications of Prostate Biopsy. *European Urology*, *64*(6), 876–892. https://doi.org/10.1016/J.EURURO.2013.05.049

Lojanapiwat, B., Anutrakulchai, W., Chongruksut, W., & Udomphot, C. (2014). Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. *Prostate International*, *2*(3), 133–139. https://doi.org/10.12954/PI.14054

Makarov Danil. (2017). *What's the Difference between Active Surveillance and Watchful Waiting when Treating Prostate Cancer?* . Urology Care Foundation. https://www.urologyhealth.org/healthy-living/urologyhealth-extra/magazine-archives/winter-2017/ask-the-experts-whats-the-difference-between-active-surveillance-and-watchful-waiting-when-treating-prostate-cancer

Makarov, D. V., & Carter, H. B. (2006). The Discovery of Prostate Specific Antigen as a Biomarker for the Early Detection of Adenocarcinoma of the Prostate. *Journal of Urology*, *176*(6), 2383–2385. https://doi.org/10.1016/j.juro.2006.08.019

Mohler, J., Bahnson, R. R., Boston, B., Busby, J. E., D'Amico, A., Eastham, J. A., Enke, C. A., George, D., Horwitz, E. M., Huben, R. P., Kantoff, P., Kawachi, M., Kuettel, M., Lange, P. H., MacVicar, G., Plimack, E. R., Pow-Sang, J. M., Roach, M., Rohren, E., … Walsh, P. C. (2010). Prostate Cancer. *Journal of the National Comprehensive Cancer Network*, *8*(2), 162–200. https://doi.org/10.6004/JNCCN.2010.0012

Morgan, R. M., Steele, R. J. C., Nabi, G., & McCowan, C. (2013). Socioeconomic Variation and Prostate Specific Antigen Testing in the Community: A United Kingdom Based Population Study. *Journal of Urology*, *190*(4), 1207–1212. https://doi.org/10.1016/j.juro.2013.04.044

Morrell, C. H., Pearson, J. D., Carter, H. B., & Brant, L. J. (1995). Estimating Unknown Transition Times Using a Piecewise Nonlinear Mixed-Effects Model in Men with Prostate Cancer. *Journal of the American Statistical Association*, *90*(429), 45–53.

Moses, K. A., Zhao, Z., Bi, Y., Acquaye, J., Holmes, A., Blot, W. J., & Fowke, J. H. (2017). The impact of sociodemographic factors and PSA screening among low-income Black and White men: data from the Southern Community Cohort Study. *Prostate Cancer and Prostatic Diseases*, *20*(4), 424–429. https://doi.org/10.1038/pcan.2017.32

Moslimani, M., & Passel, J. (2024). *Key findings about U.S. immigrants*. Pew Research Center. https://www.pewresearch.org/short-reads/2024/09/27/key-findings-about-us-immigrants/

Mostafavi Zadeh, S. M., Tajik, F., Gheytanchi, E., Kiani, J., Ghods, R., & Madjd, Z. (2023). COVID-19 pandemic impact on screening and diagnosis of prostate cancer: a systematic review. In *BMJ Supportive and Palliative Care*. BMJ Publishing Group. https://doi.org/10.1136/spcare-2023-004310

Moyer, V. A. (2012). Screening for prostate cancer: U.S. preventive services task force recommendation statement. *Annals of Internal Medicine*, *157*(2), 120–134. https://doi.org/10.7326/0003-4819-157-2-201207170-00459/ASSET/IMAGES/LARGE/10FF2.JPEG

Muthén, B. (2003). Statistical and Substantive Checking in Growth Mixture Modeling: Comment on Bauer and Curran (2003). *Psychological Methods*, *8*(3), 369–377. https://psycnet.apa.org/doi/10.1037/1082-989X.8.3.369

Nagin D. (2005). *Group-Based Modeling of Development*. Harvard University Press. https://doi.org/10.4159/9780674041318

Nagin, D. S. (1999). Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychological Methods*, *4*(2), 139–175. https://doi.org/https://psycnet.apa.org/doi/10.1037/1082-989X.4.2.139

Nagin, D. S. (2005). DEVELOPMENTAL TRAJECTORY GROUPS: FACT OR A USEFUL STATISTICAL FICTION? *Criminology*, *43*(4), 873–904. https://doi.org/https://doi.org/10.1111/j.1745-9125.2005.00026.x

Ng, M. K., Van As, N., Thomas, K., Woode-Amissah, R., Horwich, A., Huddart, R., Khoo, V., Thompson, A., Dearnaley, D., & Parker, C. (2009). Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. *BJU International*, *103*(7), 872–876. https://doi.org/10.1111/J.1464-410X.2008.08116.X

O'Brien, M. F., Cronin, A. M., Fearn, P. A., Savage, C. J., Smith, B., Stasi, J., Scardino, P. T., Fisher, G., Cuzick, J., Møller, H., Oliver, R. T., Berney, D. M., Foster, C. S., Eastham, J. A., Vickers, A. J., & Lilja, H. (2011). Evaluation of prediagnostic prostate-specific antigen dynamics as predictors of death from prostate cancer in patients treated conservatively. *International Journal of Cancer*, *128*(10), 2373–2381. https://doi.org/10.1002/IJC.25570

Petrelli, F., Vavassori, I., Coinu, A., Borgonovo, K., Sarti, E., & Barni, S. (2014). Radical Prostatectomy or Radiotherapy in High-Risk Prostate Cancer: A Systematic Review and Metaanalysis. *Clinical Genitourinary Cancer*, *12*(4), 215–224. https://doi.org/10.1016/J.CLGC.2014.01.010

Pinsky, P. F., Andriole, G., Crawford, E. D., Chia, D., Kramer, B. S., Grubb, R., Greenlee, R., & Gohagan, J. K. (2007). Prostate-specific Antigen Velocity and Prostate Cancer Gleason Grade and Stage. *Cancer*, *109*(8), 1689–1695. https://doi.org/10.1002/cncr.22558

Preston, M. A., Gerke, T., Carlsson, S. V., Signorello, L., Sjoberg, D. D., Markt, S. C., Kibel, A. S., Trinh, Q. D., Steinwandel, M., Blot, W., Vickers, A. J., Lilja, H., Mucci, L. A., & Wilson, K. M. (2019). Baseline Prostate-specific Antigen Level in Midlife and Aggressive Prostate Cancer in Black Men. *European Urology*, *75*(3), 399–407. https://doi.org/10.1016/J.EURURO.2018.08.032

Prostate Condition Education Council. (2023). *Gleason Score*. https://www.prostateconditions.org/about-prostate-conditions/prostate-cancer/newly-diagnosed/gleason-score

Purushotham, A., Roberts, G., Haire, K., Dodkins, J., Harvey-Jones, E., Han, L., Rigg, A., Twinn, C., Pramesh, C., Ranganathan, P., Sullivan, R., & Aggarwal, A. (2021). The impact of national non-pharmaceutical interventions ('lockdowns') on the presentation of cancer patients. *Ecancermedicalscience*, *15*. https://doi.org/10.3332/ECANCER.2021.1180

Rawla, P. (2019). Epidemiology of Prostate Cancer. *World Journal of Oncology*, *10*(2), 63–89. https://doi.org/10.14740/wjon1191

Rendon, R. A., Mason, R. J., Marzouk, K., Finelli, A., Saad, F., So, A., Violette, P., & Breau, R. H. (2017). Canadian Urological Association recommendations on prostate cancer screening and early diagnosis. *Canadian Urological Association Journal*, *11*(10), 298. https://doi.org/10.5489/CUAJ.4888

Rindskopf, D. (2003). Mixture or Homogeneous? Comment on Bauer and Curran (2003). *Psychological Methods*, *8*(3), 364–368. https://psycnet.apa.org/doi/10.1037/1082-989X.8.3.364

Schoenborn, N. L., Boyd, C. M., & Pollack, C. E. (2022). Impact of the COVID-19 pandemic on cancer screening attitudes, intentions, and behaviors in older adults. In *Journal of the American Geriatrics Society* (Vol. 70, Issue 1, pp. 67–69). John Wiley and Sons Inc. https://doi.org/10.1111/jgs.17449

Schröder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L. J., Ciatto, S., Nelen, V., Kwiatkowski, M., Lujan, M., Lilja, H., Zappa, M., Denis, L. J., Recker, F., Berenguer, A., Määttänen, L., Bangma, C. H., Aus, G., Villers, A., Rebillard, X., van der Kwast, T., … Auvinen, A. (2009). Screening and prostate-cancer mortality in a randomized European study. *The New England Journal of Medicine*, *360*(13), 1320–1328. https://doi.org/10.1056/NEJMOA0810084

Schröder, F. H., Van Der Cruijsen-Koeter, I., De Koning, H. J., Vis, A. N., Hoedemaeker, R. F., & Kranse, R. (2000). PROSTATE CANCER DETECTION AT LOW PROSTATE SPECIFIC ANTIGEN. *The Journal of Urology*, *163*(3), 806–812. https://doi.org/10.1016/S0022-5347(05)67809-3

Seaman, E., Whang, M., Olsson, C. A., Katz, A., Cooner, W. H., & Benson, M. C. (1993). PSA density (PSAD). Role in patient evaluation and management. *The Urologic Clinics of North America*, *20*(4), 653–663. https://europepmc.org/article/med/7505973

Sfoungaristos, S., Katafigiotis, I., & Perimenis, P. (2013). The role of PSA density to predict a pathological tumour upgrade between needle biopsy and radical prostatectomy for low risk clinical prostate cancer in the modified Gleason system era. *Canadian Urological Association Journal*, *7*(11–12), E722. https://doi.org/10.5489/CUAJ.374

Shoaibi, A., Rao, G. A., Cai, B., Rawl, J., & Hébert, J. R. (2016). The use of multiphase nonlinear mixed models to define and quantify long-term changes in serum prostate-specific antigen: data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Annals of Epidemiology*, *26*(1), 36-42.e2. https://doi.org/10.1016/j.annepidem.2015.10.003

Siegel, D. A., O'Neil, M. E., Richards, T. B., Dowling, N. F., & Weir, H. K. (2020). Prostate Cancer Incidence and Survival, by Stage and Race/Ethnicity — United States, 2001–2017. *Morbidity and Mortality Weekly Report*, *69*(41), 1473. https://doi.org/10.15585/MMWR.MM6941A1

Siyez, E. (2022). Effects of the COVID-19 Pandemic on Prostate Cancer Screening and Diagnosis. *Journal of Men's Health*, *18*(8). https://doi.org/10.31083/j.jomh1808167

Smith, L., Cancer Society, C., John, S., Ryan Woods, L., Brenner, D., Bryan, S., Louzado, C., Shaw, A., Turner, D., Manitoba, C., Hannah Weir, M. K., Demers, A., Ellison, L., & Dixon, M. (2019). Canadian Cancer Statistics 2019. *Canadian Cancer Society*.

Srigley, J. R., Humphrey, P. A., Mahul, ;, Amin, B., Chang, S. S., Egevad, L., Epstein, J. I., Grignon, D. J., Mckiernan, J. M., Montironi, R., Renshaw, A. A., Reuter, V. E., & Wheeler, T. M. (2009). Protocol for the Examination of Specimens From Patients With Carcinoma of the Prostate Gland. In *Arch Pathol Lab Med* (Vol. 133).

Statistics Canada. (2023, November 15). *Census Profile, 2021 Census of Population*. Statistics Canada. https://www12.statcan.gc.ca/census-recensement/2021/dp-pd/prof/details/page.cfm?LANG=E&GENDERlist=1,2,3&STATISTIClist=4&DGUIDlist=2021A000011124&HEADERlist=30,23&SearchText=Canada

Statistics Canada. (2024a). *Census Profile. 2021 Census of Population.* https://www12.statcan.gc.ca/census-recensement/2021/dp-pd/prof/index.cfm?Lang=E

Statistics Canada. (2024b). *Population estimates on July 1, by age and gender*. https://doi.org/https://doi.org/10.25318/1710000501-eng

Statistics Canada. (2024c). *The Canadian Index of Multiple Deprivation Dataset, 2021*. *45200001*, 16. https://www150.statcan.gc.ca/n1/pub/45-20-0001/452000012023001-eng.htm

Taplin, M.-E. (2003). Biochemical (Prostate-Specific Antigen) Relapse: An Oncologist's Perspective. In *REVIEWS IN UROLOGY* (Vol. 5).

Thompson, I. M., Ankerst, D. P., Chi, C., Goodman, P. J., Tangen, C. M., Lucia, M. S., Feng, Z., Parnes, H. L., & Coltman, C. A. (2006). Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial. *JNCI: Journal of the National Cancer Institute*, *98*(8), 529–534. https://doi.org/10.1093/JNCI/DJJ131

Thompson, I. M., Pauler, D. K., Goodman, P. J., Tangen, C. M., Lucia, M. S., Parnes, H. L., Minasian, L. M., Ford, L. G., Lippman, S. M., Crawford, E. D., Crowley, J. J., & Coltman, C. A. Jr. (2004). Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤4.0 ng per Milliliter. *Https://Doi.Org/10.1056/NEJMoa031918*, *350*(22), 2239–2246. https://doi.org/10.1056/NEJMOA031918

Tourinho-Barbosa, R. R., Srougi, V., Nunes-Silva, I., Baghdadi, M., Rembeyo, G., Eiffel, S. S., Barret, E., Rozet, F., Galiano, M., Cathelineau, X., & Sanchez-Salas, R. (2018). Biochemical recurrence after radical prostatectomy: what does it mean? *International Brazilian Journal of Urology : Official Journal of the Brazilian Society of Urology*, *44*(1), 14. https://doi.org/10.1590/S1677-5538.IBJU.2016.0656

Ulmert, D., Serio, A. M., O, M. F., Becker, C., Eastham, J. A., Scardino, P. T., Björk, T., Berglund, G., Vickers, A. J., Lilja, H., & Federico, F. S. (2008). Long-Term Prediction of Prostate Cancer: Prostate-Specific Antigen (PSA) Velocity Is Predictive but Does Not Improve the Predictive Accuracy of a Single PSA Measurement 15 Years or More Before Cancer Diagnosis in a Large, Representative, Unscreened Population. *J Clin Oncol*, *26*, 835–841. https://doi.org/10.1200/JCO.2007.13.1490

US Preventive Services Task Force. (2018). Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*, *319*(18), 1901–1913. https://doi.org/10.1001/jama.2018.3710

Vardhanabhuti, V., & Ng, K. S. (2021). Differential Impact of COVID-19 on Cancer Diagnostic Services Based on Body Regions: A Public Facility-Based Study in Hong Kong. *International Journal of Radiation Oncology Biology Physics*, *111*(2), 331–336. https://doi.org/10.1016/j.ijrobp.2021.05.010

Vickers, A. J., Wolters, T., Savage, C. J., Cronin, A. M., O'Brien, M. F., Pettersson, K., Roobol, M. J., Aus, G., Scardino, P. T., Hugosson, J., Schröder, F. H., & Lilja, H. (2009). Prostate-Specific Antigen Velocity for Early Detection of Prostate Cancer: Result from a Large, Representative, Population-based Cohort. *European Urology*, *56*(5), 753–760. https://doi.org/10.1016/J.EURURO.2009.07.047

Wallis, C. J. D., Saskin, R., Choo, R., Herschorn, S., Kodama, R. T., Satkunasivam, R., Shah, P. S., Danjoux, C., & Nam, R. K. (2016). Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. *European Urology*, *70*(1), 21–30. https://doi.org/10.1016/J.EURURO.2015.11.010

Wallner, L. P., Frencher, S. K., Hsu, J. W. Y., Chao, C. R., Nichol, M. B., Loo, R. K., & Jacobsen, S. J. (2013). Changes in serum prostate-specific antigen levels and the identification of prostate cancer in a large managed care population. *BJU International*, *111*(8), 1245–1252. https://doi.org/10.1111/J.1464-410X.2012.11651.X

Wang, Q., Chen, F., Jiang, D., Kabani, A., & Sokoro, A. R. A. H. (2020). Prostate-Specific Antigen Test Utilization in a Major Canadian City. *American Journal of Clinical Pathology*, *153*(6), 776–780. https://doi.org/10.1093/AJCP/AQAA003

Washington, S. L., Baskin, A. S., Ameli, N., Nguyen, H. G., Westphalen, A. C., Shinohara, K., & Carroll, P. R. (2020). MRI-based prostate-specific antigen density predicts gleason score upgrade in an active surveillance cohort. *American Journal of Roentgenology*, *214*(3), 574–578. https://doi.org/10.2214/AJR.19.21559/ASSET/IMAGES/LARGE/03_19_21559_02_CMYK.JPEG

Weinrich, S. P., Ellison, G. L., Boyd, M., Hudson, J., Bradford, B., & Weinrich, M. (2000). Participation in prostate cancer screening among low-income men. *Psychology, Health & Medicine*, *5*(4), 439–450. https://doi.org/10.1080/713690218

Wolf, A. M. D., Wender, R. C., Etzioni, R. B., Thompson, I. M., D'Amico, A. V., Volk, R. J., Brooks, D. D., Dash, C., Guessous, I., Andrews, K., DeSantis, C., & Smith, R. A. (2010). American Cancer Society Guideline for the Early Detection of Prostate Cancer: Update 2010. *CA: A Cancer Journal for Clinicians*, *60*(2), 70–98. https://doi.org/10.3322/caac.20066

World Health Organization. (2022). *Promoting Cancer Early Diagnosis*. https://www.who.int/activities/promoting-cancer-early-diagnosis