**Validating Gene Expression Signature Associated with Metastatic Prostate Cancer Using Independent Prostate Cancer Dataset**

**Executive Summary**

Prostate cancer is the most common non-cutaneous cancer diagnosis and third leading cause of cancer death in United States men. Many primary treatment options exist to treat prostate cancer such as radical prostatectomy and radiation. Unfortunately, these therapies are not without consequences, because they are associated with life-changing morbidities such as erectile dysfunction, urinary and bowel incontinence. Prostate cancer is relatively slow growing and occurs late in life; thus, many men will die with their cancer rather than from it. Furthermore, many prostate tumors are indolent and would not progress even in the absence of treatment. Thus, there are concerns that prostate cancer is overtreated, especially in the United States population where most cases are identified through serum prostate specific antigen (PSA) screening. Ideally, patients with aggressive and potentially deadly disease should be treated at an early stage before the disease has spread, and patients with indolent disease should not receive treatment, thus minimizing overtreatment. Although evaluating the cancer grade via Gleason score can help identify the most aggressive disease, there are no clinically acceptable methods that can accurately distinguish indolent cancer from aggressive cancer at the time of diagnosis in men with intermediate Gleason scores. Therefore, it is essential to identify prognostic biomarkers capable of differentiating between indolent and aggressive disease.

The purpose of this study is to validate the expression of 29 genes associated with metastatic prostate cancer using an independent dataset. Briefly, fifty-nine frozen prostatectomy tissues were obtained and categorized based on a minimum of a five-year long-term outcome as: no evidence of disease (NED), biochemical recurrence (BCR), or metastatic disease (MET). Total RNA was isolated from tumor tissues; quantity and quality were assessed. Whole genome gene expression measurements were collected via Illumina Expression BeadChip array. Differential gene expression analysis via Linear Models for Microarray and RNAseq Analysis (LIMMA) and Agilent GeneSpring identified differentially expressed genes between NED and MET tumors. Additionally, Gene Set Enrichment Analysis (GSEA) validated previously reported findings and additionally identified novel pathways associated with metastatic disease. TaqMan low density arrays were used to validate the expression level of genes differentially expressed between NED and MET outcome tumors. Twenty-eight genes were differentially expressed between NED and MET outcome tumors (adjusted p-value < 0.05, fold change >=2). Only four of these genes are components of currently available prostate cancer prognostic tests: AZGP1 (Oncotype DX), CDC20 (Prolaris), MYBPC1 and TNFRSF19 (Decipher). GSEA results revealed previously reported pathways such as “Cell Cycle” and “TGF-Beta Signaling” in addition to novel enriched pathways such as “Axon Guidance” and “Peroxisome.” Gene expression signatures in prostate cancer based on patient outcome (NED versus MET) can capture additional prognostic and biological pathway information to help identify prostate tumors with the potential to metastasize at the time of diagnosis.

An independent set of samples were identified: GSE70770. While this dataset does not have time to metastatic event, time to biochemical recurrence is associated with poor prostate cancer outcomes. Using the 29 genes identified from my dissertation, we will investigate whether these genes are associated with poor prostate cancer outcomes.

**Business Objectives**

The goal of this project is to investigate whether the 29 gene signature identified in my dissertation dataset are associated with poor prostate cancer outcomes in an independent dataset: GSE70770. To this end, we will answer the following questions:

1. Are the 29 genes differentially expressed between low Gleason score and high Gleason score prostate cancer cases?
2. Are the 29 genes independently associate with time to biochemical recurrence?
3. Is the 29 gene signature sufficient to classify good Gleason 7 cases from bad outcome Gleason 7 cases?

This project adds value because it will verify whether these genes provide added predictive prognostic abilities for patients diagnosed with prostate cancer. Since prostate cancer is so slow growing and both physician and patient are concerned with over treating, identification of useful prognostic markers will empower both physician and patient to make optimal decisions about how and when to treat prostate cancer.

**Background**

Prostate adenocarcinoma is the most common non-cutaneous cancer diagnosis and third leading cause of cancer deaths in U.S. men[13, 14]. Utilization of prostate specific antigen (PSA) as a clinical diagnostic biomarker led to a significant spike in indolent prostate cancer diagnoses, resulting in many cases that may never progress being low grade and slow growing tumors [173, 174]. Prostate cancer treatments are associated with life-changing comorbidities including urinary incontinence (65% of patients) and low potency rate during the first year after a radical prostatectomy (29% potency rate) [128, 129]. To reduce treatment-related comorbidities while advancing the prostate cancer precision medicine field, there is renewed interest in identifying biomarkers associated with prostate cancer aggression at the time of diagnosis.

Prostate cancer genomic panels were developed to inform clinicians of the risk of metastatic potential at the time of diagnosis. These prognostic risk assessment tools utilize both clinical and transcriptomic patient data to tailor patient-specific prostate cancer treatment strategies. Currently, there are three prostate cancer prognostic gene expression panels: Decipher[116, 117], Prolaris[118], and Oncotype DX[119, 120]. Gene expression profiles of primary prostate tumors reveal an association between aggressive prostate cancer and altered expression of genes involved in androgen signaling, metabolism, extracellular matrix formation and vascularization [53, 175-177]. Recent literature also demonstrates a strong relationship between stromal responses and abnormal immune activity in gene expression profiles from normal adjacent tissues collected from individuals with aggressive prostate cancer[178, 179].

These studies deriving gene expression prognostic markers are limited by their use of Gleason score in defining aggressive disease. Gleason score, although associated with prostate cancer aggressiveness, is a modest predictor of lower grade diagnoses. One study found approximately 30% of prostate cancer mortality cases had Gleason scores less than 7[122]. Since Gleason does not completely correlate with prostate cancer outcome, deriving gene expression data from patients based on prostate cancer long-term outcome may prove a better alternative.

Although most studies analyzing candidate biomarkers measured whole gene expression levels using RNA isolated from paraffin samples, there is a lack of consensus on the type of samples optimal to discover gene expression patterns associated with aggressive prostate cancer. Some genomic markers were discovered using biopsy diagnostic tissue whereas others used prostatectomy tissues; however, biopsies may not adequately sample tumors in the prostate [116-120]. Additionally, RNA quality is commonly not reported. RNA quality does affect messenger RNA measurements, which could result in inaccurate identification of genes that are differentially expressed[180, 181].

To address limitations encountered in previous studies, we identified genes differentially expressed in primary prostate tumors rather than biopsies. Instead of Gleason score, we defined aggressive disease in terms of patient outcome. Outcome was determined by following patients after prostatectomy a minimum of five years or until they developed metastatic disease. Post follow-up, patients were designated as no evidence of disease (i.e., remission), biochemical recurrence, or metastatic disease. In addition to using only MET and NED samples for this study, RNA quality was used as an exclusion criterion to reduce spectrum bias. These genes will then be tested in the independent dataset GSE70770 using time to biochemical recurrence in place of time to metastatic event.

**Scope**

The scope of this project only deals with two datasets, data collected from the gene expression aim of my dissertation and dataset GSE70770. Since the goal of this study is validation of the 29 gene signature, we are only interested in answering the following questions:

1. Are the 29 genes differentially expressed between low Gleason score and high Gleason score prostate cancer cases?
2. Are the 29 genes independently associate with time to biochemical recurrence?
3. Is the 29 gene signature sufficient to classify good Gleason 7 cases from bad outcome Gleason 7 cases?

**Functional requirements**

The only functional requirement is the following: all statistical analyses will be conducted using R.

**Personnel requirements**

In addition to myself, I will need one more statistician, each working a total of 80 hours for the entirety of the project. Each statistician needs to be comfortable working in R.

**Delivery schedule**

My team and I will adhere to the following schedule stated otherwise:

* Week 1: Download data
* Week 2: Create quality assessment plots and figures

Perform LIMMA on 29 genes in low Gleason vs high Gleason cancer cases

* Week 3: Perform Cox Proportional Hazard Model to test if expression of 29 genes are associated with time to biochemical recurrence
* Week 4: Use supervised clustering to classify good prognosis Gleason 7 cases from poor prognosis Gleason 7 cases
* Week 5: Complete presentation
* Week 6: Present findings

**Other requirements**

There are no additional requirements.

**Assumptions**

A major assumption my team and I are making is our equipment will work. I have a history of computer failures. As a result, I identified and developed back up plans such as working on my work computer, pushing regularly to Git repo and saving my code in multiple places.

**Limitations**

All personnel involved in this project are working multiple jobs. This makes finding time to meet via Zoom even more of a challenge. We do, however, have a plan to overcome this limitation. I already created a system to keep everyone informed of the status of this project at all times. For those that cannot meet via Zoom at the scheduled meeting time, everything discussed will be saved in the meeting minutes. Also, all files will be added to our Slack channel with bookmarks to each file saved in the “Final Project Files” bookmark folder in our Slack channel.

**Risks**

Foreseeable risks include unplanned illnesses and family emergencies. Another risk includes inability to meet in virtually at the same time. To mitigate these potential risks, I am committed to creating meeting minutes and posting all relevant files into Slack using bookmarks to organize the files.

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