CHAPTER 2: A Review of Biomarkers in Prostate Cancer

Cancer is a clonal disease. In that, certain clones display growth advantage over differentiated clones and render it cancerous. As shown in Figure 2.1 a normal cell undergoes a series of mutations to form a cancer cell that clonally expands and form the bulk of the tumor (Bradshaw et al., 2016). The cause for clonal diversity can be tissue-specific and is often genetic in nature.

![Figure 2.1 Clonal evolution model of cancer](image)

Though now it is well established that certain types of somatic variations acquired by cells can be triggered by lifestyle leading to cancer. For example, smoking is associated with lung cancer; meat consumption is associated with colon cancer; hormonal treatment with breast cancer and so on. Revealing the genetic basis of cancer has gained importance in the management and treatment of cancer. Drug targeting has also been shown to correlate with genetic nature of cancer. For example, individuals with BRAF-V600E mutation in melanoma responds to drug Vemurafenib whereas the same drug has no effect on the individuals with no BRAF-V600E mutation (Bhatia et al., 2015). Recent studies have reported BRAF-V600E mutation in other cancer types like colorectal (Barras, 2015) and lung (de Langen and Smit, 2017) cancer. These studies provide an insights on how the drugs specific to this mutation can be used as a general treatment regime for many cancer types. The expression levels of the target genes are also correlated with drug efficacy (Fisher and Larkin, 2012). For example, HER2 expression level is a companion diagnostics for treatment of breast cancer with HERCEPTIN (Scheerens et al., 2017). More recently, PDL1 expression levels were correlated with response to PDL1 inhibitors (Abdel-Rahman, 2016).

Prostate is an exocrine gland in the male reproductive system that produces 50–70% of the seminal fluids. Prostate cancer (PCa) is the second most commonly diagnosed malignant disease and the sixth leading cause for cancer related death among men worldwide (Haas et al., 2008). It’s a heterogeneous disease in which the clinical behavior ranges from slow-growing tumors with no or little clinical
significance to aggressive metastatic and lethal form (Phin et al., 2013). Side effects from treatment of indolent prostate cancer can reduce quality of life from no to little benefit. Currently prostate-specific antigen (PSA) test is widely used in prostate cancer diagnosis. Although PSA gene expression is correlated with prostate cancer, it is not cancer-specific due to elevated levels of serum PSA under benign conditions, like benign prostate hyperplasia, urinary retention, trauma, or physical manipulation (Oesterling, 1991). Clinical trials have shown that the PSA testing and screening is associated with an over-diagnosis and as a consequence an overtreatment of patients with indolent disease (Andriole et al., 2009; Hugosson et al., 2010; Schröder et al., 2009). The use of novel biomarkers has the potential to improve the diagnosis of cancer, especially in the identification of cancer at an early stage with potential curative therapeutic options.

Biomarkers are molecules that can provide information about a disease. They can be useful for the evaluation of the disease predisposition, screening, prognosis, prediction of drug response and monitoring (Sawyers, 2008). Biomarkers should be detectable in a given tissue obtained by biopsy or surgical resection or in bodily fluids like blood, urine, and semen. They can range from being specific cells, proteins (enzymes, hormones), metabolites, DNA or an epigenetic modification of DNA, and expression levels of RNA transcripts, including non-coding RNAs (ncRNAs) (Prensner et al., 2012).

Broadly, there are seven common clinical roles for biomarkers, which address specific clinical questions when managing cancer patients or patients suspected to have a malignancy:

- Disease predisposition: What is a patient’s risk of developing cancer in the future?
- Screening: Does earlier detection of patients with cancer decrease mortality?
- Diagnostic: Who has cancer? What is the grade of the cancer?
- Prognostic: What clinical outcome is most likely if therapy is not administered?
- Predictive: Which therapy is most appropriate?
- Monitoring: Was therapy effective? Did the patient’s disease recur?
- Pharmacogenomic: What is the risk for adverse reaction to the prescribed therapeutic dose?

First reported biomarker for prostate cancer was human prostatic acid phosphatase (PAP) (Gutman and Gutman, 1938). Proteomics and genomic technologies have enhanced the discovery of potential biomarkers. Below mentioned
are the various molecules, which have shown potential as biomarkers for prostate cancer including those that are already commercially available.

### 2.1 Coding genes based biomarkers in Prostate Cancer

Transcripts are the coding part of the genome. It encompasses the functional elements of the genome and are usually very tissue and condition specific. There are a lot of coding transcripts, which have been reported to be prostate cancer specific. Several studies have reported overexpression of human glandular kallikrein 2 (KLK2) in prostate cancer tissues (Herrala et al., 2001). Human KLK2 is one of the 15 KLKs in humans, sharing roughly 80% sequence homology with PSA. It is expressed primarily by the prostate gland, and is androgen-regulated. A prediction model for prostate cancer, using serum levels of four kallikrein markers (total PSA, free PSA, intact PSA, and KLK2), called 4Kscore test, has been developed. It has been validated in previously screened cohorts and found to reduce biopsy rates by 36% to 71%. (Konety et al., 2015). This test combines four kallikrein markers with patient age and digital rectal exam status to determine the likelihood of aggressive prostate cancer prior to a biopsy.

The cytokines in the TGF-β1 family of polypeptides have been implicated in numerous steps of tumor development and are found to be overexpressed in neoplastic prostatic epithelium when compared to normal prostate tissue. A number of studies have documented the positive correlation between elevated plasma levels of TGF-β1 and prostate cancer progression (Djavan et al., 1999). A direct correlation was demonstrated between concentration of TGF-β1 in urine and various stages of prostate cancer (dos Reis et al., 2011).

AMACR encodes an enzyme involved in the regulation of beta-oxidation of branched chain fatty acids, and is related to an increased risk of prostate cancer. This gene is overexpressed in all stages of malignant transformation of prostate. AMACR expression in sections of prostate tissue with histochemical analysis yielded high sensitivity (83-90%) and substantial specificity (100%) for prostate cancer diagnosis (Ananthanarayanan et al., 2005). Different studies have also demonstrated that the detection of AMACR protein or transcript levels in urine samples is predictive of prostate cancer (Hessels and Schalken, 2013).

Telomerase activity is another urine based biomarker, which requires the presence of a RNA component (human telomerase RNA). This test requires a protein subunit hTERT whose levels are associated with the incidence of tumor invasion. (Martignano et al., 2017). In expressed prostatic secretions (EPS), hTERT expression is enriched.
2.2 Long non-coding RNA based biomarker in Prostate Cancer

More recently the non-coding parts of the genome have also found its place as biomarkers. The most prominent non-coding RNA based biomarker emerging for prostate cancer is prostate cancer antigen 3 (PCA3). PCA3 is a long noncoding RNA (lncRNA) that displays elevated levels of expression in >90% of prostate cancer tissues, but not in normal prostate tissues—an important distinction in serum PSA. The high sensitivity and specificity of PCA3 in urine led to studies of PCA3 as a non-invasive biomarker. Over the past decade, several iterations of PCA3 urine tests have emerged, and currently a clinical-grade assay based on transcription-mediated amplification is available (Ploussard et al., 2010). A particularly important attribute of PCA3 is the fact that, unlike PSA, urine PCA3 levels are independent of prostate size thus offer improved specificity. In 2012, PCA3 was approved by the FDA as a diagnostic test for prostate cancer in the setting of a prior negative prostate biopsy (Sartori and Chan, 2014).

Prostate cancer gene expression marker 1 (PCGEM1) was originally identified as a prostate tissue-specific long non-coding RNA. It is involved in the inhibition of apoptosis by delaying p53 and p21 induction in an androgen-dependent manner (Fu et al., 2006). PCGEM1 is overexpressed in at least half of all prostate tumors. Single nucleotide polymorphism (SNP) in PCGEM1 is also associated with prostate cancer susceptibility. Two SNPs, rs1456315 and rs7463708 in the chromosome 8q24, which is a gene desert region, were shown to be most significantly associated with prostate cancer susceptibility. Knockdown of PCGME1 inhibits AR target gene regulation in a DHT-dependent manner and is associated with tumor growth in CRPC xenograft model (Chung et al., 2011).

Growth arrest-specific 5 (GAS5) gene is another lncRNA, which is known to have a direct interaction with AR and subsequent modulation of cofactors (SRA). Another lncRNA (CTBP1-AS) is known to enhance AR activity by regulating the co-repressor or co-activator of certain epigenetic modification in prostate cancer. (Smolle et al., 2017).

Prostate cancer-associated ncRNA transcript-1 (PCAT-1), identified through global transcriptome sequencing, is located in the 8q24 gene desert implicated in prostate cancer. PCAT-1 expression is inversely correlated with expression of the EZH2, a histone methyltransferase that encodes components of PRC2 and a marker for prostate cancer progression; thus, PRC2 represses PCAT-1 expression. PCAT-1 induces cell proliferation in vitro and has a predominantly repressive effect on gene expression, most notably on the expression of the tumor suppressor gene breast cancer 2 (BRCA2). PCAT-1 also interacts with the SUZ12 component of PRC2. (Prensner et al., 2014a).
Second Chromosome Locus Associated with Prostate 1 (SchLAP1) is transcribed from within an intergenic gene desert on 2q31.1. It was originally identified in an analysis of intergenic lncRNAs that are selectively up-regulated in aggressive prostate cancer samples. SchLAP1 is highly expressed in 25% of prostate tumors and shows increased expression in metastatic cancer cells (Cimadamore et al., 2017). SchLAP1 is involved in the regulation of the switch/sucrose non fermenting (SWI/SNF) complex. This complex canonically controls transcription by using ATP hydrolysis to remodel chromatin and physically mobilizes nucleosomes, particularly at the gene promoters. SchLAP1 co-immunoprecipitates with SNF5 and prevents it from binding to the genome, thus antagonizing tumor-suppressive SWI/SNF-mediated gene regulation. Using another cohort of 1008 patients, SchLAP1 was identified and validated as the highest-ranked overexpressed gene in prostate cancer with metastatic progression. These findings demonstrated the usefulness of SchLAP1 as a biomarker of prostate cancer progression (Prensner et al., 2014).

2.3 miRNA based biomarker for Prostate Cancer

MicroRNAs are small (18-24 nucleotides) non-coding RNA that modulate protein expression post transcriptionally by interfering with mRNA and promoting degradation. Various miRNAs participate in cell cycle regulation and apoptosis and their dysregulation may contribute to tumor development and progression. Urine based miRNA biomarkers have been associated with urological malignancies especially in bladder and prostate cancers. High levels of miR-107 and miR-574-3p are found in urine pellet of prostate cancer patients. miR-107 levels could predict patient outcomes during different therapies (Batra et al., 2014).

mir-21 has been found to be over-expressed in many pathologies and in particular is often up-regulated in most types of cancer as it can interact with key factors such as PTEN, PI3K, FasL, TIMP3 and TPM (Wu et al., 2016). miR-205, miR-214, miR-99b and miR-221 were strongly down-regulated in prostate cancer tissues (Srivastava et al., 2013).

miR-183 can promote proliferation of prostate cancer and directly regulate PSA expression increasing intracellular and serum PSA levels. miR-183 targets DKK-3 and SMAD4 that play a role in Wnt signaling pathway in cancer progression thus its overexpression can cause cancer cell proliferation (Larne et al., 2015).

miR-888 regulates important tumor-related factors such as SMAD4 or RBL1, and seems to promote proliferation, migration and tumor progression. High levels of miR-888 in EPS urine correlates with high-grade disease and aggressiveness in prostate cancer (Lewis et al., 2014).
2.4 Methylation based biomarkers in Prostate Cancer

Hypermethylation of CpG islands in the promoter regions of cancer-associated genes are linked to prostate cancer. Three of these genes include GSTP1 involved in DNA detoxification (Harden et al., 2003); APC involved in cell apoptosis, migration and adhesions (Schneikert and Behrens, 2007); and RSSF1, which is involved in cell cycle regulation (Jerónimo et al., 2004). GSTP1 methylation occurs in up to 90% of prostate cancer samples, while it is only seen in 5% of noncancerous controls. GSTP1 is also the most widely reported hypermethylated gene in prostate cancer and is hypermethylated early during oncogenesis therefore is ideally suited for prostate cancer detection (Harden et al., 2003).

2.5 DNA based biomarkers in Prostate Cancer

Family history of prostate cancer increases the risk level by almost 40%. Various studies have identified sixty prostate cancer susceptibility loci and multiple single nucleotide polymorphisms (SNPs) correlating with risk of developing disease. Individuals carrying five of these risk alleles are almost tenfold more likely to develop prostate cancer than men carrying no risk alleles. It has been shown that rarer variants are associated with higher relative prostate cancer risk. Coding variants in the homeobox B13 (HOXB13) were found in 1.4% of patients with a strong family history of early-onset prostate cancer, while it was found only in less than 0.1% of control (Karlsson et al., 2014).

Germline BRCA mutations, which are known to have dramatic genetic implications in breast and ovarian cancer, are also associated with prostate cancer. BRCA1 and BRCA2 play central roles in DNA repair by homologous recombination, which is the mechanism that cells use to repair double-stranded breaks induced. Previous studies have demonstrated that BRCA1 and BRCA2 mutations are predictive factors for response to platinum-based chemotherapy in breast and ovarian cancer. BRCA2 mutations have subsequently been shown to confer a higher risk of prostate cancer in men ≤65 years of age, and they were an independent prognostic factor for disease-specific survival in all stages of prostate cancer including localized disease (Godet and Gilkes, 2017). BRCA2 is associated with intraductal carcinoma, an early-onset aggressive prostate cancer with a poor prognosis and are also race and ethnicity dependent.

Gains or losses of chromosomal DNA (i.e., NKX3.1) can have carcinogenic consequences (Palapattu et al., 2005). Specific chromosome 8 abnormalities, and loss of 8p22 was associated with an increased risk of metastatic progression. Loss of 8p22 in prostate biopsy specimens was also associated with prostate cancer radioresistance (Locke et al., 2012). Studies have found 20 most significant CNVs (15 deletions, five amplifications) in two independent prostate cancer cohorts and found
that gain of MYC and deletion of PTEN were significantly associated with prostate cancer related death (Liu et al., 2013). Specific DNA-based biomarkers were associated with advanced disease stages (loss at 8p23.2) and were found to be predictive of postoperative recurrence (gain at 11q13.1) independent of tumor stage and grade. PTEN deletion dephosphorylates lipid-signaling intermediates resulting in deactivation of PI3K signaling, thus controlling cell proliferation and growth. A higher frequency of PTEN loss is reported in advanced cases (castrate-resistant prostate cancer [CRPC] compared with localized disease in RP [radical prostatectomy] cases) and PTEN loss is associated with shorter progression-free survival (PFS) in ERG-positive tumors. Homozygous PTEN deletion in prostate specimens was independently associated with BCR risk after RP and was clearly associated with TMPRSS2: ERG gene expression (Zafarana et al., 2012).

2.6 Splice isoform based biomarkers in Prostate Cancer

Splicing is a well-known post transcriptional event that increases the protein diversity in the cell. Splice isoforms of various genes have been reported to be either tissue specific or condition specific. One such example in prostate cancer is a splice isoform of androgen receptor called AR-V7. The androgen receptor splice variant 7 (AR-V7) mRNA status was established on the CTCs of individual patients. PSA level which is used as an efficacious biomarker for enzalutamide or abiraterone, do not change in AR-V7 positive patients receiving these treatment (Antonarakis et al., 2014). AR-V7 and other AR modification in prostate tissue can be predicted using CTCs. Despite differential response to the drug in AR-V7 positive patients a recent analysis has shown that AR-V7-positive patients respond to taxane-based chemotherapy in a similar fashion as AR-V7-negative patients (Nakazawa et al., 2015).

2.7 Gene fusion based biomarkers in Prostate Cancer

Transcript fusion or gene fusion is yet another hallmark of cancer. Almost 80% of blood cancer is known to be caused due to one such chimeric transcript like BCR-ABL as mentioned in section 1.6. However recently, transcript fusion have also been discovered in solid tumor. In prostate cancer, approximately 50% of patients are positive for a gene fusion product (TMPRSS2-ERG) arising from a translocation of the androgen-induced transmembrane protease, serine 2 (TMPRSS2) gene with the transcription factor erythroblastosis virus E26 oncogene homolog (ERG) (Park et al., 2014). TMPRSS2-ERG fusions are specific for prostate cancer, and can even be detected in precursor lesions, such as prostate intraepithelial neoplasia. The detection of TMPRSS2-ERG RNA in patient urine has also been reported. TMPRSS2-ERG urinary test in conjunction with PCA3 was found be more sensitive than either of the test alone. Similarly, a large study consisting of prostate tissue samples of 1300 individual demonstrated recently that combined measurement of PCA3 and TMPRSS2-ERG in urine outperformed serum PSA for prostate cancer diagnosis (Yang
et al., 2016b). There has been some contradiction as to whether the presence of a TMPRSS2-ERG fusion is in itself a prognostic biomarker when detected in tissues. While several groups have reported an association between TMPRSS2-ERG and aggressive prostate cancer, others have not observed this association (Demichelis and Rubin, 2007). Although only TMPRSS2 has been reported as a 5’ fusion partner of ERG, additional 5’ partners have been identified for ETV1, ETV4 and ETV5. These 5’ partners include TMPRSS2, SLC45A3, HERV-K_22q11.23, C15orf21, CANT1 and KLK2, which are prostate-specific, while HNRPA2B1 has a ubiquitous housekeeping expression (Kumar-Sinha et al., 2008).

### 2.8 Circulating Tumor Cells based biomarkers in Prostate Cancer

More recently it has been established that circulating cell-free DNA in peripheral blood is a surrogate for tissue biopsy. The amount of tumor DNA in circulating blood can be associated with cancer progression. miRNA-375 and miRNA-141 specific to prostate tissue has been shown to be present in the plasma of prostate cancer patients (Tiryakioğlu et al., 2013). Five genes (KLK3, KLK2, HOXB13, GRHL2 and FOXA1), which were frequently detected in prostate cancer cells were also detectable in whole blood transcripts and CTCs. The transcripts KLK3, PCA3 and TMPRSS2:ERG, which are hallmarks of prostate cancer could be detected in the peripheral blood of CRPC patients but not in healthy controls (Danila et al., 2014). Decreased expression levels of these genes, however, were noted after docetaxel treatment, suggesting a potential role for treatment efficacy. A biomarker panel using CTC count and lactate dehydrogenase (LDH) expression have shown its impact in a Phase III trial for CRPC patients (Scher et al., 2015).

### 2.9 Prostate Cancer Biomarker under Development or Evaluation

Advances in genomic technologies, such as microarray and sequencing technologies have accelerated our understanding of prostate cancer biology. As these technologies have become more available and affordable, we have witnessed an explosion of data pertaining to prostate cancer which is helping in development of novel diagnostic and prognostic panels. Following are a few examples of commercially available tests for prostate cancer detection coming out of this data explosion.

#### 2.9.1 PC antigen 3 and Progensa

Progensa assay which is produced by Hologic Inc., has been approved by the FDA since 2012 to help determine whether a repeat biopsy is necessary after a previous negative result. Progensa is a nucleic acid amplification test measuring the concentration of PCA3 and PSA RNA molecules in urine (Nicholson et al., 2015). A ratio of PCA3 RNA to PSA RNA is then calculated to provide the PCA3 score. In patients with an initially negative prostate biopsy, a PCA3 score of <25 is associated
with a decreased likelihood of prostate cancer. In 7 out 11 combined clinical studies using Progensa test, the sensitivity increased from 53% to 69% and the specificity increased from 71% to 83%. The Progensa PCA3 assay has been included in the EAU guidelines for repeat biopsy decision making.

### 2.9.2 Prostarix Risk Score

Prostarix Risk Score is offered by Boswick Laboratories. This test aims to help physicians decide if an initial or repeat biopsy is necessary for patients with a mildly elevated PSA levels. Prostarix measures the concentration of four urinary metabolites including sarcosine, alanine, glycine, and glutamate (Zhuang and Johnson, 2016). The first study conducted on such metabolomic profiles have provided evidences that they may serve as promising diagnostic and prognostic tools.

### 2.9.3 Mi-Prostate Score urine test

Mi-Prostate Score developed by The University of Michigan is a multiplex analysis of urine tests for PCA3, TMPRSS2:ERG, and PSA levels, producing a risk assessment for aggressive disease (Tomlins et al., 2016). Although TMPRSS2:ERG is specific for prostate cancer, most tumors have multiple foci and are heterogeneous in TMPRSS2:ERG expression. To overcome this limitation, TMPRSS2:ERG has been combined with other biomarkers. In this report, models applying PCA3 and TMPRSS2:ERG to cohort samples improved the association of PSA with prostate cancer and high-grade disease on biopsy (Tomlins et al., 2016). This test is not yet FDA approved.

### 2.9.4 ProMark

ProMark test developed by Metamark Genetics Inc. is based on the prostate pathology and comprises an eight-biomarker (CUL2, DERL1, FUS, HSPA9, PDSS2, pS6, SMAD4, and YBX1) proteomic assay for intact tissue biopsies (Shipitsin et al., 2014). This test uses a fully automated, quantitative, multiplex immunofluorescence assay. The recent clinical validation study met its primary endpoints which includes (i) separating favorable from unfavorable pathology and (ii) Gleason score 6 versus non-Gleason score 6 pathology. ProMark provided independent prognostic information relative to current risk stratification systems.

### 2.9.5 ConfirmMDx

ConfirmMDx offered by MDxHealth is a multiplex DNA methylation assay. This test evaluates epigenetic biomarkers, especially the methylation of glutathione S-transferase pi 1, adenomatous polyposis coli, and Ras association (RatGDS/AF-6). The test aims to predict true negative prostate biopsies from those with possible occult cancer. Two validation studies have been conducted thus far. In the retrospective MATLOC trial, a multivariate model showed that this epigenetic assay was
significantly associated with patient outcome with an odds ratio of 3.17 (95% confidence interval 1.81–5.53) (Stewart et al., 2013). In another study called DOCUMENT, the assay was independently associated with prostate cancer detection in a repeat biopsy collected at an average of 13 months after an initial negative result and demonstrated an 88% negative predictive value (Partin et al., 2014).

2.9.6 Prostate Core Mitomic Test

Prostate Core Mitomic Test is created by MDNA Life Sciences Inc. This test is based on the emerging link between mitochondrial function with regulation of oncogenes and tumor suppressors. The goal of this test is to correctly identify true negative prostate biopsies by utilizing a concretization field effect to identify the molecular changes in the mitochondrial DNA. In a clinical validation study, this test was associated with a negative predictive value of 91%, a sensitivity of 84%, and a specificity of 54% (Legisi et al., 2016). This test has not been reviewed by the FDA.

2.9.7 Oncotype DX

Oncotype DX prostate cancer assay called Genomic Prostate Score (GPS) is developed by Genomic Health Inc. This tissue-based assay measures the expression of 17 genes related to the following four different molecular pathways: androgen (FAM13C, KLK2, AZGP1, and SRD5A2), stromal response (BGN, COL1A1, and SFRP4), cellular organization (FLNC, GSN, TPM2, and GSTM2), and proliferation (TPX2). Gene expression was quantified by reverse transcription-polymerase chain reaction. In the validation study, the GPS was associated with high grade and high stage at surgical pathology, as well as high-grade and/or high-stage disease after controlling for established clinical factors (Klein et al., 2014). Recently, GPS assay show correlation with biochemical relapse and time to metastases and was strongly associated with adverse pathology in patients with very low, low, or intermediate risk after RP (Cullen et al., 2015). The GPS has been shown to provide a net increase in recommendations and/or adoption of active surveillance in patients with newly diagnosed prostate cancer.

2.9.8 Prolaris score

Prolaris score is developed by Myriad Genetics, produces a cell cycle progression (CCP) score based on the expression of 46 genes, consisting of 31 cell cycle progression genes and 15 housekeeping genes (Cuzick et al., 2011). The test was first elaborated in 2011 and has since been validated in four studies. Prolaris panel has also been shown to detect subtle gene expression differences between incidental and clinically detected prostate cancer. However, this expensive test has been criticized for the lack of cost-effectiveness data. The clinical utility of Prolaris awaits evaluation by prospective and randomized clinical trials.
2.9.9 Decipher PC test

Decipher PC test is created by GenomeDX Biosciences. Conducted on tissue sample, this test measures 22 RNA biomarkers in multiple biological pathways in order to classify post-surgery patients with intermediate- and high-risk prostate cancer into genomic risk categories for metastasis. Decipher PC test demonstrated better associations with metastatic disease than clinical-based models alone in multiple studies (Cooperberg et al., 2015; Den et al., 2014, 2015).

2.10 Gap Areas

Until recently, genomics, transcriptomics, epigenomics and proteomics were considered or treated as different research areas demanding unique domain-specific skills for generating, handling and interpreting respective datomes. However, the creation of large data repositories from each of these domains has provided opportunities for bioinformatics domain to act as a melting pot for the integration of datomes from various omics technologies to study a given biological context. Meaning, the gene-to-transcript-to-protein of the central dogma can now be transcended into genome-to-epigenome-transcriptome-to-proteome for a given context under bioinformatics domain. More recently, efforts to integrate various types of datomes in cancer are being reported. However, a much warranted systematic integration of all the omics datomes for a given biological context in biomarker discovery remains a challenge. Here, we propose to utilize the growing body of datomes of diverse types in the public repositories to decipher prostate cancer-specific mutations, histone modifications, methylation, transcript expression, splice variants and protein expression to study the interplay between these elements using bioinformatics approaches. A few high confidence candidate molecules were subjected to downstream validation using in vitro assays.