Long non-coding RNAs and their potential impact on diagnosis, prognosis, and therapy in prostate cancer: Racial, ethnic, and geographical considerations

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Abstract

Introduction: Advances in high-throughput sequencing have greatly advanced our understanding of long non-coding RNA (lncRNAs) in a relatively short period of time. This has expanded our knowledge of cancer, particularly how lncRNAs drive many important cancer phenotypes via their regulation of gene expression.

Areas covered: Men of African descent are disproportionately affected by PC in terms of incidence, morbidity, and mortality. LncRNAs could serve as biomarkers to differentiate low risk from high-risk disease. Additionally, they may represent therapeutic targets for advanced and castrate-resistant cancer. We review current research surrounding lncRNAs and their association with PC. We discuss how lncRNAs can provide new insights and diagnostic biomarkers in African American men. Finally, we review advances in computational approaches that predict the regulatory effects of lncRNAs in cancer.

Expert opinion: PC diagnostic biomarkers which offer high specificity and sensitivity are urgently needed. PC specific lncRNAs are compelling as diagnostic biomarkers owing to their high tissue and tumor specificity and presence in bodily fluids *Recent studies indicate that PCA3* clinical utility might be restricted to men of European descent. Further work is required to develop lncRNA biomarkers tailored for men of African descent.

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Keywords

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1. Introduction

Prostate cancer (PC) is one of the most prevalent cancers worldwide, particularly affecting men living a western lifestyle and of African descent, suggesting risk factors that are genetic, environmental, and socioeconomic in nature. Despite major advances in the diagnosis and treatment of PC, the disease remains a global health problem. PC is the second most diagnosed non-skin cancer in men worldwide [1, 2]. Currently there is considerable interest in lncRNAs and their regulatory roles in developmental processes and disease/ cancer states [3, 4]. Prior to high-throughput sequencing technologies becoming common place, lncRNAs were simply considered transcriptional "noise" and largely ignored by the scientific community [5–7]. With increased sequencing sensitivity in combination with innovative bioinformatic tools, in the past decade researchers finally started to uncover the functional roles of lncRNAs. Two emerging discoveries include the realization that they act upon a wide range of cell processes and are differentially expressed in disease states including various cancers [8, 9].

Computational predictions have identified over 10,000 lncRNAs, and researchers have been keen to characterise them functionally, identify their regulatory roles and exploit this knowledge in biomedical research, diagnostics and therapeutic development [10]. In parallel, bioinformatics methods are also being rapidly improved to better predict the regulatory roles of lncRNAs in cancer and determine their full extent as regulatory modulators. This review provides a detailed overview of lncRNAs and particularly in the context of PC. Firstly, we cover lncRNAs, their history, newly discovered functions, and correlation with cancer. We then review PC, racial differences in disease presentation and why lncRNAs are relevant in this context. Lastly, we provide a summary of tools dedicated to deciphering the functional roles of lncRNAs.

2. What is a Long Non-Coding RNA?

lncRNAs are defined as transcripts longer than 200 nucleotides that are putatively not translated into proteins [8]. Both short (<=200 base pairs) and lncRNAs may contain coding regions [11]. Short non-coding transcripts, and particularly microRNAs (miRNAs) have been studied more extensively than lncRNAs and contribute to the development and progression of many cancers [12]. Prior to the genomic era, lncRNAs were considered 'junk RNA' and were largely ignored by the scientific community. The first lncRNA to be identified was *h19* in 1984. Although at first mistakenly categorised as a messenger RNA (mRNA) [13], *h19* has subsequently been recognised as an epigenetic regulator, differentially expressed in several cancers where it acts as a tumor suppressor [3, 14–16]. In 2002, lncRNAs were finally assigned as functional RNA molecules by the Functional Annotation of the Mammalian Genome (FANTOM) project [17]. Like mRNAs, lncRNAs are transcribed by RNA polymerase II, polyadenylated, capped and spliced [18, 19].

Subcellular localisation provides a lens to define lncRNA functional classes [7, 20]. The identification and number of lncRNAs is continually increasing, however, many remain poorly annotated and are not experimentally validated [12, 21].

As of January 2021, LNCBook, a curated lncRNA database contains 268,848 documented lncRNAs (obtained from publicly accessible databases including GENCODE v27, NONCODE v5.0, LNCipedia v4.1 and MiTanscriptome beta). However, there is a large gap between documented lncRNAs and lncRNAs which have a known link to a molecular or biological function. Of the 268,848 recorded lncRNAs on LNCBook, only 1,867 have been categorised as experimentally validated (linked with functional mechanisms/biological processes and identified in relevant publications) [21, 22]. LncRNAs are classified as either 1) intergenic (lincRNAs), transcribed from intergenic regions located between two genes [5, 23, 24] 2) bidirectional (divergent lncRNAs) transcribed on the reverse strand of a coding transcript located no more than 1000 base pairs away [5, 24] 3) intronic lncRNAs, transcribed only from intronic regions of protein coding genes, 4) antisense lncRNAs transcribed from antisense strands of protein coding genes and 5) sense lncRNAs transcribed from sense strands of protein coding genes [6, 25, 26].

Understanding how lncRNAs are regulated and how they in turn regulate their target genes is an important research area [27]. Thus far, several functional roles of lncRNAs have been established. The most common lncRNA functional groups include guides (e.g., *HOTAIR*) [6, 28], scaffolds (e.g., *TERC*) [6, 29], signals (e.g., *XIST*) [6, 7] and decoys (e.g., *MALAT1*) [6, 30]. There are also a series of documented multifunctional lncRNAs. An example is *NEAT1 [31]*. *NEAT1* was identified as differentially expressed in numerous tumor contexts including lung, colorectal, and prostate cancer [31]. *NEAT1* is an important mediator in the regulation of clear cell renal cell carcinoma (ccRCC) progression and predicts poor prognosis and decreased survival in patients with ccRCC [7, 32–34]. Guide lncRNAs can bind and tether (epigenetic complex machinery) to a target gene locus directing gene expression either in cis or in trans. Guide lncRNA can direct chromatin-modifying enzymes (e.g., histone methylases, acetylases, and deacetylases) to a particular gene target locus which can lead to the activation or repression of local genes [35, 36]. Scaffold lncRNAs recruit epigenetic complexes together, thus acting as a molecular scaffold. They recruit RNA-binding factors to form RNA-proteins complexes which promote or inhibit gene transcription [35, 36]. Signal lncRNAs possess signalling properties that promote guidance of epigenetic complexes to specific locations. These lncRNAs possess enhancer functions which alter the structure of chromatin and guide transcriptional complexes to gene targets enabling transcriptional activity [35, 36]. Finally, decoy lncRNAs can lure epigenetic complexes to different genomic locations. These lncRNAs can recruit and decoy a transcriptional complex to a distinct location for suppression of gene expression [35, 36]. Many reviews have documented the molecular functions of lncRNAs (for example, reference 23) however none have considered the computational aspects of predicting lncRNA functions and their targets. Our review addresses this shortcoming.

3. Long Non-Coding RNAs and Prostate Cancer

The number of patients presenting with urological cancers (malignancies of the genital and urinary organs of men and the urinary organs of women) is on the increase [37, 38]. Currently, urological cancers of the prostate, bladder, and renal stand among the top 10 most diagnosed cancers in men [39]. Despite their frequency, biomarkers for urological cancers are limited. Those that are available typically lack sensitivity in low grade disease e.g., urine cytology for bladder cancer and low specificity e.g., the Prostate Specific Antigen (PSA) [39–41]. lncRNAs are now frequently being linked with urological cancers, and many have been designated as playing roles in the development and progression of these malignancies including prostate cancer [42]. Table 1 summarises selected lncRNAs that are differentially expressed in urological cancers, which may have potential as biomarkers or therapeutic targets [6, 7, 31].

Despite major advances in the diagnosis and treatment of PC, the disease remains a global health problem. PC is the second most diagnosed non-skin cancer in men worldwide [43]. Recent estimates indicate that 1 in 7 men will be diagnosed with PC during their lifetime. In 2018 alone, 359,000 recorded deaths from PC occurred globally [44, 45]. Racial differences are common in PC. Men of African descent are adversely affected in terms of both incidence and mortality rates compared to European based counterparts. lncRNAs are now considered to contribute to these racial differences [46, 47].

Evidence to date suggests that lncRNAs can alter gene expression at both transcriptional and post-transcriptional levels thus playing roles in important biological processes including carcinogenesis and metastasis [48]. Some lncRNAs function as tumor suppressors, possess the ability to interact with oncogenes, inhibit or accelerate proliferation, and influence apoptosis [30, 49, 50]. Other lncRNAs are commonly aberrantly expressed, deleted, amplified and/or mutated in multiple cancers [9, 51]. lncRNAs have been shown to have roles in numerous forms of cancer [52]. Figure 1 displays lncRNAs correlated with numerous cancer types. The specific cancer types and relevant body tissues are highlighted. Table 2 provides a summary of lncRNAs which have been identified as differentially expressed in various malignancies.

Presently, three areas that merit particular attention; 1) Identification of novel diagnostic and prognostic biomarkers for PC, with an emphasis on diagnostic biomarkers for early stage PC which differentiates low-risk from high-risk tumors [40, 53], 2) An urgent need to better understand biological differences in disease presentation in men of African and Northern European descent [54] and 3) Efficient therapies for advanced and castrate-resistant PC [55]. LncRNAs are emerging as biomarkers or therapeutic targets for these areas, as explained below.

4. lncRNAs as Prostate Cancer Biomarkers

It has been widely accepted that the identification of biomarkers should not exclusively focus upon protein coding genes [56]. A key factor for biomarker utility is whether the proposed biomarker is detectable in bodily fluids. Liquid based biomarkers provide

many benefits over traditional tissue-based biomarkers from a 'no surgery requirement and recovery time' perspective, painless non-invasive testing, decreased costs, and more rapid diagnostics [57]. lncRNAs are attractive as PC biomarkers owing to their high tissue and tumor specificity [27] and are detectable in bodily fluids, including *PCA3* and *PCAT18* [57, 58].

Biomarkers with high specificity and sensitivity are particularly needed to help address the over treatment of clinically insignificant PC. The over diagnosis and treatment of low-risk PC remains a common problem, primarily due to use of the Prostate Cancer Specific Antigen (PSA) tests [59] which offer high sensitivity but low specificity [40]. The introduction of the PSA test in the early 1990s was highly criticized for the over-diagnosis and the peak of PC incidence rates [60–62]. Furthermore, PSA tests have poorer diagnostic performance in men of African descent [63]. Therefore, a current need in PC research is the identification of diagnostic biomarkers which can not only offer high specificity and sensitivity but are also universally reliable for all races.

PC specific lncRNAs are compelling as diagnostic biomarkers for clinical use [27]. Possibly the most well-known is *PCA3* (Prostate Cancer Specific Antigen 3). *PCA3* was first observed as highly expressed in PC tumors in 1999 and has since been characterized as over expressed in 95% of all PC cells [64, 65]. Urine-based measurements of *PCA3* provide greater PC specificity than PSA testing [12]. In 2012, the PROGENSA PCA3 assay developed by Gen-Probe Inc was the first lncRNA PC biomarker to obtain Food and Drug Administration (FDA) approval. This lncRNA molecular test is used to help guide urologists in determining the need for repeat biopsies in men aged 50 years or older who had previously presented with a negative biopsy result [66, 67]. However, its practicability as a first use test remains controversial and it cannot predict PC aggressiveness [68, 69]. Several studies have also documented *PCA3* expression in PC progression, however further research is required to confirm its feasibility as a PC prognostic biomarker [70]. Additionally, *PCA3*'s clinical utility might be restricted to men of European descent. O'Malley, *et al.* examined the clinical significance of the urinary biomarkers (*PCA3* & *T2ERG*) in 718 African American and non-African American men and assessed whether they provided increased utility for the detection of PC. Their results indicated that *PCA3* and *T2ERG* enhanced clinical utility however this result was only observed in non-African American men [71]. A major limitation of this study was the relatively small number of African American samples (72) in comparison to non-African American men. Further research with larger ethnically diverse datasets would facilitate more rigorous assessment.

Other studies have yielded varied outcomes in contrast to the initial findings from the O'Malley study. Feibus, *et al.* conducted a study using 304 patients, 60% of which were African American and noted that measurements of *PCA3* enhanced predictability of high-grade PC in African American men [63] while an earlier study by Adam *et al.* using South African men challenged these results. Of 105 South African men referred for prostate biopsy, Adam *et al*, found that *PCA3* levels were not significantly increased in black men who had tested positive for the disease [72]. Again, larger cohorts would provide greater statistical power.

Several other lncRNAs have been established as possible biomarkers of PC, including *PCAT1* (Prostate Cancer Associated Transcript 1). *PCAT1* is a highly PC specific lncRNA [27] and was upregulated in patients presenting with high-risk (Gleason score ≥ 7) PC and metastatic disease [27, 73]. Prensner *et al*, 2011 identified 121 unannotated PC ncRNAs through the analysis of 102 prostate tumor tissues and cell lines, among these was *PCAT1* [74]. *PCAT1* was significantly overexpressed in most PC tumors but particularly in tumors that had metastasised. The group remarked that *PCAT1* was likely contributing to cell proliferation and potentially could serve as a urine-based biomarker given the prior success with *PCA3* [75]. Interestingly, *PCAT1* is located at chromosome 8q24, a chromosome location frequently correlated with PC risk due to its common amplification and the presence of PC susceptibility single nucleotide polymorphisms (SNPs) [76, 77]. Yhan *et al.* and Prensner *et al.* concluded that *PCAT1* supports cell proliferation in PC with Prensner and colleagues noting that it may represent a suitable candidate for biomarker development [73, 78]. *PCAT18* is over expressed in PC. Using tissue samples from patients diagnosed at the Stephanshorn clinic in Switzerland and plasma samples collected in Canada, Crea *et al.* found that *PCAT18* was overexpressed in the plasma of patients with localised and advanced forms of the disease compared to healthy individuals. The results from this study displayed a positive correlation between *PCAT18* and PC stage, with the highest levels observed in metastatic castrate resistant PC. Thus, *PCAT18* could have prognostic value, including to discriminate between localised and metastatic forms of PC, and is a possible therapeutic target for advanced PC [79]. *MALAT1* (Metastasis Associated Lung Adenocarcinoma Transcript 1) is a lncRNA originally correlated with lung cancer however it has been found to be over-expressed in several cancers including PC. In 2013, Ren *et al.* identified *MALAT1* as detectable in plasma and serum and suggested it had the potential to be a diagnostic biomarker [80]. Wang *et al.* identified *MALAT1* as over-expressed in urine samples of Chinese PC patients and noted its potential as a urine-based biomarker [81].

lncRNAs correlated with advanced PC include *PCAT7* (Prostate Cancer Associated Transcript 7), *SChLAP1* (SWI/SNF Complex Antagonist Associated with Prostate Cancer 1) and *PCAT18*. *PCAT7* has previously correlated with disease progression in nasopharyngeal and non-small cell lung cancer [82, 83]. Lang, *et al*, 2020 noted that *PCAT7* has the potential to be a therapeutic target for men presenting with PC bone metastasis via disruption of the constitutive loop between *PCA7* and TGF-β signalling [84]. *PCAT7* also has the potential to be a prognostic biomarker. *SChLAP1* (SWI/SNF 'Complex Antagonist Associated With Prostate Cancer') has been proposed as a biomarker of lethal PC. Cimadamore *et al.* documented that lncRNA *SChLAP1* it is critical in the development and progression of PC [85]. Prensner *et al.* identified that *SChLAP1* is highly expressed in ~25% of PCs analysed (including metastatic PC) and may promote tumor cell invasion (*in vitro*) as well as metastasis (*in vivo*) [86–88]. Additionally, Prensner *et al.* observed *SChLAP1* expression in urine and correlated with higher-risk PC patients suggesting its potential as a biomarker to differentiate between low-risk and high-risk tumors [89]. *SChLAP1* has also been associated with adverse clinical outcomes in post radical prostatectomy and considered a potential tissue based prognostic biomarker by Mehra, *et al* [87]. Similarly, Chua *et al.* suggested *SChLAP1* expression was linked with increased biochemical relapse and metastasis PC subsets cribriform architecture and intraductal carcinoma [90].

PCGEM1 is highly PC specific, has been linked to PC progression by androgen receptor transcriptional co-regulators and could also decrease apoptosis in PC cell lines [86, 91, 92]. Petrovics *et al*. observed that *PCGEM1* expression was significantly higher in PC cells of men of African descent compared to men of Northern European descent [91]. An additional study by Lee *et al*. observed similar results where *PCGEM1* was significantly over-expressed in prostate tumors of African-American but not European-American men [93].

Despite a better understanding of the roles of lncRNA and the number identified as potential biomarkers of localized and advanced PC, few lncRNAs have met the success of *PCA3*. A primary reason for this is that lncRNA research is still in its infancy with thousands of predicted lncRNAs requiring laboratory experimental validation of their utility and confirmation in separate patient cohorts. Moreover, the overwhelming majority of candidate biomarkers fail to achieve clinical utility [58]. The candidate PC biomarkers summarised above require analytical and clinical validation to better assess their utility. To date numerous articles have been published detailing lncRNAs directly related to PC (refer to references 38, 51, 53, 54, 55 and 68), however our review differs in two specific ways, 1) more in-depth detail relating to PC and racial differences and 2) computational methods and software now available for identifying potential lncRNA biomarkers in the disease.

5. Racial Differences in Prostate Cancer

Racial differences are common among cancers, examples include multiple myeloma, colorectal and breast cancer. Multiple myeloma is the most common hematologic cancer in patients of African descent [94]. Although it is a rare disease, diagnoses are twice as high in patients of African descent compared to European descent. Reasons for these differences are currently unknown and the disease remains uncurable [95–97]. In the USA, colorectal cancer patients of African descent experience decreased stage specific survival in comparison to patients of European descent irrespective of socioeconomical background, age, treatment, and stage at diagnosis [98]. Invasive breast cancer mortality rates also differ between patients of African and Northern European descent. In the USA, African American women are more likely to die from the disease than European-American women [99]. African American women also experience worse prognosis and decreased survival times compared to European-American women regardless of their socioeconomical background, age, and stage at diagnosis [100].

Prostate cancer has one of the largest racial disparities of all cancer types. In the U.S.A., African Americans have among the highest mortality and lowest survival rates of any race or ethnic group [101]. PC is also the top cause of cancer mortality among men of African descent living in Caribbean and Sub-Saharan Africa [102]. Similar disparities exist in the UK, where men of African descent are 2–3 times more likely to develop PC than Caucasian men and have a 30% higher mortality rate [103]. Non biological factors contributing to PC racial disparities include diminished societal trust in the medical community, level of education attained, and financial concerns. Access to healthcare plays an important role in PC mortality. However, African American men have higher PSA values and higher tumor grades even at the same cancer stage, compared with non-African American men

within the same healthcare system such as the Veterans Administration in the USA [104]. The reasons underlying these racial differences remain an area of active research. Many biological explanations have been presented including dietary factors such as alcohol intake, vitamin D deficiency and lycopene and isoflavone consumption [104–108]. Biological factors including genetic alterations – African Americans have higher rates of variations in tumor suppressor genes such as *EPHB2* and are susceptible to higher prevalence of chromosome 8q24 variants [47, 54, 76, 109–111].

An emerging area of research is the role of lncRNAs in cancer development and progression in the context of racial differences. Frequently, lncRNAs are reported as differentially expressed in numerous cancers and are known to be involved in tumorigenesis and metastasis [48]. However, there is a lack of research investigating lncRNA differences between racial groups.

Much remains to be uncovered about the mechanisms by which lncRNAs regulate transcriptional and translational processes that drive oncogenesis. A lncRNA previously found to be significantly correlated with both PC and men of African ancestry is *PCGEM1* (Prostate Cancer Gene Expression Marker 1). *PCGEM1* is highly PC specific and has been linked to PC progression by androgen receptor transcriptional co-regulators and attenuates apoptotic processes in PC cell lines [86, 91, 92]. Petrovics *et al*, identified *PCGEM1* expression as being significantly higher in PC cells of men of African descent compared to men of Northern European descent [91]. An additional study by Lee *et al*, 2016 observed similar results where *PCGEM1* was significantly over-expressed in prostate tumors of African-American but not in European-American men [93].

Recently, Yuan, *et al*, 2020 examined genomic and transcriptomic differences among African American and European-American PC patients. The 470 samples which were analysed consisted of RNA-sequencing of 57 African American and 413 European-American patients from The Cancer Genome Atlas project (TCGA) prostate adenocarcinoma (PRAD) portal. The significantly lower amount of African American samples represents a common challenge in health disparities research, with genomic studies typically being constrained to populations of European descent [112].

Yuan, *et al*, identified 1868 (31%) of the differentially expressed transcripts between African American and European-American patients were lncRNAs. Patient and disease characteristics (age and Gleason score) were accounted for [47]. Of these differentially expressed lncRNAs, all were significantly enriched and regulated at least one target gene identified by the Long Noncoding RNA Heterogeneous Regulatory Network integrator (LongHorn) algorithm. LongHorn predictions are based on reverse-engineered canonical interactions, determined experimentally as part of the Encyclopaedia of DNA Elements (ENCODE) project including the crosslinking and immunoprecipitation assay (eCLIP) and chromatin immunoprecipitation sequencing (ChIP-seq) data [30, 47]. The researchers also showed that nearly 90% of lncRNAs differentially expressed between racial groups remain uncharacterised, underlining the need for continued lncRNA research. Of the 28 characterised lncRNAs differentially expressed between African and European-American men, 13 were PC specific including *PCA1* and *PCAT10*. The researchers noted that

the differentially expressed lncRNAs potentially contribute to disease progression and influencing PC racial differences. Further work is required to understand the regulatory functions of uncharacterised lncRNAs differentially expressed between racial groups [47].

Given the evidence highlighting the potential roles of lncRNA in PC tumorigenesis, there is an urgent need to understand the functional consequences of lncRNA differences between African and Northern European PC patients. One of the pressing challenges for integrative computational biology and statistical genetics in racial disparities research is predicting genotype-to-phenotypes. The ability to identify the key drivers among the multitude of interacting molecules is challenging. Additional obstacles include the rapid growth of data, the unavailability of data through issues with incompleteness, inaccuracies, heterogeneity, and data silos [113, 114]. LncRNAs may be prioritised according to their impact upon the gene regulatory network through graph theoretic and systems biology approaches [115, 116]. Understanding the biological underpinnings of racial differences in PC will ultimately provide an opportunity to help eliminate them by identifying possible PC diagnostic and prognostic biomarkers as well as potential therapeutic targets for men of African descent.

6. lncRNAs as Potential Therapeutic Targets for Advanced and Castrate Resistant Prostate Cancer

Advanced PC is traditionally defined as a disease which has spread (metastasized) outside the prostate gland [117]. Cancers generally metastasize preferentially to specific distant organ sites [118]. In most cases of advanced PC, metastasis targets the bones [119]. Androgen Deprivation Therapy (ADT) is clinically used as a palliative treatment for patients diagnosed with advanced PC [120–122]. In healthy men, the androgen testosterone and its derivative dihydrotestosterone are required for normal functioning of the prostate however, researchers have identified it is also vital for PC tumor growth [123]. Despite initial success with ADT, nearly all patients relapse and develop castrate-resistant PC (CRPC) after a mean duration of 2–3 years [124, 125]. CRPC is defined as the progression of PC despite ADT and may present as one or any combination of a steady growth in PSA levels, progression of pre-existing disease, or the emergence of new metastases [126] Currently CRPC remains uncurable and most patients with non-metastatic tumors will develop metastasis within 36 months of diagnosis, 90% of which will experience metastasis to the bone [127, 128]. The survival probability of metastatic PC patients depends on a variety of circumstances from which organ sites the disease has metastasized to, the patient response to treatment and the extent of the metastasis [129]. However, once the disease has spread, survival rates are bleak with 29% five-year survival [130]. Drug resistance in cancer therapies continuously present as a major obstacle [131]. lncRNAs are now considered as possible components to promote drug resistance and enhance drug sensitivity in cancer treatments [131]. Drug resistance refers to intolerance build up against pharmaceutical drugs [132]. Drug sensitivity corresponds to restoring sensitivity to drugs after tolerance has been developed [131].

In PC, there remains an urgent need to identify therapeutic targets for CRPC and advanced forms of the disease. lncRNAs are being proposed as alternative therapeutic targets for slowing the progression of PC, several of which include *HOTAIR* (Hox Transcript Antisense

Intergenic RNA), *MALAT1* (Metastasis Associated Lung Adenocarcinoma Transcript 1), and *GAS5* (Growth Arrest Specific Transcript 5) [56]. The majority of lncRNAs identified as potential CRPC and metastatic PC therapeutic targets are specifically associated with the androgen receptor (AR) signalling pathway [133, 134]. Notably, the AR is vital in all stages of PC because it stimulates cell growth and survival [135]. Thus, most newly suggested therapeutic targets for PC centre around this [136, 137].

Several lncRNAs proposed as candidate therapeutic targets for CRPC and metastatic PC are primarily associated with the AR, including *HORAS5* (*LINC00161*) [138], *CTBP1-AS* (C-Terminal Binding Protein 1 Antisense RNA) [139] and *PCAT29* (Prostate Cancer Associated Transcript 29) [135]. lncRNAs can be directly influenced by androgen regulation [140] and many have been documented to participate in the advancement of PC through direct contact with the AR [141].

Parolia *et al*, 2019 found that *HORAS5* facilitated the progression of CRPC in an AR dependent manner by regulating AR mRNA stability [138] and found that reduction in *HORAS5* expression had a knock-on effect on the expression of the AR and its associated cancerous AR targets such as *KIAA0101* [138]. lncRNA *CTBP1-AS* has been observed to have similar results for both CRPC and hormone dependent PC principally by promoting tumor growth [139]. Yakayama, *et al*. found that *CTBP1-AS* can suppress expression levels of *CTBP1*, a transcriptional corepressor known to regulate expression of tumor suppressors, and several genes involved with cell apoptosis [139, 142]. *CTBP1-AS* had androgen-dependent functions which could hinder the expression of tumor suppressors in both hormone dependent PC and CRPC suggesting potential as a therapeutic target [139]. *PCAT29* is a PC specific lncRNA which has also been linked to the AR [135] Malik. *et al*, identified *PCAT29*, as a tumor suppressor of PC which is suppressed by the AR. *PCAT29* has PC suppressive effects including hindering cellular proliferation, tumor growth, cellular migration, and metastasis [135]. Lower expression of *PCAT29* is correlated with decreased survival in PC patients [135].

Several other studies have identified lncRNAs linked to PC and the AR. An associated lncRNA is *HOTAIR [143]. HOTAIR* is categorised as ubiquitously expressed and associates with multiple illnesses such as cardiovascular diseases, and cancers including breast, gastric, colorectal [144]. Zhang, *et al*, 2015 identified that *HOTAIR* is repressed by androgens and overexpressed in CRPC [145]. Further research supports the hypothesis that *HOTAIR* contributes to the progression from hormone dependent to CRPC [146]. Taken together, these results suggest *HOTAIR* is a key player in numerous cancers including CRPC [145]. Another lncRNA lately associated with the AR is *ARLNC1* (AR-regulated long non-coding RNA 1). Zhang, *et al*, 2018 identified *ARLNC1* was strongly correlated with AR signalling in the advancement of PC and deemed it a possible therapeutic target with further detailed study [147]. Several further lncRNAs have been correlated with the androgen receptor (AR) signalling pathway in PC either to inhibit or promote tumor growth. Therefore, lncRNAs can act as key drivers of PC and have potential as therapeutic targets. Figure 2 presents a schematic overview of AR associated lncRNAs that either inhibit or promote PC pathophysiology [133]. This schematic summarizes key lncRNAs and their role in up- and

down-regulation of the AR, and the role of these key lncRNAs in promoting and inhibiting carcinogenesis and interplay with miRNAs and proteins.

7.   LncRNA Interaction Catalogues and Prediction Tools

Exploratory studies suggest that lncRNAs have an extensive interactome; however, current validation data is insufficient; therefore, many lncRNAs lack known interaction partners and their function remains elusive. lncRNA interactions may be acquired from public databases, some of which are considered below. However, existing annotations do not capture all the possible mechanisms and contexts in which lncRNAs may control gene expression. Experimental determination of lncRNA interactions is labour-intensive and costly, not least due to the large space of potential interactions, and so lncRNA function prediction software is required.

7.1.   Databases related to lncRNAs

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Presented by Zhou and colleagues, the experimentally validated functional lncRNA database (EVlncRNA) 2.0 is an updated version of the EVlncRNA database which comprises only functional lncRNAs have been experimentally validated though low-throughput techniques [148]. The update, which involved the manual curation of over 19,000 lncRNA-associated publications, includes information on 4010 curated lncRNAs across 124 species, 1082 diseases and 6,244 interactions. Importantly, interaction network integrated into the tool's online platform (https://www.sdklab-biophysics-dzu.net/EVLncRNAs2/) provides users the ability to easily browse information retained within the database.

Despite the quality of lncRNA annotated within EVlncRNA 2.0, it could be considered much less comprehensive than alternative databases such as RNAInter (RNA Interactome Database) or RISE (RNA Interactome from sequencing experiments) which rely heavily on data from high-throughput studies and thus possess substantially more lncRNA interactions [149–151].

lncTarD database (http://bio-bigdata.hrbmu.edu.cn/LncTarD/) is a manually curated resource retaining information corresponding to 2822 lncRNA-target regulatory interactions that have proven relevance in 177 human diseases. For prostate cancer specifically, the database possesses data on 73 lncRNA-target interactions along with the mechanism of interaction and its functional consequences [74]. LIVE (lncRNA Interaction Validated Encyclopedia) is a database of manually curated and experimentally validated lncRNA interactions [152]. Consequently, LIVE is small with just 572 lncRNA interactions at the time of writing.

Importantly, the database contains information relating to lncRNA interactions with multiple cellular components including proteins and transcription factors in addition to disease associations.

lnCaNet (LncRNA-Cancer gene co-expression Network) was first introduced in 2016 and is currently available as a web-based tool (http://lncanet.bioinfo-minzhao.org/)[153]. It operates as a database containing lncRNA-gene co-expression predictions for 11 cancers (colon, lung, breast etc.), with co-expression data sourced from Mitranscriptome, an online data repository of long polyadenylated RNA transcripts identified by RNA-seq [154]. lnCaNet includes lncRNA-gene expression correlations for 2,544 cancer genes and 17,250 lncRNAs

7.2. Prediction Tools

In the absence of experimental evidence, predictive algorithms are used; however, benchmarking has revealed room for improved predictive performance [155, 156]. For RNA-RNA prediction algorithms, most take into consideration the sequence of the RNA molecule when determining interactions. For example, both IntaRNA and LncRRIsearch methods utilise the minimum free energy of interaction, a thermodynamic principle affected by the number, type, and arrangement of nucleotides of an RNA molecule, to predict interactions [157–159]. In addition, the RIScoper tool is capable of extracting RNA-RNA interactions through literature text mining which is highly valuable given that findings would be experimentally validated [160].

lncRNA-DNA interactions mostly occur through RNA-DNA triplex formation, estimations of such structures are useful substitutes in lieu of experimental evidence. For example, the recently developed Triplex Forming Potential Prediction (TriplexFPP) is a machine learning based model which considers triplex formation capacity of a lncRNA based on computational methods in addition to triplex formation sites in DNA based on experimental data in a machine learning model to predict triplex formation [160]. In theory, such a method would be able to outperform more traditional methods such as Triplexator as it able to consider beyond the limits of the computational model through the inclusion of experimental data [160, 161].

Capsule-LPI tool considers sequence, motif, physicochemical and secondary structure features from lncRNAs and proteins within a lncRNA-protein pair to determine lncRNA-protein interactions [162]. Despite its complex mathematical architecture, the authors have compiled Capsule-LPI into a web-based tool (http://csbg-jlu.site/lpc/predict) allowing users to capture lncRNA-protein interactions by providing up to 100 lncRNA and protein sequences in Fasta format. Importantly, under 5-fold cross validation, Capture-LPI was found to possess the highest precision and the second highest sensitivity highlighting the tools utility and its room for improvement.

Interestingly, methods are available to translate interaction information into functional predictions. For example, MechRNA is a pipeline for lncRNA functional prediction based on RNA-RNA and RNA-protein interaction data. This approach utilises the IntaRNA2 algorithm to predict RNA-RNA interactions along with publicly available CLIP-seq (cross-

linking immunoprecipitation sequencing) data and the GraphProt computational framework to determine RNA-protein interactions before combining data and predicting function based on several pre-determined possibilities [163, 164].

Possibly the most well-known method for lncRNA regulatory predictions is the LongHorn algorithm, which derives lncRNA interactions based on four predefined models of lncRNA regulation.

These models include activity as decoys, miRNA sponges, co-factors/ guides, and switches [30]. In a seminal publication, Chiu et al. applied the algorithm to TCGA data and predicted lncRNA–gene interactions predictions for individual cancers of interest. The lncRNA-gene predictions are available presently for 13 tumor contexts including prostate adenocarcinoma, lung adenocarcinoma and ovarian serous cystadenocarcinoma. For PC, Longhorn was applied to TCGA data including RNA, miRNA expression and copy number profiles of 371 prostate adenocarcinoma tumors. PLAIDOH (Predicting lncRNA Activity through Integrative Data-driven Omics and Heuristics) was developed at Washington University School of Medicine and applied to identify lncRNAs associated with non-Hodgkin lymphoma [165]. PLAIDOH offers users the opportunity to analyse both publicly and privately owned datasets, analyse statically small datasets and ultimately rank lncRNAs in order of importance based on customizable metrics [165]. One limitation is that it only predicts lncRNA targets that are located within a genomic window limit of 800kb. Using PLAIDOH, researchers have validated predictions through identifying well recognised lncRNA gene regulatory pairs such as HOTAIR matching with HOX genes and familiar lncRNA-protein binding pairs such as NEAT1 and NONO [165], new lncRNA interactions have also been uncovered and subsequently validated, demonstrating the utility of this tool.

lncRNA-screen is interactive platform that operates as a fully functional analysis pipeline which performs all major steps involved with typical RNA-Sequencing processing, its main objective is to facilitate the computational discovery of lncRNA candidates that can be further examined by functional experiments [150]. This pipeline can automatically download and prepare raw FASTQ (sequencing) files from multiple public repositories and performs data quality control, pre-processing, alignment, annotation, differential expression and novel lncRNA identification and classification. After analysis, lncRNA-screen provides users with an interactive HTML summary report that can be searched and filtered to suit users' individual needs. Information includes locus, number of exons, a genome snapshot and lncRNA–mRNA interactions. lncRNA-screen is limited to lncRNA-gene predictions by physical location (neighbouring genes).

These databases and computational tools may be applied to understand the regulatory impact of lncRNAs upon map oncogenes and tumor suppressors [166, 167]. The resultant predictions are useful for identification of candidate cancer biomarkers and therapeutic targets, in concert with traditional biochemical methods [168].

8. Concluding Remarks

lncRNAs are now established regulators of a vast number of biological processes as well key mediators for the development and progression of various cancers. This is remarkable, considering that lncRNAs were relatively recently branded as 'junk' with no regulatory capabilities. Despite significant progress, there is still much to learn about lncRNAs and their potential value as cancer biomarkers or in therapy.

9. Expert Opinion

At present there are three areas of prostate cancer research that require focus: 1) understanding fundamental biological reasons as to why men of African descent are significantly more prone to disease morbidity and mortality, 2) improved therapeutic treatments for advanced and castrate-resistant PC, and 3) the necessity for biomarkers which can differentiate low risk and high-risk disease and assess PC racial disparities. Elucidating the functional roles of lncRNAs will help drive advances in each of these areas and will lead to better diagnosis and treatment of PC.

Despite these advances, opinions in the scientific community as to whether lncRNAs provide realistic therapeutic, prognostic, or diagnostic targets is varied at this time. This will add to the complexity of implementing clinical testing based on lncRNA diagnostics. The Clinical Laboratory Improvement Amendments (CLIA) federal regulatory standards require that clinical laboratories determine and detail their own performance specifications for laboratory-developed tests to guarantee accurate and precise results prior to implementation of the test. Characteristics that must be established typically include accuracy and precision, range for reporting, analytical sensitivity and specificity and reference intervals. Although both a positive and negative attribute, the sheer number of lncRNAs typically predicted by computational tools presents challenges for both clinical and research practice. The hundreds to thousands of lncRNAs which may be identified computationally cannot be feasibly validated in a clinical setting. This elevates the need for more sophisticated computational algorithms based on deep learning approaches which not only predict accurate lncRNAs but also facilitate stringent thresholds and intelligent approaches to triage specific lncRNAs subsets for laboratory-based testing and ultimately clinical implementation.

As precision medicine approaches evolve and become more inclusive the greatest impact that this research will realize is the advancement of knowledge of racial differences among prostate and other cancers. Several studies have determined that lncRNAs may play a role in differences in racial outcomes in cancer. There remain considerable and persistent racial disparities in prostate cancer outcomes. Reduced access to health care services contributes to racial disparities in PC outcomes, but even in equal access health care systems such as the Veterans Administration (VA) in the USA, AA Veterans have higher PSA levels and higher-grade tumors than compared to EA Veterans even when presenting with the same stage of disease. Unfortunately, medical mistrust issues and their associated indicators among AA patients has an adverse effect in recruiting sufficient sample numbers of ethnic minorities and their participation in clinical trials. Distrust in the health care system and

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fear associated with detection and treatment are responsible for late diagnosis in AA men. There is a paucity of samples from racial minorities in public genomic databases to detect moderately common genomic alterations in AA, which is contributing to the gap in PC disparities. We anticipate that as the lncRNA research field develop and matures greater emphasis will be placed on identifying lncRNAs that play key roles in the development and progression of cancer across all ethnic groups.

This field has already significantly progressed in a relatively short period of time, from the first lncRNA identified (*h19*) to the realization that lncRNAs do in fact process regulatory capabilities. With novel lncRNAs being identified daily and associated with cancer, pressure to experimentally validate these emerging candidates is increasing. In the future, we expect lncRNA computational tools will become an essential tool for both research and clinical laboratories and for a variety of diseases beyond cancer. We also expect significant growth in curated lncRNA databases with improved functional predictions of lncRNAs. We anticipate increased commercial activities based around lncRNA therapeutic, prognostic and diagnostics.

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Declaration of Interest

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Article Highlights

- Racial differences continue to persist in prostate cancer

- lncRNAs possess regulatory functions and can become diagnostic, prognostic, and therapeutic targets

- The vast majority of lncRNAs are yet to be experimentally validated and their molecular function elucidated

- lncRNA validation cannot rely solely on experimental validation

- There is a clear need for computational software which can predict lncRNA molecular functions
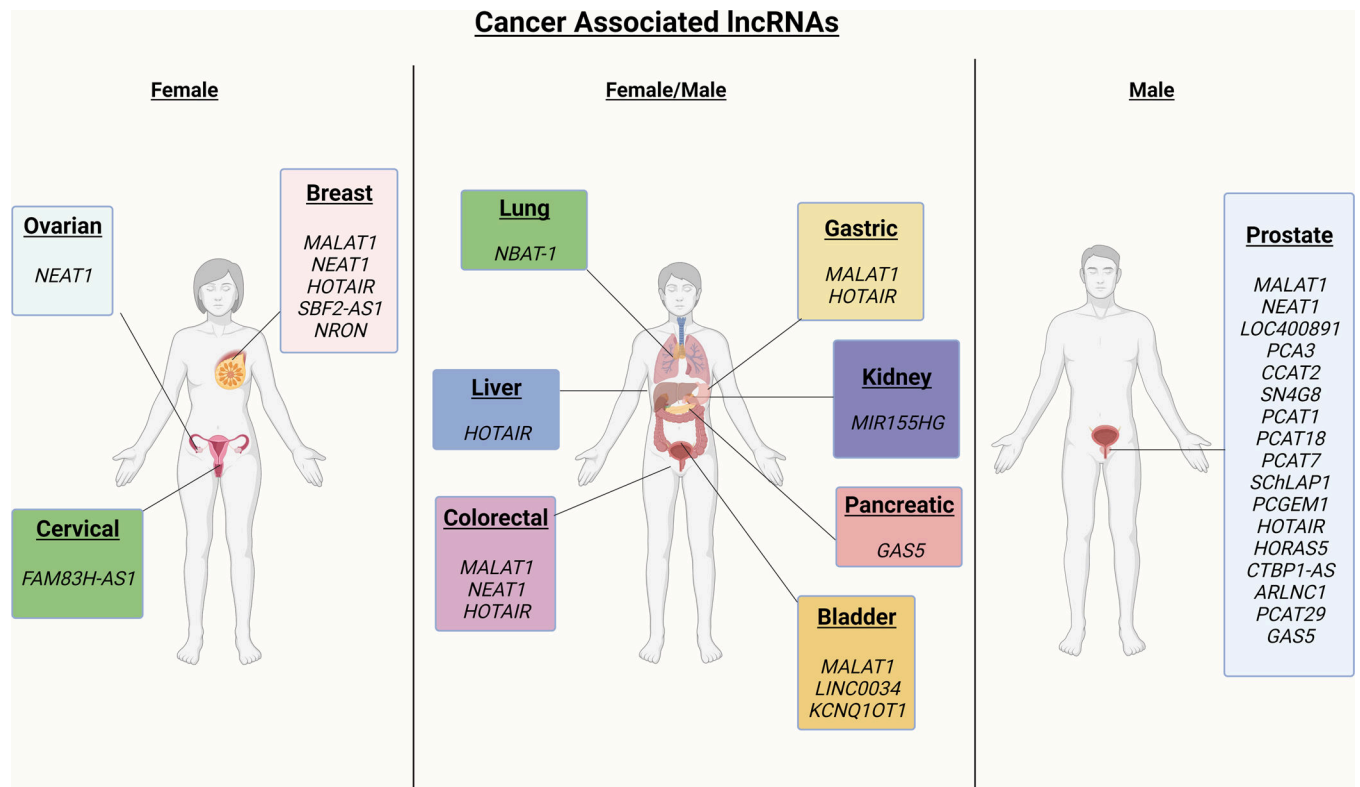
Figure 1. Cancer associated lncRNAs.

Key lncRNAs associated with various cancers are highlighted as to the body tissue and cancer type.
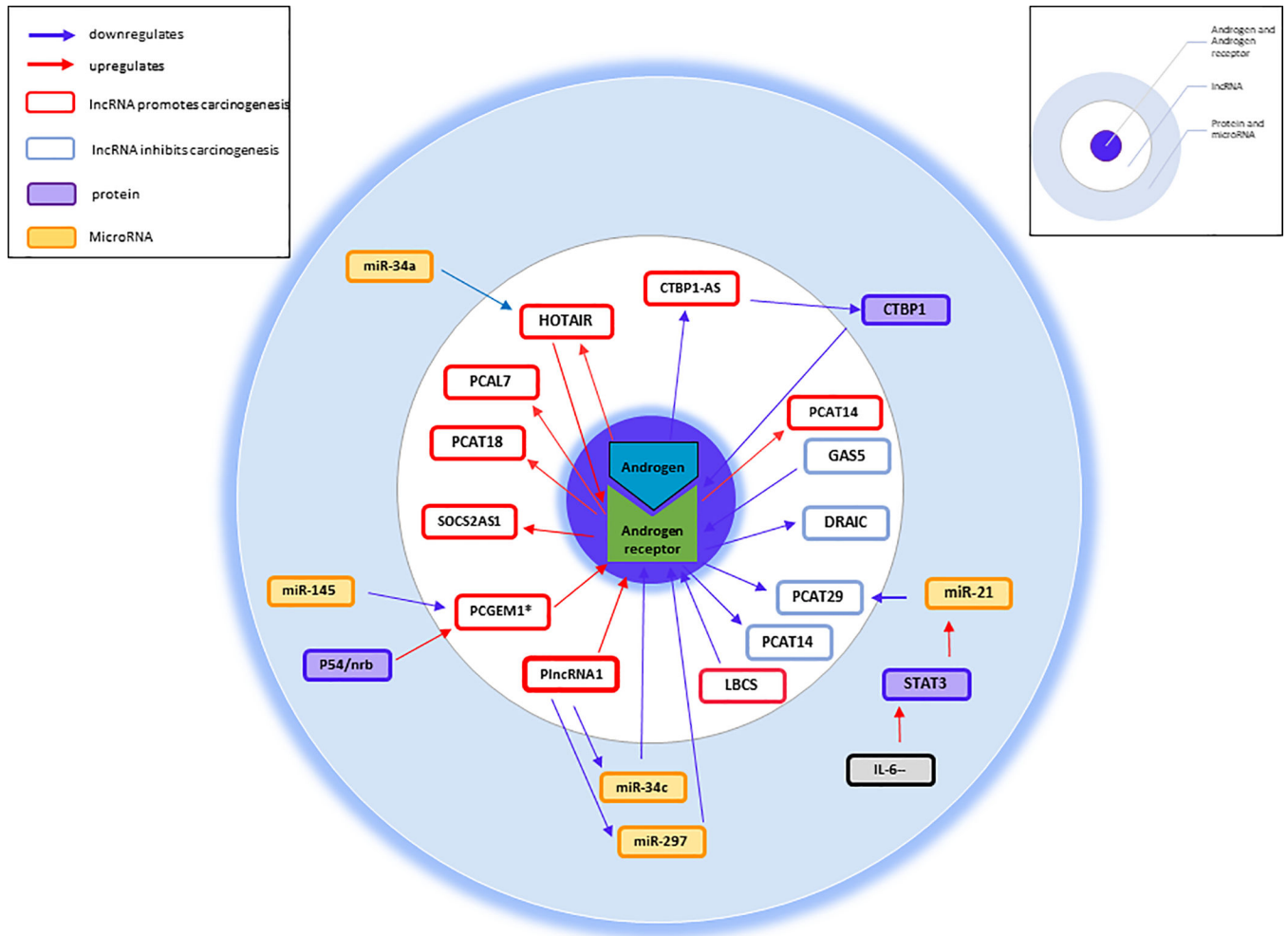
Figure 2. Androgen receptor (AR) signalling pathway associated PC lncRNAs (Adapted from Aird *et al.* [118]).

This schematic provides a summary on key lncRNAs and their role in up- and down-regulation of the AR. The role of these key lncRNAs in promoting and inhibiting carcinogenesis and the interplay with miRNAs and proteins is highlighted.

Table 1

Urological cancer associated lncRNAs

lncRNA	lncRNA functional group *	Urological cancer type	Sample size	Differential Expression	Fold change	Potential Cancer Impact	Hazard ratio	Study reference
MALAT1	Scaffold [169] Decoy [170]	Bladder	95	Upregulated	Not described	Poor survival	1.26 (0.68–2.13)	[171]
		Prostate	14	Upregulated	Not described	Not described	Not described	[80]
NEAT1	Scaffold [7] Decoy [7]	Prostate	30	Upregulated	2.101	Not described	Not described	[172]
LINC00346	Not described	Bladder	52	Upregulated	Not described	promotes bladder cancer migration and invasion	Not described	[173]
KCNQ1OT1	Guide [174] signal [175]	Bladder	30	Upregulated	Not described	*KCNQ1OT1* facilitates the progress-sion of bladder cancer by targeting MiR-218–5p/HS3ST3B1	Not described	[176]
LOC400891	Not described	Prostate (All patients underwent radical prostatectomy or laparo-scopic radical prostatectomy)	81	Upregulated	Gene chip – 4.1 QPCR – 2.4	Unfavor-able prognosis	Multi-variate Tumor stage - 1.823 Multi-variate *LOC400891* expression - 2.116	[177]
PCA3	Scaffold [178]	Prostate	56	Upregulated	10–100-fold overexpression	Not described	Not described	[64]
PCAT1	Decoy [179]	High-risk prostate cancer (Gleason 7) and metastasis prostate cancer	58 prostate cancer tissues 20 prostate cancer xeno-grafts	Upregulated	Not described	Not described	Not described	[73]
PCAT18	Not described	Prostate	160	Upregulated	8.8–11.1 fold	potential therapeutic target for metastatic prostate cancer	Not described	[79]
PCAT7	Decoy [84]	Prostate cancer with bone metastasis	57	Upregulated	Not described	promotes PCa bone metastasis	1.85 3.97	[84]
SChLAP1	Decoy [180]	Prostate	208	Upregulated	Not described	SChLAP1 expression is associated with prostate cancer progression	univariate (hazard ratio = 2.343. multivariate (hazard ratio = 1.99	[87]
PCGEM1	Scaffold [181]	Prostate (cells of African American patients)	Not described	Upregulated	Not described	increased expression level with high-risk CaP patients and African-American race is significantly related to *PCGEM1* expression in tumor cells	Not described	[91]
PCGEM1		Prostate (African American patients)	30 patients (15 African-Amer-ican, 15	Upregulated	Not described	Not described	Not described	[93]

lncRNA	lncRNA functional group *	Urological cancer type	Sample size	Differential Expression	Fold change	Potential Cancer Impact	Hazard ratio	Study reference
			(Caucasian-Amer-ican)					
HOTAIR	Scaffold [181] Guide [6]	Prostate (CRPC)	Not described	Upregulated	Not described	Drives Castration-Resistant Prostate Cancer	Kaplan-Meier analysis of PCa outcome using the GEO: GSE21034 dataset	[145]
HORAS5	Not described	Prostate	Not described	Upregulated	12.51	Poorer clinical outcome in human PCa samples	Disease-free survival based on HORAS5 expression [cBioportal, TCGA PCa database, 456 vs 35 (Elevated HORAS5) patients]	[138]
CTBP1-AS	Decoy [180]	Prostate	105 prostate cancer samples	Upregulated	Not described	Associated with prostate cancer castration-resistant tumour growth and activates AR signals	Not described	[139, 182]
ARLNC1	Not described	Prostate	14 prostate cancer cell lines	Upregulated	Not described	Strongly associated with AR signaling in prostate cancer progression	Not described	[147]
PCAT29	Decoy [183]	Prostate	Not described	Downregulated	0.29 ± 0.15 in tumor tissues as compared to normal tissues	Supp-resses prostate cancer cell proliferation	Not described	[182]
GAS5	Scaffold [184] Decoy [6]	Prostate	Not described	Downregulated	Not described	Pro-apoptosis	Not described	[185]

*
lncRNA functional groups subject to change

Table 2

Cancer associated lncRNAs.

lncRNA	lncRNA class	Cancer Type	Differential Expression	Reference
MALAT1	Antisense	Colorectal	Upregulated	[186]
	Antisense	Gastric	Upregulated	[187]
	Antisense	Breast	Upregulated	[188]
NEAT1	Intergenic	Ovarian	Upregulated	[189]
		Colorectal	Upregulated	[190]
		Breast (triple negative breast cancer)	Upregulated	[34]
HOTAIR	Intergenic	Breast	Upregulated	[191]
		Gastric	Upregulated	[192]
		Colorectal	Upregulated	[193]
		Liver	Upregulated	[194]
FAM83H-AS1	Intergenic	Cervical	Upregulated	[195]
SBF2-AS1	Antisense	Breast	Downregulated	[196]
NRON	Antisense	Breast	Downregulated	[197]
NBAT-1	Intergenic	Lung	Downregulated	[198]
GAS5	Antisense	Pancreatic	Downregulated	[199]