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Review

Biomarkers for Prostate Cancer Diagnosis from Genetic Perspectives

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HIGHLIGHTS

- Estimation of the fPSA/tPSA ratio and Multiparametric-magnetic resonance imaging (mp-MRI) can expand the prostate cancer diagnosis accuracy.
- Several biomarkers are considered in testing panels like ConfirmMDx, Prostate Core Mitomic Test (PCMT), TMPRSS2-ERG, The PTEN gene, ProMark, 4K score.
- Liquid biopsy components like can CTCs help the clinician to decide in the re-biopsy step.

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ABSTRACT

Prostate cancers (PC) are mainly diagnosed by screening prostate-specific antigen (PSA) quantity in the blood or a digital rectal exam (DRE). PC typically does not have symptoms contrary to advanced cancers that are diagnosed due to significant symptoms. Diagnosis of PC is established with the transrectal ultrasound (TRUS) guided biopsy. Estimation of the free PSA to total PSA (fPSA/tPSA) ratio and Multiparametric-magnetic resonance imaging (mp-MRI) can expand the diagnosis accuracy. Several molecular biomarkers have improved PC diagnosis like Confirm MDx, Prostate Core Mitomic Test (PCMT), TMPRSS2-ERG, The PTEN gene, ProMark, 4K score including, and Circulating Tumor Cells (CTCs). These molecular biomarkers are considered both genetic and epigenetic (DNA methylation) hallmarks of PC. We aim to present an overview of all molecular biomarkers of PC and their implication in improving the management of PC patients.

Keywords: Prostate Cancer; Diagnosis; Biomarker

Introduction

Prostate cancers (PC) are frequent types of cancer in men. In 2019, in the United States alone, there were about 174,650 new cases reported which resulted in 31,620 deaths (1). Some PC patients may stay asymptomatic and die from unrelated causes. This can be the result of the older age that leads to slower cell division and tumor growth (2). Improved consideration of the genetic and molecular pathways of PC can indicate the reason why some tumors present as a clinically silent disease, contrary to some others which are life-threatening. The change of prostate epithelial cells to tumor formation and prostate cancer can be the consequence of intricate chains of both genetic, epigenetic, and environmental issues (3).

Some risk factors like age, heritage, and having a positive history of prostate malignancies can cause

a timely alarm of PC which results in overtreatment, expenses, and changing the patient's life quality. The U.S. Preventive Services Task Force (USPSTF) suggested in contradiction to the PSA testing in 2012 that unfortunately resulted in the increased incidence of metastatic PC (4, 5). Prostate cancer can rarely be observed in men≤40 years and its risk rises as patients aged. Just about ten percent of PC patients are detected in men less than sixty years and signify as early-onset PCa. Records from the Surveillance, Epidemiology, and End Results (SEER) Database indicate the early-onset growing PC (6). More than age, the ancestry of PC can be a determining risk factor and it is shown that PC risk is dramatically greater in blacks, intermediate in whites, and low in native Japanese (7). More than the age and origin of the PC patients, having a positive family history of PC can increase the cancer occurrence, because PC is highly heritable (8). About 5-10% of PC patients are supposed to be mainly triggered by high-risk inherited genetic aspects or PC predisposition genes. The meta-analysis of thirty-three epidemiologic studies indicates that the risk is more for men whose brothers have cancer more than for the men with affected fathers (9). The PC hazard enlarged when a first-degree relatives (FDR) were identified with PC in the age less than sixty five years (10).

Prostate Cancer Diagnosis

PC exact diagnosis and sufficient staging have an important role in patient medical care and treatment. PC conventionally is detected by digital rectal examination (DRE), prostate-specific antigen (PSA), and tracked by transrectal ultrasound (TRUS) guided biopsy. PC can be very heterogeneous cancer varies from insignificant, indolent, low-grade to big, aggressive, and life-threatening tumors.

Prostate-Specific Antigen (PSA) is a 34kDa protein with serine protease or *Kallikerin Related Peptidase-3 (KLK3)* functioning which is coding by the gene, on chromosome 19. Its biological role is the hydrolysis of semenogeline-1, producing velocity of seminal ejaculate to assist spermatozoa mobility. Its half-life is about two days. The three/forth of circulating PSA is linked to α-1 anti-chymotrypsin and α-2 macroglobulin that can be metabolized through the liver. The residual one/fourth percent of PSA is free and is excreted into the urine. It is detectable in extraordinary amounts in seminal fluid and its detection as prostate cancer serum biomarker can happen alongside forensic analysis of seminal fluid. The age-specific reference range is based on the National Institute for Health and Care Excellence (NICE) is >2.0 for 40-49 years, >3.0 for 50-59, >4.0 for 60-69, and >5.0 for age more than 70.

PSA Density is the serum PSA level per ml (PSA/ml serum) of prostate tissue. PSA levels are more in men who have the bigger sized glands of the prostate. The PSA concentration is occasionally considered for the size management of large prostate in BPH (benign prostate hyperplasia). The prostate gland size is measured through transurethral ultrasound (TRUS) or computed tomography (CT) scans. The cut off for PSA density is 0.15ngml-1 that more than this can be an indicator of prostate cancer.

PSA doubling time and PSA velocity are PSA alterations over time. PSA velocity is reported as ng/ml/year and predictor factor. By way of illustration, a PSA of 2 ng/ml and a PSA velocity of 0.5 ng/ml/year can predict to have a PSA of 2.5 ng/ml in 12 months. PSA doubling time is defined as the months needed for PSA levels to double.

In cases with steady PSA levels (estimated changes from 6 to 6.1 ng/ml over a year), doubling time is not reliable. So, these patients are normally shown as the "doubling time>10 years" or similar.

Digital Rectal Examination is the common prostate testing of inserting the lubricated, gloved index finger of a physician into the rectum to detect rectal cancer. DRE is an initial method to detect inflammation, abnormal growth, or cancer of the prostate and diagnose nerve difficulties specified by a decline of the usual tone of the muscles of the rectal sphincter.

Despite several new suggesting diagnostic examinations, TRUS prostate biopsy is still the gold standard test. However, due to the wrong needle placing in the exact tumor location TRUS biopsies have false-negative results of about 15%–46% (11). To solve false-negative biopsy results, there are suggestions of random biopsies from the prostate consisting of a sequence of 6 samples spread out in the same way which is called random 6-score biopsies (12). This can increase the chances of cancer diagnosis in men with high PSA levels and decrease false negatives. Doctors at NYU Langone's Perlmutter Cancer Center developed the national standard for a 12-core prostate biopsy which increases the samples from 6 to 12 with samples from the far edges of the gland. This method can reduce the likelihood of missed cancer significantly (13). The imaging algorithm in patients with elevated PSA is presented in figure 1.

A novel blood testing has been suggested for accurate diagnosis of aggressive PCa, based on the Queen Mary University of London reports. There is hope that the newly developed liquid biopsy components like circulating tumor cells (CTCs) would improve the biopsy results or even take the place of traditional biopsy samples. Total PSA (tPSA) is the basic biological test for cancer diagnosis. Unfortunately, PSA is an organ-specific antigen, so elevated PSA amount is seen in benign pathologies (BPH), prostatitis, and PC (14). The original PC Prevention Trial

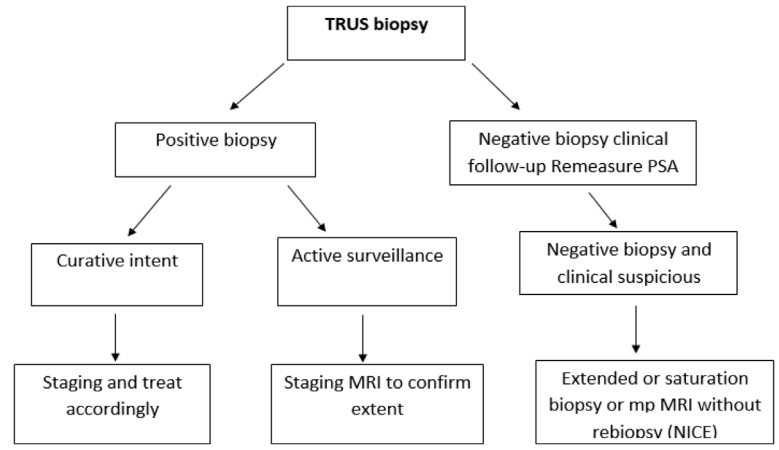

Figure 1. Imaging algorithm in patients with increased PSA based on Brandy's book

(PCPT) PC Risk Calculator (PCPTRC) posted in 2006, that if PSA more than 4.0ng/ml or if an atypical DRE was distinguished, a biopsy was recommended (15).

In 2014, the updated PCPTRC 2.0 was suggested with the extra potential of discrimination between low-grade (Gleason grade<7) from high-grade prostate cancer (16). To increase specificity the age-adjusted PSA suggested cut off 2.5, 3.5, 4.5, and 6.5ng/ml in men in their 40s, 50s, 60s, and 70s, respectively (17). The ratio fPSA/tPSA is considered on the occasions of having regular DRE and PSA between 4 and 10ng/mL. The inferior percentage of less than 15% can be seen in men with cancer (18). In a recent publication by Ping T. et al, it is indicated to PSA (4.0 to 10.0ng/ml) can experiencing early prostate biopsy and fPSA/tPSA increase diagnostic accuracy, contrary to the PSA alone in patients more than sixty years old (19). A new method to expand the medical presentation of PSA is to pool blood testing results of tPSA, fPSA, and [-2] pro PSA by a calculated formula named the Prostate Health Index (Phi). The Phi test exactly practices the formula ([-2] pro PSA/fPSA × tPSA) to recover as the complementary diagnostic biomarker when the serum PSA level is about 2–10ng/mL (20). The Gleason Score is a grading system to define the violence of cancer (21,22).

The Gleason Score varies from 1-5 and explains the degree of biopsy similarity to normal tissue or abnormal tissue. The PC is mostly heterogeneous and is composed of tumor cells with various grades. So, two grades are allocated to individuals, the first one is known to explain the cells that make the major part of the tumor and the second one specifies the cells of the next prevalent region. For example, the Gleason Score 3+4=7 indicates that the tumor is mostly in grade 3 and then the possible tumor is grade 4, collectively resulting in the Total Gleason Score. The typical Gleason Scores vary from 6 to10. Scores≤6 define cancer cells that appear like normal cells and propose that the cancer is probable to enlarge gradually. The score=7 shows the middle risk for aggressive prostate cancer, and scores of 8≤indicated quick tumor spread; these tumors are often specified as poorly differentiated or high grade.

Multiparametric-magnetic resonance imaging (mp-MRI) has recently revealed favorable outcomes in diagnosis, risk stratification, tumor locus, and staging of PCa (23). The systematic TRUS biopsy has the problem of underestimation and results in inaccurate risk stratification and wrong therapeutic options. So, the US and the Canadian Task Force on Preventive Health Care, just have suggested that the risks of PSA testing can be more than its profits (24). The mp-MRI combines the morphological calculation of T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) perfusion imaging, and spectroscopic imaging (MRSI) (25, 26). Especially T2WI and DWI have exposed important promise in cancer recognition, localization, and prostate tumor staging (27, 28). In figure 2 a summary of PCa common diagnosis strategies is presented.

Genes and molecular biomarkers for prostate cancer diagnosis

There is a developing interest to find molecular biomarkers as the predictable clinical and pathologic factors to accurate prostate cancer diagnosis and personalized cancer treatment. Nevertheless, a combination of biomarkers into the standard clinical practice needs robust analytical validity supports. Several molecular biomarkers ranging from DNA mutation, DNA Methylation, and mRNA are considered for both PCa diagnosis and prognosis.

PCA3 mRNA is a long noncoding RNAs can have a role in the prostate carcinogenesis pathway. Some long non-coding RNAs (lncRNA) are described as the important ones in PCa including Prostate-specific transcript 1 non-protein-coding (PCGEM1), PCa Associated Transcript 1

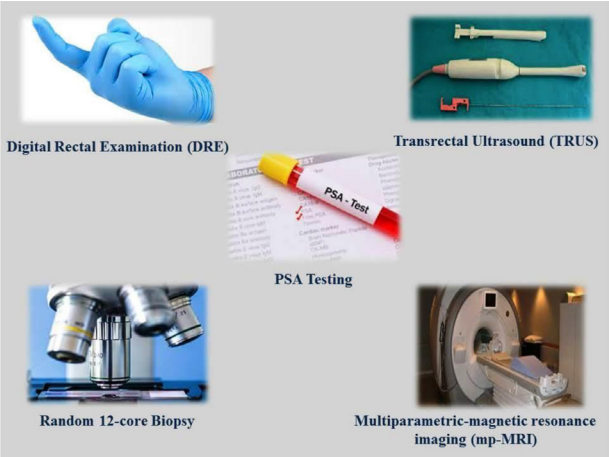

Figure 2. Common clinical testing method of prostate cancer

(PCAT-1), and the PC gene 3 *(PCA3)*. The *PCA3* gene, firstly named Differential Display Code 3 . The coding gene of *PCA3* is positioned on chromosome 9q21-22 and is composed of 4 exons and 3 introns. There is different polyadenylation at the locus of exon 4 (4a, 4b, and 4c) resulting in three transcripts with different lengths. New genomic structure of progression *PCA3* gene insertion in the intron of other genes like *PRUNE2* or *BMCC1PCA3* regulates their expression by double-stranded RNA (dsRNA) formation (29). The quantity of the mRNA PCA3 is calculated by the quantitative real-time polymerase chain reaction (qRT-PCR) technique after extracting it from urine.

The PCA3 test gained the Conformité européenne in 2006 and was accepted by the FDA in 2012. The PCA3 test was officially confirmed by the FDA as the prostate cancer diagnostic tool in determining re-biopsy is essential or in the follow-up of prostate cancer patients in active surveillance strategy (30). Based on the published result of a meta-analysis, the general sensitivity, specificity, and area under curve (AUC) values of PCA3 mRNA were equal to 0.63, 0.88, and 0.82, respectively (31).

The Oncotype DX® is a panel of several gene expression through RT-PCR that was recognized for fixed paraffin-embedded (FPE) diagnostic prostate needle biopsies about 1 mm (32). The Oncotype DX® PC assay dealings expression of twelve genes involving molecular pathways and five algorithmically shared genes based on the Genomic Prostate Score (GPS). The Oncotype DX PC Assay indicates single biological pathways with an identified role in prostate tumorigenesis: the androgen pathway *(Zinc-alpha-2-glycoprotein (AZGP1)*, *Kallikrein Related Peptidase 2 (KLK2)*, *Steroid 5 Alpha-Reductase 2 (SRD5A2)*, and *Family With Sequence Similarity 13 Member C (FAM13C)*, cellular organization *(Filamin-C (FLNC)*, *Gelsolin (GSN)*, *β-Tropomyosin (TPM2)*, and *Glutathione S-transferase Mu 2 (GSTM2)*, proliferation *Xenopus kinesin-like protein 2 (TPX2)*, stromal response *(Biglycan (BGN)*, *Collagen Type I Alpha 1 Chain (COL1A1)*, and *Secreted Frizzled Related Protein 4 (SFRP4))* (33). Reference gene standardization is considered for pre-analytical and analytical contradiction as well as a grant for variable RNA inputs and is predictable clinical/pathologic elements (34). The Oncotype DX® has been valid from tissue biopsy and enhances medical parameters like National Comprehensive Cancer Network (NCCN) scores (33, 35).

Decipher® Prostate Cancer Test (GenomeDx Biosciences, San Diego, CA) is according to the more than twenty gene expression panel which offerings precise understanding in calculating clinical metastasis (0.75–0.83) and cancer-specific mortality (0.78) . It is based on a microarray technique including 1.4 million probes complementary to target genes that detect both coding and non-coding RNA expression levels (36). These genomic marks have been advanced, protected, and authenticated based on the Genomic Classifier data (37). The control of postoperative radiotherapy (adjuvant vs. salvage) can be shown regarding Decipher scores that can calculate the risk of tumor metastasis and recurrence in patients treated with radical prostatectomy (38). This test is the first self-determining sign of tumor metastasis in patients with biochemical recurrence after surgery that can consider in the individualized medication of prostate cancer.

ConfirmMDx for Prostate Cancer (MDxHealth, Irvine, CA) complexes epigenetic analysis that processes DNA methylation of *Glutathione S-Transferase Pi 1 (GSTP1)*, *Adenomatous polyposis coli (APC)*, and *Ras Association Domain Family Member 1 (RASSF1)*. It is an epigenetic assay to the exact diagnosis of true-negative biopsy (39). The national comprehensive cancer network (NCCN) guidelines suggested ConfirmMDx because several institutional review observations wanted this panel to be added to the repeated biopsy setting. After all, it adds value in men with a raised PSA and previous negative biopsy results (Table 1) (40). The MATLOC (Methylation Analysis to Locate Occult Cancer) confirmation established the cost-effective value of the ConfirmMDx test (41). The actual power of the ConfirmMDx test is in its negative predictive value of more than 90%.

The Prostate Core Mitomic Test™57 (PCMT, Mitomics, CO, USA) is a test based on several mitochondrial DNA (mtDNA) deletion and states molecular modification of malignant tumor cells in normal-appearing tissue (42). It is the usual cancer diagnostic tool in men in the first world. Since 2011, the PCMT counts a 3.4-kb mtDNA genetic deletion toughly connected to the PC, and in New Jersey about fifty urology practices retrieving pathology services of the PCMT successfully (43).

TMPRSS2-ERG fusion gene can happen in 40% - 80%

Table 1. Substitutes to immediate biopsy can expand the specificity of PSA testing. The 2018 NCCN Guidelines mention that clinicians study biomarkers and mpMRI before performing a biopsy

Test	Source	Component
PHI	Serum	PSA, fPSA, -2proPSA
4KScore	Serum	PSA, fPSA, intact PSA, kallikrein-related peptidase2
ExoDX Prostate	Urine	ETS transcription factor, ERG PCA3
Michigan Prostate Score	Urine	PCA3, PSA, TMPSS2:ERG
Select MDX	Urine	mRNA DLX1, HOXC6
Confirm MDX	Tissue	DNA methylation, GSTP1, RASSF1

PSA: Prostate Specific Antigens; fPSA: free PSA; DLX: Distal-Less Homeobox 1; HOXC6: Homeobox C6; GSTP1: glutathione S-transferase pi gene; RASSF1: Ras association domain-containing protein 1

of PCa in humans. The v-ets erythroblastosis virus E26 oncogene homolog 1 (ERG) genes over expressions have roles in prostate cancer mediated by androgen receptor signaling pathway. TMPRSS2-ERG is a fusion between the transmembrane protease serine 2 (TMPRSS2) genes and the ERG gene which is linked to clinically substantial cancer (44). A combination of biomarker assays can expand prognostic precision paralleled to the procedure of separate markers (Figure 3). Calculation of post-DRE urine TMPRSS2-ERG, in grouping with urine PCA3, boosted the value of serum PSA level for expecting cancer risk (45).

PTEN gene deletion is related to the higher Gleason grade, risk of tumor progression, and recurrence after therapy (46). PTEN is a tumor suppressor gene whose genomic aberrations are mostly common in PC patients and this gene deletion or mutation is recognized in about 20% of primary tumor samples at radical prostatectomy and in almost 50% of castration-resistant tumors (47). For patients with high-grade prostatic intraepithelial neoplasia (HGPIN) or an atypical diagnosis, PTEN assay is a practical method to discriminate between nonaggressive HGPIN or an atypical diagnosis in men at greater risk of PC.

ProMark is an advanced prognostic test established exactly for PC for biopsy Gleason Score of 3+3 or 3+4 automated image recognition technology to tell the risk of aggressive PC (48). The ProMark scores between 1 and 100. A personalized score specifies the aggressiveness of the PC to define the correct treatment strategy. It is involved in the National Comprehensive Cancer Network (NCCN) Clinical Care Guidelines (49).

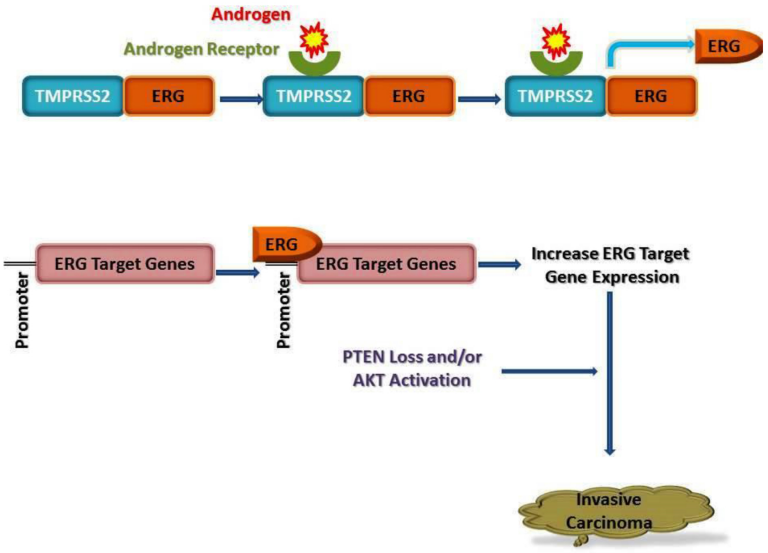

Figure 3. Schematic presentation of TMPRSS2-ERG fusion

4K score is a four-kallikrein panel including kallikrein-related peptidase 2 (hK2), intact PSA, fPSA, and tPSA. The 4Kscore blood test precisely identifies men with aggressive PC before prostate biopsy with or without DRE information (50). The 4Kscore Test is a pre-biopsy blood test that includes four prostate protein biomarkers and clinical information to control a man's risk for high-grade, aggressive (Gleason ≥7) PCa (50).

Circulating tumor cells (CTCs) are tumor cells which are released from solid tumor and are circulating in the bloodstream. CTCs are the main component of "Liquid Biopsy" indicating the analysis of tumor cells and tumor cell products such as cell-free nucleic acids (51). Very recently, circulating tumor cells (CTCs) have been studied in PC. It is suggested that CTC testing act as the highly-accurate new blood test for PCa to avoid invasive biopsies (52). More CTCs number in the blood of CRPC patients can be an indicator of worse outcomes. Checking the gene expression profile of each CTCs and its markers can improve the knowledge of PC (53). CTCs can be useful even for predicting treatment efficacy and survival outcomes. However, CTC detection techniques with upgraded sensitivity are under investigation.

Conclusions

The PC diagnosis is commonly done by PSA, DRE, TRUS, and mpMRI to determine the Gleason score of PC. Several molecular biomarkers can improve the diagnosis and solve the problem of the false-negative result of the biopsy. These biomarkers are ConfirmMDx, Prostate Core Mitomic Test (PCMT), *TMPRSS2-ERG*, The *PTEN* gene, ProMark, 4K score, and CTCs that help the clinician to decide in the re-biopsy step.

Authors' contributions

FKH wrote the original draft, SMKA is mainly designed and supervised the project, AS and MHKH were responsible for data curation, and SSH reviewed and edit the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical statement

Not applicable.

Data availability

Data will be provided by the corresponding author on request.

Abbreviations

CTCs	Circulating Tumor Cells
DRE	Digital rectal exam
ERG	ETS-related gene
fPSA/tPSA	Free PSA to total PSA
HGPIN	High-grade prostatic intraepithelial neoplasia
mp-MRI	Multiparametric-magnetic resonance imaging
PC	Prostate cancers
PCMT	Prostate Core Mitomic Test
PSA	Prostate-specific antigen
TMPRSS2	Transmembrane Serine Protease 2
TRUS	Transrectal ultrasound
USPSTF	U.S. Preventive Services Task Force

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34.
2. Ruijter E, van de Kaa C, Miller G, Ruiter D, Debruyne F, Schalken J. Molecular genetics and epidemiology of prostate carcinoma. Endocrine reviews. 1999;20(1):22-45.
3. Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28.
4. Negoita S, Feuer EJ, Mariotto A, Cronin KA, Petkov VI, Hussey SK, et al. Annual Report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and disease characteristics. Cancer. 2018;124(13):2801-14.
5. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force recommendation discouraging prostate-specific antigen–based screening. Journal of Clinical Oncology. 2015;33(22):2416-23.
6. Salinas CA, Tsodikov A, Ishak-Howard M, Cooney KA. Prostate cancer in young men: an important clinical entity. Nature Reviews Urology. 2014;11(6):317.
7. Bunker CH, Patrick AL, Konety BR, Dhir R, Brufsky AM, Vivas CA, et al. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: the Tobago Prostate Cancer Survey. Cancer Epidemiology and Prevention Biomarkers. 2002;11(8):726-9.
8. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. The prostate. 1990;17(4):337-47.
9. Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PloS one. 2011;6(10):e27130.
10. Albright F, Stephenson RA, Agarwal N, Teerlink CC, Lowrance WT, Farnham JM, et al. Prostate cancer risk prediction based on complete prostate cancer family history. The Prostate. 2015;75(4):390-8.
11. Kvåle R, Møller B, Wahlqvist R, Fosså SD, Berner A, Busch C, et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population□based study. BJU international. 2009;103(12):1647-54.
12. Scattoni V, Maccagnano C, Capitanio U, Gallina A, Briganti A, Montorsi F. Random biopsy: when, how many and where to take the cores? World journal of urology. 2014;32(4):859-69.
13. Örtegren J, Holmberg JT, Lekås E, Mana S, Mårtensson S, Richthoff J, et al. A randomised trial comparing two protocols for transrectal prostate repeat biopsy: six lateral posterior plus six anterior cores versus a standard posterior 12-core biopsy. Scandinavian journal of urology. 2019:1-5.
14. Oesterling JE, Rice DC, Glenski WJ, Bergstralh EJ. Effect of cystoscopy, prostate biopsy, and transurethral resection of prostate on serum prostate-specific antigen concentration. Urology. 1993;42(3):276-82.
15. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. Journal of the National Cancer Institute. 2006;98(8):529-34.
16. Ankerst DP, Hoefler J, Bock S, Goodman PJ, Vickers A, Hernandez J, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low-vs high-grade prostate cancer. Urology. 2014;83(6):1362-8.
17. Oesterling JE, Jacobsen SJ, Cooner WH. The Use of Age-Specific Reference Ranges for Serum Prostate Specific Anitgen in Men 60 years Old or Older. The Journal of urology. 1995;153(4):1160-3.
18. Lee R, Localio AR, Armstrong K, Malkowicz SB, Schwartz JS, Group FPS. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology. 2006;67(4):762-8.
19. Tang P, Du W, Xie K, Deng X, Fu J, Chen H, et al., editors. Transition zone PSA density improves the prostate cancer detection rate both in PSA 4.0–10.0 and 10.1–20.0 ng/ml in Chinese men. Urologic Oncology: Seminars and Original Investigations; 2013: Elsevier.
20. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A multicenter study of [-2] pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. The Journal of urology. 2011;185(5):1650-5.
21. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. Jama. 1997;277(18):1445-51.
22. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. European urology. 2016;69(3):428-35.
23. Ghai S, Haider MA. Multiparametric-MRI in diagnosis of prostate cancer. Indian journal of urology: IJU: journal of the Urological Society of India. 2015;31(3):194.
24. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, et al. Screening for prostate cancer: a review of the evidence for the US Preventive Services Task Force. Annals of internal medicine. 2011;155(11):762-71.
25. Schimmöller L, Quentin M, Arsov C, Hiester A, Buchbender C, Rabenalt R, et al. MR-sequences for prostate cancer diagnostics: validation based on the PI-RADS scoring system and targeted MR-guided in-bore biopsy. European radiology. 2014;24(10):2582-9.
26. Panebianco V, Barchetti F, Sciarra A, Ciardi A, Indino EL, Papalia R, et al., editors. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urologic Oncology: Seminars and Original Investigations; 2015: Elsevier.
27. Lawrence EM, Gallagher FA, Barrett T, Warren AY, Priest AN, Goldman DA, et al. Preoperative 3-T diffusion-weighted MRI for the qualitative and quantitative assessment of extracapsular extension in patients with intermediate-or high-risk prostate cancer. American Journal of Roentgenology. 2014;203(3):W280-W6.
28. Jie C, Rongbo L, Ping T. The value of diffusion-weighted imaging in the detection of prostate cancer: a meta-analysis. European radiology. 2014;24(8):1929-41.
29. Clarke RA, Zhao Z, Guo A-Y, Roper K, Teng L, Fang Z-M, et al. New genomic structure for prostate cancer specific gene PCA3 within BMCC1: implications for prostate cancer detection and progression. PloS one. 2009;4(3):e4995.
30. Crawford ED, Rove KO, Trabulsi EJ, Qian J, Drewnowska KP, Kaminetsky JC, et al. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases. The Journal of urology. 2012;188(5):1726-31.
31. Cui Y, Cao W, Li Q, Shen H, Liu C, Deng J, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. Scientific reports. 2016;6:25776.
32. Knezevic D, Goddard AD, Natraj N, Cherbavaz DB, Clark-Langone KM, Snable J, et al. Analytical validation of the Onco type DX prostate cancer assay–a clinical RT-PCR assay optimized for prostate needle biopsies. BMC genomics. 2013;14(1):690.
33. Cooperberg M, Simko J, Falzarano S, Maddala T, Chan J, Cowan J, et al. 2131 Development and validation of the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance. The Journal of Urology. 2013.
34. Chang EM, Punglia RS, Steinberg ML, Raldow AC. Cost Effectiveness of the Oncotype DX Genomic Prostate Score for Guiding Treatment Decisions in Patients With Early Stage Prostate Cancer. Urology. 2019;126:89-95.
35. Klein EA, Maddala T, Millward C, Cherbavaz DB, Falzarano SM, Knezevic D, et al. Development of a needle biopsy-based genomic test to improve discrimination of clinically aggressive from indolent prostate cancer. American Society of Clinical Oncology; 2012.
36. Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PloS one. 2013;8(6):e66855.

37. Loeb S, Ross AE. Genomic testing for localized prostate cancer: where do we go from here? Curr Opin Urol. 2017;27(5):495-9.
38. Marrone M, Potosky AL, Penson D, Freedman AN. A 22 gene-expression assay, Decipher®(GenomeDx Biosciences) to predict five-year risk of metastatic prostate cancer in men treated with radical prostatectomy. PLoS currents. 2015;7.
39. Waterhouse Jr RL, Van Neste L, Moses KA, Barnswell C, Silberstein JL, Jalkut M, et al. Evaluation of an Epigenetic Assay for predicting repeat prostate biopsy outcome in African American men. Urology. 2019;128:62-5.
40. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, et al. NCCN guidelines insights: prostate cancer early detection, version 2.2016. Journal of the National Comprehensive Cancer Network. 2016;14(5):509-19.
41. Partin AW, Van Neste L, Klein EA, Marks LS, Gee JR, Troyer DA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. The Journal of urology. 2014;192(4):1081-7.
42. Legisi L, DeSa E, Qureshi MN. Use of the prostate core mitomic test in repeated biopsy decision-making: real-world assessment of clinical utility in a multicenter patient population. American health & drug benefits. 2016;9(9):497.
43. Blute Jr ML, Abel EJ, Downs TM, Kelcz F, Jarrard DF. Addressing the need for repeat prostate biopsy: new technology and approaches. Nature Reviews Urology. 2015;12(8):435.
44. Wang Z, Wang Y, Zhang J, Hu Q, Zhi F, Zhang S, et al. Significance of the TMPRSS2:ERG gene fusion in prostate cancer. Mol Med Rep. 2017;16(4):5450-8.
45. Salami SS, Schmidt F, Laxman B, Regan MM, Rickman DS, Scherr D, et al., editors. Combining urinary detection of TMPRSS2: ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. Urologic Oncology: Seminars and Original Investigations; 2013: Elsevier.
46. Geybels MS, Fang M, Wright JL, Qu X, Bibikova M, Klotzle B, et al. PTEN loss is associated with prostate cancer recurrence and alterations in tumor DNA methylation profiles. Oncotarget. 2017;8(48):84338-48.
47. Jamaspishvili T, Berman DM, Ross AE, Scher HI, De Marzo AM, Squire JA, et al. Clinical implications of PTEN loss in prostate cancer. Nature Reviews Urology. 2018;15:222.
48. Falzarano S, Ferro M, Bollito E, Klein E, Carrieri G, Magi-Galluzzi C. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. Minerva urologica e nefrologica= The Italian journal of urology and nephrology. 2015;67(3):211-31.
49. Carroll PH, Mohler JL. NCCN guidelines updates: prostate cancer and prostate cancer early detection. Journal of the National Comprehensive Cancer Network. 2018;16(5S):620-3.
50. Zappala SM, Dong Y, Linder V, Reeve M, Sjoberg DD, Mathur V, et al. The 4Kscore blood test accurately identifies men with aggressive prostate cancer prior to prostate biopsy with or without DRE information. International journal of clinical practice. 2017;71(6):e12943.
51. Pantel K, Alix-Panabieres C. Liquid biopsy in 2016: Circulating tumour cells and cell-free DNA in gastrointestinal cancer. Nature Reviews Gastroenterology & Hepatology. 2017;14(2):73.
52. Xu L, Mao X, Grey A, Scandura G, Guo T, Burke E, et al. Non-in-

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