Introduction

The advent of both formal prostate cancer screening and ad-hoc testing based on prostate-specific antigen (PSA) has led to improved detection and therefore an increase in the reported incidence of the disease in recent years (1). We now know that prostate cancer is a complex, heterogeneous disease therefore it is unlikely that a single biomarker is likely to have the sensitivity and specificity to detect all prostate cancers (2). The merits and limitations of PSA will be discussed here, along with future biomarkers which may augment or replace PSA as the biomarkers of choice for diagnosis, prognosis or risk stratification of prostate cancer. These biomarkers have been summarised (Figure 1).

In cancer, biomarkers are used for early detection, screening, diagnosis, prognosis, prediction and the identification of therapeutic targets and surrogate endpoints (3). PSA is mainly used for screening and diagnosis of prostate cancer, though it has some additional predictive and prognostic value. These new biomarkers are in various stages of development and seem most likely to impact on clinical practice alongside PSA in prostate cancer disease management.
Diagnosis of all cancers or just aggressive disease?

The majority of men with prostate cancer will die with the disease, not of it, leading to large numbers of men who undergo unnecessary procedures under active surveillance, or interventions with significant side effects who may not need to be diagnosed with prostate cancer at all. A biomarker assay that could only identify those men with aggressive disease that is likely to be life limiting without treatment would revolutionise patient care. When examining the potential of novel biomarkers it is important to distinguish those that detect all prostate cancers versus those that can distinguish between indolent and aggressive disease. The most useful diagnostic biomarkers must be able to detect cancer in an easily obtainable patient sample such as blood or urine, with high sensitivity and specificity resulting in low false positive and false negative values. The use of tissue in a diagnostic test requires a biopsy which has associated risks and assumes a biopsy is representative of the whole tumour while containing sufficient tumour cells to perform the biomarker assay.

PSA

PSA, also known as KLK3, is a secreted, androgen-regulated, glycoprotein belonging to the kallikrein-related peptidase family (4) that is often elevated in prostate cancer (5). Since the 1980s, PSA has been used as a biomarker for early detection of prostate cancer, with screening programs introduced in Europe and the USA, but not the UK. (6, 7). While the advent of such screening programs has correlated with improved survival, it should be noted that this data is artificially inflated by the identification of large numbers of low grade cancers, and concurrent improvements in awareness and treatments. One limitation of PSA is that it is also raised in non-cancerous conditions, e.g. benign prostatic hyperplasia and prostatitis, or interventions such as prostate biopsies or surgery (3). Additionally, the numbers needed to scan and numbers needed to treat to save one life may outweigh the benefits of screening. Furthermore, the true upper normal limit PSA is hard to define as the clinical cut-off of 4 ng/ml is inaccurate, with 20% of men whose PSA is below this limit having prostate cancer, and many men above the limit being cancer free (7-10). As such, prostate cancer screening based on PSA has led to significant over-diagnosis and over-treatment of men with low-risk prostate cancer (6).

Progress in PSA

There has been some advancement in the use of PSA in recent years, owing to increasing understanding of its molecular activity. Traditional PSA testing recognises total PSA in serum. However, there are several subtypes of PSA in the bloodstream that can be detected separately. PSA can either exist in its free form, (fPSA) accounting for 5-35% of total PSA (tPSA), or in complex with alpha-1-antichymotrypsin and/or macroglobulins. fPSA can be further subdivided into three molecular forms: the precursor proenzyme proPSA, benign (or ‘nicked’) PSA (bPSA) and intact PSA (iPSA) (3). It has been found that the ratio of fPSA to tPSA is lower in prostate cancer, which could be used to improve the specificity of cancer detection in men with tPSA in the 4-10 ng/ml range who have a normal digital rectal exam (DRE) (11). ProPSA accounts for roughly a third of fPSA and exists as several different isoforms with different lengths of pro-leader peptides (7). [-2] proPSA is the most cancer-specific of the molecular subtypes of PSA, being significantly elevated in the serum of men with prostate cancer versus benign prostatic hyperplasia, and unlike tPSA can it be used for both early detection and determining the aggressiveness of the disease (12).

The 4KScore is a laboratory developed test (LDT) available in the USA. The test combines four kallikreins (fPSA, tPSA, iPSA and hK2 (Human Kallikrein 2)) in serum samples, along with age and optional results of a DRE. If the cut-off point of the assay is appropriate, this assay can also be used to selectively avoid diagnosis of low grade cancers, o Analysis of the ProtecT study found that use of
these markers could reduce the number of unnecessary biopsies while missing very few high grade cancers (13). An economic analysis of this method found that savings of around US$1 billion could be made by replacing PSA testing with the four-kallikrein panel, due to the avoidance of 48%-56% of biopsies (14).

Prostate health index (PHI), is an FDA approved test for the diagnosis of prostate cancer. This test includes three forms of PSA combined using the calculation ([−2] proPSA/fPSA) x PSA^{1/2} (15). The sensitivity and specificity of PHI has been shown to be superior to PSA, with particular utility in the 2-10 ng/ml range in men over the age of 50 with normal DRE, and correspondingly improved cost-effectiveness and quality of life (16).

Thus the use of PSA isoforms can improve on tPSA alone, however these tests generally still diagnose all cancers rather than just aggressive, potentially life-limiting ones. The 4KScore assay can be adjusted to avoid diagnosis of low grade cancers, offering some diagnostic utility, but moving forward, further diagnostic biomarkers must be able to make this distinction.

Identifying men at risk of developing prostate cancer

If we can identify men at risk of developing prostate cancer, we can monitor them more closely and hopefully diagnose the disease at an earlier stage. Men on active surveillance programmes can then make lifestyle changes such as undertaking exercise, which has been shown to reduce the proportion of patients undergoing active treatment, as well as modulating the biological processes involved in tumour progression (17). Although PSA is not useful in diagnosing aggressive versus indolent prostate cancer, it does show promise as a risk biomarker in the identification of men in their early 50s who would benefit from closer monitoring. A recently published population-based study followed up on a cohort of PSA screened versus unscreened men from 17 years ago in Sweden. PSA cut-offs were initially 3ng/ml and then 2.5ng/ml from 2005 onwards. The authors determined screening for prostate cancer using PSA can decrease prostate cancer mortality among men aged 50-54 yr, with 57 fewer deaths per 10,000 men (18).

A polygenic risk score has also been identified using genome wide association studies of over 40,000 European prostate cancer and control cases. This risk score has utility in identifying men at particularly high or low risk of prostate cancer (19). Further investigation of this and other cohorts has identified a pattern of single nucleotide polymorphisms (SNPs) that covers 39 regions of the genome, and is significantly associated with increased risk of prostate cancer while also helping to explain prostate cancer heritability (20). Data such as this could greatly enhance the prostate cancer diagnostic pathway if carried out alongside PSA testing. A prostate-specific SNP panel could be developed as a cost-effective tool to be carried out in excess blood collected for PSA testing, which would provide additional information for the clinical team to take into consideration when planning the patient’s care. A cost-benefit analysis would be beneficial in predicting the economic implications of such additional testing, which would incur additional costs but could prevent costs associated with overdiagnosis and/or overtreatment of low grade prostate cancer.

Multiparametric Magnetic Resonance Imaging (mpMRI)

mpMRI is an emerging non-invasive biomarker for diagnosing prostate cancer, which is increasingly demonstrating effectiveness in determining the location, size and grade of prostate cancer, and may be particularly effective in discriminating between indolent and aggressive tumours. In particular mpMRI can distinguish between Gleason 3 cancers that are relatively indolent and more aggressive Gleason 4 cancers that often require treatment. A recent study in men with Gleason score of ≤6 determined that inclusion of mpMRI imaging in active surveillance decision making could help to identify aggressive disease in men with indolent prostate cancer earlier than traditional methods,
through the prevention of under-grading and under-staging that can occur from random biopsy sampling, and can distinguish more aggressive prostate cancer even when indolent prostate cancer is the biopsy diagnosis (21). mpMRI can be carried out alongside PSA testing, with bloods being taken prior to imaging through the cannula being used to introduce the contrast agent. In many cases, both the mpMRI and PSA data agree, with mpMRI confirming the PSA result and aiding the clinical team in making a treatment plan based on its ability to identify aggressive tumours. However in some cases, a patient can exhibit low PSA but have a visible tumour by mpMRI, underpinning the importance of carrying out diagnostic mpMRIs in the current setting. In the future, improved liquid biomarkers could replace the need for this if they could provide higher sensitivity and specificity than PSA, and the ability to discriminate aggressiveness as well as or better than mpMRI.

Prostate Cancer Antigen 3

Prostate cancer antigen 3 (PCA3) is a long non-coding RNA with 6-34 times increased mRNA expression in tumour versus benign prostate tissue (22). Unlike PSA, PCA3 levels are assessed in urine samples which are more easily obtained than serum and do not require a skin piercing procedure for the patient. However, this urine sample must be taken following a prostatic massage to increase the cellularity of the urine sample which is impractical and can introduce variability between physicians, and prevents the assay being used for population-wide screening. PCA3 score is calculated as a comparison of PCA3 levels with PSA levels in the Progensa test, which has offered slightly (but significantly) improved overall accuracy compared with tPSA and the ratio of fPSA (3).

The PCA3 score may be useful in diagnosing prostate cancer in combination with other factors including PSA, typically in patients who have already had a negative biopsy result (3). There is a correlation between PCA3 and Gleason score, though the ability of PCA3 to predict Gleason score is limited to tumours that are lower than Gleason 7 which means it is more likely to over diagnose indolent cancers (23). In one analysis of 809 patients, PCA3 sensitivity and specificity of 81 and 45 respectively were recorded, with a positive predictive value (PPV) of 49 and a negative predictive value (NPV) of 79, though other smaller cohorts have exhibited sensitivity ranging from 47-81, specificity of 45-83, PPV of 24-65 and NPV of 74-90(3). As with many of the biomarkers mentioned in this text (except %fPSA STHLM3 and Decipher), these studies are retrospective rather than prospective, which limits the utility of the data. Prospective trials should be carried out investigating the clinical utility of PCA3 along with the other biomarkers mentioned here.

TMPRSS2-ERG Fusion

ERG (erythroblast transformation-specific related gene) is a transcription factor of the ETS family, which are involved in chromosomal translocations in multiple cancers (24). In 2005, it was observed that ERG was frequently overexpressed in around half of all prostate cancers, and associated with recurrent genomic rearrangement between ERG and the first exon of TMPRSS2 (transmembrane protease, serine 2), an androgen regulated gene that is preferentially expressed in the prostate (25, 26). It is thought that TMPRSS2-ERG fusion may be a cancer initiating event as fusions are typically observed in lower grade tumours (27). Like PCA3, TMPRSS2-ERG fusion can be detected in urine, with 37% sensitivity and 93% specificity for detecting a prostate cancer on biopsy (28). TMPRSS2-ERG fusion could be of particular use in small cell carcinoma (SCC), which represents 2% of prostate cancer cases and does not express increased levels of PSA, in establishing prostatic origin in SCCs of unknown primary (29). TMPRSS2-ERG fusion status is not a strong predictor of prostate cancer recurrence or cancer-specific mortality (30). It has been suggested that there could be diagnostic utility in combining TMPRSS2-ERG and PCA3 testing in urine samples (26). The Mi-Prostate Score combines TMPRSS2-ERG, PCA3 and PSA tests to form a score which may predict aggressive cancer, which has been investigated in 2000 prostate cancer samples (31).
Stockholm 3 (STHLM3) study

The STHLM3 study set out to find an improved screening platform for prostate cancer which would reduce the number of false positives observed with PSA testing, while maintaining sensitivity for high grade (Gleason ≥7) prostate cancer. The test is comprised of a set of plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB (Beta-microseminoprotein) and MIC1 Macrophage Inhibitory Cytokine 1), genetic polymorphisms (232 SNPs), and clinical variables (age, family, history, previous prostate biopsy, prostate exam) which were compared against conventional serum PSA. The STHLM3 model performed significantly better than PSA alone in identifying cancers that were Gleason 7 or higher, thereby offering an alternative test that would reduce the issue of false negatives without compromising the identification of cancer in the important cohort of patients with aggressive disease. The authors of the study suggest that the use of the STHLM3 model could reduce the number of biopsies by 32% and could avoid 44% of benign biopsies in men aged 50-69 years (32). Large validation studies of STHLM3 are currently underway.

ConfirmMDx

ConfirmMDx (MDxHealth) is based on DNA methylation comprising three epigenetic markers (GSTPi, RASSF1 and APC), which can detect alterations in cancer-adjacent cells through the tumour’s ‘halo effect’. The test is performed on tissue samples from a minimum of 8 core biopsies from the left/right base, mid and apex and two additional locations, and can be used to distinguish true negative histology from those who may have occult cancer (33).

Oncotype DX Genomic Prostate Score

Oncotype DX (Genomic Health) comprises a 17 gene panel for the prediction of aggressiveness as well as near and long-term outcomes for prostate cancer patients (34). The gene list includes 5 reference genes for normalization, 4 androgen pathway genes (AZGP1, KLK2, SRD5A2, and RAM13C), 4 cellular organization genes (FLNC, GSN, TPM2, and GSTM2), 1 proliferation marker (TPX2) and 3 genes related to stromal response (BGN, COL1A1 and SFRP4), which have been validated in combination in multiple cohorts (35). The test is performed on tissue biopsy specimens, and provides insight into the biology of the tumour, allowing for the clinical team to determine whether the patient should receive surgery or be placed on active surveillance. This stratification is based on the combination of the results of the test (termed Genomic Prostate Score) with established risk factors to discriminate between very low, low and modified intermediate risk in order to identify those patients who are suitable for active surveillance (35).

Cell Cycle Progression (CCP) Score

The CCP score (also called the Prolaris Test (Myriad Genetics)) is a tissue biopsy assay based on assessment of cell cycle progression as a marker of malignancy, and comprises a list of 31 target genes and 15 housekeeping genes (36). With cells cycling faster in rapidly proliferating cancers, it follows that low expression of this 46 gene panel is associated with a low risk of disease progression, and higher expression is associated with higher risk of disease progression. High risk patients identified by the test can then be closely monitored and treated if necessary (15). Early CCP score studies have been criticised for the selection of cohorts that were predominantly advanced stage at diagnosis, with recent studies attempting to address this concern. However, even the most recent CCP investigation has been criticized for similar lack of validity (37, 38).

Prostarix

Prostarix (Bostwick Laboratories) measures 4 metabolites (sarcosine, alanine, glutamate and glycine) which have been shown to be associated with prostate cancer, using liquid chromatography-mass...
some of the biomarkers discussed here must also be incorporated into the clinical management of prostate cancer. As such, biomarkers that must also ask whether the patient’s cancer will be aggressive or not, and what treatments should be offered. As such, biomarkers that identify risk in younger men or offer prognostic and predictive potential must also be incorporated into the clinical management of prostate cancer. It is clear that some of the biomarkers discussed here may be of use in risk stratification and predicting treatment

Conclusions

There are numerous biomarkers for prostate cancer in various stages of development and with different purposes such as diagnosis, prognosis and risk stratification and prediction of treatment response in prostate cancer (Figure 1). Many of these biomarkers are in need of significant further testing and prospective clinical trials must be carried out to assess any clinical utility they may have. But is there still a role for PSA? To answer this we must consider which questions are the most crucial to ask when choosing a biomarker based test. It is crucial to ask whether the patient has cancer or not, and PSA remains an important biomarker for prostate cancer diagnosis. However, just asking this one question, using a single biomarker, is no longer sufficient to diagnose all cancers. We must also ask whether the patient’s cancer will be aggressive or not, and what treatments should be offered. As such, biomarkers that identify risk in younger men or offer prognostic and predictive potential must also be incorporated into the clinical management of prostate cancer. It is clear that some of the biomarkers discussed here may be of use in risk stratification and predicting treatment

Decipher

Decipher (GenomeDx Biosciences) tests for a 22 RNA panel of prostate cancer markers in a radical prostatectomy specimen. This panel includes 4 cell proliferation/differentiation markers (LASP1, IQGAP3, NFIB and S1PR4), 5 markers of cell structure, adhesion and mobility (THBS2, ANO7, PCDH7, MYBPC1 and EPPK1), 2 markers of immune response (TSBP and PBX1), 5 markers of cell cycle progression and mitosis (NUSAP1, ZWILCH, UBE2C, CAMK2N1 and RABGAP1) and 3 markers of unknown function (PCAT-32, GLYATL1P4/PCAT-80 and TNFRSF19) (40). Decipher is a particularly promising biomarker assay since it has been reported to predict aggressive disease in multiple validation cohorts, including 3000 retrospective cases and 5000 prospective cases (41). Specifically, the expression pattern of the panel of RNAs can augment PSA testing by allowing for the risk stratification of patients to predict metastasis and cancer-related mortality, as well as guiding first line treatment decisions, indicating the need for adjuvant versus salvage radiotherapy. As the test is carried out at the time of radical prostatectomy, it provides a snapshot of information which can be taken into account alongside sequential PSA testing. The test can also be used to guide treatment decisions in patients who exhibit biochemical recurrence, indicating the need for early/multimodal salvage radiotherapy versus salvage radiotherapy alone (42).

PTEN

PTEN deletion was first identified as a predictive biomarker in androgen deprivation therapy when PTEN nuclear status was compared in matched tumour pairs (one before and one after androgen deprivation therapy relapse), and was found to be independently associated with poor disease specific survival, specifically in castration-sensitive tumour specimens (43). More recently, PTEN deletions have been associated with shorter survival (14 months versus 21 months) in patients treated with docetaxel and abiraterone (44, 45). As such, PTEN status could be used in the future as predictive biomarker to augment PSA data before and after androgen deprivation therapy, though further translational studies are required to elucidate whether both PSA and PTEN data would be required or whether PTEN could be used alone. PTEN would likely be more useful as a constituent of a predictive biomarker panel, and prospective clinical trials are needed combining this with other markers before incorporating this into clinical practise.

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response in those who have already been diagnosed with prostate cancer. These tests, in particular mpMRI, OncotypeDX and Decipher could be of great benefit in differentiating between indolent and aggressive tumours, allowing clinicians to identify potentially life-limiting disease and treat the patient accordingly. %fPSA, Decipher and STKLM3 have all been tested prospectively, although prospective trials are needed before the rest of the biomarkers discussed here can be considered reliable alternatives to PSA. However, population based screening is still important in order to ensure prostate cancer cases are identified at as early a stage as possible. Herein lies the continuing role for PSA testing, though not in its current form. The main issue with PSA testing today is the large rate of over diagnosis, resulting in unnecessary stress for the patient and unnecessary, invasive and costly biopsies. In particular, the 4KScore and PHI are PSA-based diagnostics with improved cost-effectiveness due to the reduction in these unnecessary biopsies, and corresponding improved quality of life for the patient. Recent data from the ProTECT study validated a statistical model based on kallikrein markers in a large prospective study and found that this approach reduces unnecessary biopsies while delaying diagnosis of high-grade cancers in few men (46). Additionally, [-2] proPSA offers additional prognostic ability which further improved upon standard PSA testing. Further development in these tests should be carried out with a view to augmenting current PSA screening programs worldwide. Circulating tumour cells (CTCs) and circulating cell free DNA may also be used in the future to identify relapse and track response to therapy, once protocols become more practical to carry out routinely and once prospective clinical trials have been carried out investigating their effectiveness. The current PSA screening system is not enough anymore – the ability to detect aggressiveness and predict treatment outcomes alongside diagnosis will soon be a reality with further prospective studies, and it will be imperative that this technology is fully utilised.

Final Assessment:

Case study or clinical scenario:

Bob is a 62 year old man who has been referred to clinic with a PSA of 8ng/ml.

1. Could any other approved biomarker test be used to diagnose or rule out prostate cancer?
2. If a biopsy is performed and the result is negative, could any biomarker(s) currently in development be used to identify a ‘missed’ tumour?
3. If Bob’s biopsy result is positive for prostate cancer, could any biomarkers currently in development be used to decide whether he should progress to radical treatment or not?
4. If Bob’s prostate is removed, could any biomarkers currently in development be used to determine which adjuvant therapy he should be treated with?

Correct Answers:

1. No
2. Yes – mp-MRI and ConfirmMDx.

Potential approved tests that could be carried out here include mpMRI and Progensa. mpMRI is particularly useful in distinguishing between Gleason three and Gleason four cancers, and Progensa, which compares PCA3 levels with PSA levels, offers significantly improved overall accuracy compared with testing PSA alone. However, mpMRI may detect lesions that upon histological examination turn out not to be cancer, and even if either test implied that cancer was present, the current best practise would be to carry out biopsies to confirm this diagnosis anyway.
3. Yes – OncotypeDx.

OncotypeDx is a gene panel test that predicts both the aggressiveness and the near- and long-term outcomes of the prostate tumour. This allows the clinical team to decide between active treatment and active surveillance options for the patient.


Decipher is an RNA panel used to test radical prostatectomy specimens which can be used to predict aggressive disease. This allows the clinical team to decide between adjuvant and salvage radiotherapy.

Question:
What are three subtypes of free PSA (fPSA)?

1. tPSA, PSA complex (with serine protease inhibitors), proPSA
2. PSA complex (with serine protease inhibitors), proPSA, iPSA
3. iPSA, bPSA, proPSA
4. PSA complex (with serine protease inhibitors), iPSA, bPSA
5. tPSA, proPSA, bPSA

Correct Answer & Explanation:
3. iPSA, bPSA, proPSA

Several subtypes of freePSA exist in the bloodstream, including intact PSA, benign (or nicked) PSA and a pro form of PSA with one of several pro-leader peptides. PSA complexes with serine protease inhibitors are not considered ‘free’ as they are attached to these inhibitors, and tPSA refers to total PSA – including all of the above subtypes.

Bibliography:


Figures:
(Figures uploaded separately)
Figure Captions:

Figure 1. Summary of Prostate Cancer Biomarkers Discussed

Key biomarkers discussed are summarised here, sorted by source material, and noting approval status and type of marker. mpMRI, which does not require biological samples, is excluded. STHLM3: Stockholm 3, SNP: single nucleotide polymorphism, RNA: ribonucleic acid, RP: radical prostatectomy, LDT: laboratory developed test, FDA: food and drug administration.