Prostate cancer is the most common male malignancy and the second leading cause of male cancer-related deaths. The incidence of prostate cancer is rising. In the UK the incidence is 34,000 per year with Europe and the United States each having an incidence in excess of one quarter of a million per year. The annual mortality in the UK is constant at approximately 10,000 per year.

Current Diagnostic Pathway

The rise in incidence has been due to use of the blood serum test, Prostate Specific Antigen (PSA), as a screening test both formally in the USA and Europe, and informally in the UK. However, PSA is false positive-prone (7 out of 10 men in this category will still not have prostate cancer) and false negative-prone (3 out of 10 men with prostate cancer have no elevation in PSA). If a man has a raised PSA or other risk factors that raise a clinical suspicion of prostate cancer (e.g., family history, abnormal rectal examination, high PSA velocity or density, Black origin) he is offered a transrectal ultrasound guided (TRUS) prostate biopsy. These biopsies traverse the rectal mucosa and take 6-12 biopsies in a systematic fashion throughout the whole prostate, but with no knowledge of suspicious areas within the gland. More than 30,000 men have a prostate biopsy in the UK and over one million biopsies are carried out in the USA.

Post-mortem studies have shown that many men (approximately 30-50%) over the age of 50 years who have died of other causes have insignificant prostate cancer that does not impact on their life expectancy. The inability of the current diagnostic pathway (PSA and transrectal prostate biopsy) to differentiate between significant and insignificant cancer has unarguably lead to the rising incidence of low risk prostate cancer. As a result, the implications of detection and treatment for this group of men are immense, with large burdens on the individual (biopsy, treatment and psychological morbidity) and healthcare services (biopsy costs, surgery/radiotherapy/surveillance costs, managing side-effects).

Prostate Biopsy – Problems

The impact on survival from greater detection through screening is at present unknown and will not be known for at 10 years once randomized controlled trials in the UK, Europe and the US have reported. However, what is clear from the current diagnostic pathway is that it is significantly flawed for the following reasons:

Under-detection

TRUS biopsies have a false negative rate of 30% - 45%. This is because they are carried out with no knowledge of suspicious areas. The ultrasound provides the operator with images that aid in ensuring the needle is in the prostate and a broad region within the gland, but ultrasound is poor at differentiating cancer from benign tissue. The operator therefore takes between 6 and 12 biopsies in a systematic fashion so as to sample areas of the gland ‘likely’ to harbour cancer (mainly the posterior peripheral zone). As the posterior zone is predominantly biopsied, the anterior horns of the peripheral zone, the transition zone, midline and apical areas of the prostate are under-sampled as well as large parts of the peripheral zone. These areas account for one third of all prostate cancers. Those with a persistently elevated PSA on surveillance are usually advised to undergo further TRUS biopsies with a higher sampling density. As these tend to sample the same areas albeit with a greater density of biopsies, problems of under-sampling remain.

Over-detection of insignificant prostate cancer

Overall, men undergoing systematic TRUS biopsy of 6-12 cores of prostatic tissue have a 1 in 3 probability of being diagnosed with prostate cancer. Of these, 45% are designated low risk disease based on PSA level, Gleason grade and stage. It is estimated that half of these men may be suitable for surveillance. The other 50% of low risk men harbour more disease or higher Gleason grade than designated on TRUS biopsy (see section below). It therefore follows that the majority of men presenting with an abnormal PSA do not have prostate cancer or have insignificant disease that need not be treated. If this group of men could be identified by a non-invasive test, then biopsy could be avoided. In this setting, the new non-invasive test would behave as a triage diagnostic test.
**Risk Stratification**

TRUS biopsies can be unrepresentative of the true burden of cancer due to the sampling error. For instance, in one study only three-quarters of all those found to have Gleason score 7 or greater on radical prostatectomy, were depicted as such by TRUS biopsy. The sensitivity of TRUS biopsy for high-grade disease decreases as the gland increases in size. Overall, there is both ‘over-grading’ and ‘under-grading’ in 30-75% diagnosed with cancer. Volume of cancer is an important prognostic factor and this is also underestimated. Surrogate features of volume of cancer exist such as the number of positive cores and the amount of cancer per positive core, but sampling error make these inaccurate determinants of whether cancer is significant or insignificant.

**Morbidity**

The transrectal route is subject to faecal contamination. TRUS biopsy has a number of complications such as urinary tract infection (1-8%), (life-threatening) sepsis (1%), haematuria (50%), haematospermia (30%), pain/discomfort, dysuria (most) and urinary retention (1%). Greater precision may lead to fewer biopsies and fewer infective complications.

Multi-parametric Magnetic Resonance Imaging (MRI), 1.5 Tesla, Pelvic Phased Array

The role of MRI has traditionally been embedded in local staging of high risk prostate cancer. Over the last 5 years, there has been a growing evidence base for its role in detecting and localising prostate cancer. This has been due to improved technology (higher magnetic field strengths from 0.5 Tesla to 1.5 Tesla) and use of new sequences such as contrast enhancement, diffusion weighting and spectroscopy alongside the conventional T1 and T2 weighted scans. Multi-parametric MRI uses a number of these sequences in combination in order to increase accuracy. The literature base suggests that multi-parametric MRI could achieve a sensitivity and negative predictive value of over 90%. If this were shown to be the case, multi-parametric MRI directed prostate biopsies would have the following advantages:

- Increased detection of significant prostate cancer
  This would result from better targeting of suspicious areas

- Improved risk stratification of cancer that is diagnosed
  This would result from better sampling of the tumour to obtain representative tissue cores.

- Lower detection rate of insignificant prostate cancer
  This would result from avoidance of sampling areas that had no or insignificant cancer (MRI as a triage test)

- Fewer biopsies leading to fewer complications
  A lower infection risk due to less faecal contamination may be possible with a lower urinary retention rate and haematuria due to less biopsy-induced haemorrhage/swelling.

- Precise staging of intermediate to high risk prostate cancer.
  If carried out prior to biopsy, biopsy artefact is avoided. Biopsy artefact appears as low signal areas on T2-weighted scans (similar to areas of cancer) and cause incorrect staging in 20-30% of men. T1-weighted scans only partially make up for this artefact which can last for 3-6 months. This leads to many having more aggressive therapy such as non-nerve sparing surgery or dose escalation radiotherapy. These can lead to unnecessary poor genitourinary side-effects. Knowledge of the location of cancer could also ensure that those men who have aggressive tumours within the prostate do not have suboptimal treatment such as nerve-sparing surgery which could lead to positive margins and adjuvant radiotherapy.

- An overall healthcare economic benefit
  As a result of points above, there are possible economic benefits to changing the diagnostic pathway in this manner:
  - Fewer biopsies per prostate
  - Fewer repeat biopsies due to persistently raised PSA and previous negative biopsies (20-30% of men need repeat biopsies).
  - Fewer insignificant prostate cancer diagnoses
- Improved and selective use of active surveillance
- Improved and selective use of surgery and radiotherapy

Post-Treatment follow-up

Imaging has an increasingly important role to play in treatment verification and surveillance of urologic cancers. Most image-guided therapies do not provide histological specimens for pathological analysis meaning that imaging is often the \textit{only} short-term endpoint for the completeness of the therapy.