RANDOX

EDUCATIONAL GUIDE

Ultra-low PSA & Prostate Cancer

QUALITY CONTROL

Introduction

Prostate cancer is the most common form of cancer in men. In the UK, 1 in every 8 men will be diagnosed with prostate cancer within their lifetime and an estimated 12,000 men die every year from this disease, equating to 1 death every 45 minutes[1].

There is a significant proportion of cases classified as asymptomatic, requiring active monitoring or watchful waiting rather than treatment, however, it is difficult to differentiate between asymptomatic cases and those that will progress to disease state. Diagnosis of prostate cancer is based on microscopic analysis of prostate tissue obtained through a needle biopsy[2]. The microscopic architecture and appearance of the cells within these samples are then evaluated by a pathologist who assigns a Gleason grade for both the predominant histological pattern and the highest risk pattern, on a scale of 1-5. The combination of the Gleason grade, serum PSA levels and clinical stage is used to assign a low-, intermediate-, or high-risk diagnosis and from here, therapeutic strategy is determined[2]. Those deemed low risk are usually placed on active monitoring, half of which receive treatment. However, those placed on active monitoring, with or without treatment, maintained a better quality of life compared with those who were not[2].

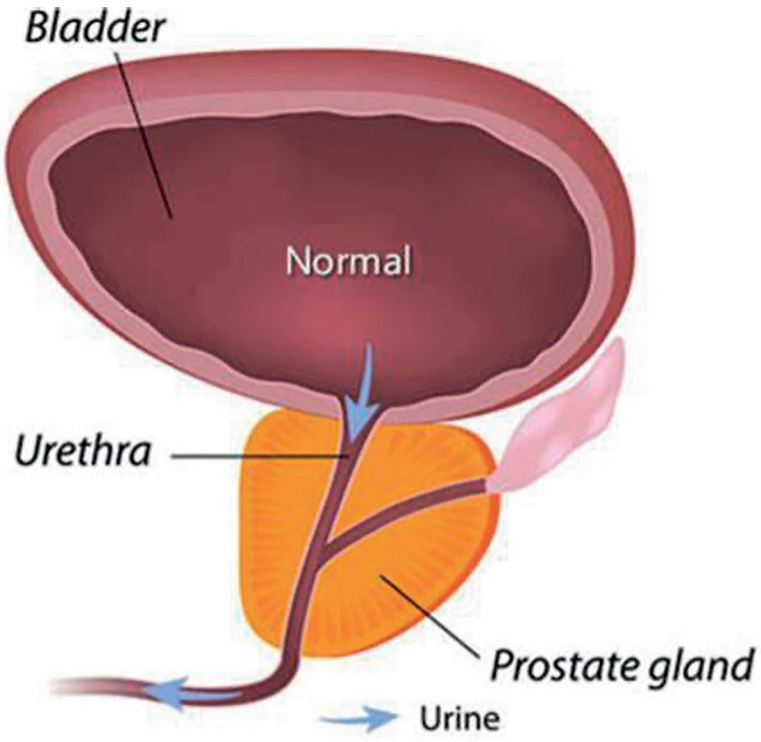

Figure 1. Illustration of the prostate gland and its location in relation to the bladder and urethra[3].

Prostate Cancer Prevalence & Risk Factors

Prostate cancer is the most frequently diagnosed cancer in men in Europe, and the second most common in men in the USA. According to research[4], between 20-40% of prostate cancer cases in both the USA and Europe may be due to overdiagnosis as a result of extensive prostate-specific antigen (PSA) testing.

While prostate cancer is not strongly associated with any modifiable risk factors, the risk factors for prostate cancer include advanced age, ethnicity, genetic factors, and family history. The table below details some of these risk factors:

RISK FACTOR	DESCRIPTION
Ethnicity	The lowest incidence in the USA is in American Indian/ Alaskan people, followed by Native and Asian/Pacific Islanders and Caucasians. The highest prevalence in the USA was displayed by African Americans. It is important to note that significantly higher PSA levels were displayed by black men than white men. However, prostate cancer incidence is around 40-fold higher in African American men than in African men, suggesting environmental factors play an important role. In addition, incidence rates were 16-fold higher in Chinese men residing in the USA when compared with those living in China[4]. These large differences may also be, in part, explained by lower frequency of testing in those regions with lower prevalence.
Family History/Genetics	An estimated 20% of prostate cancer patients report a family history of the disease, which may be a result of genetic factors or exposure to environmental carcinogens and common lifestyle habits[4].
Vitamin D	An inverse association between sunlight or UVB exposure and the occurrence of prostate cancer has been displayed, suggesting that a deficiency in Vitamin D may potentially elevate the risk of developing prostate cancer. Similarly, it has been found that people living in so called 'sunny' countries were at a lower risk of developing secondary solid tumours after melanoma when compared with those living in so called 'less sunny' countries[4].
Folate & Vitamin B12	Folate and Vitamin B12 are involved in DNA methylation, synthesis, and repair. Low levels of folate and B12 result in altered methylation and can induce the development of cancer. Studies have shown the role of folate in the development of a particularly aggressive form of prostate cancer and increases in serum folate concentration have been associated with increased proliferation of prostate cancer cells in samples from patients who have undergone radical prostatectomy[4].
Coffee consumption	Whilst more investigation is required, coffee consumption has been associated with reduced prostate cancer risk. Observational studies have shown an association between long-term coffee consumption with improved glucose and insulin metabolism. Hyperglycaemia is considered to increase the risk of the development of prostate cancer[4].

Figure 2 shows the global distribution of prostate cancer in 2018. This map clearly shows the higher prevalence of prostate cancer in developed countries. This is thought to be multifactorial; explanations include a higher testing rate in developed countries, environmental factors, cultural habits, and ethnic diversity. This map also explicitly shows the much higher mortality rate associated with low and middle-income countries. This suggests that testing capabilities and frequency are crucial to reduce mortality associated with prostate cancer.

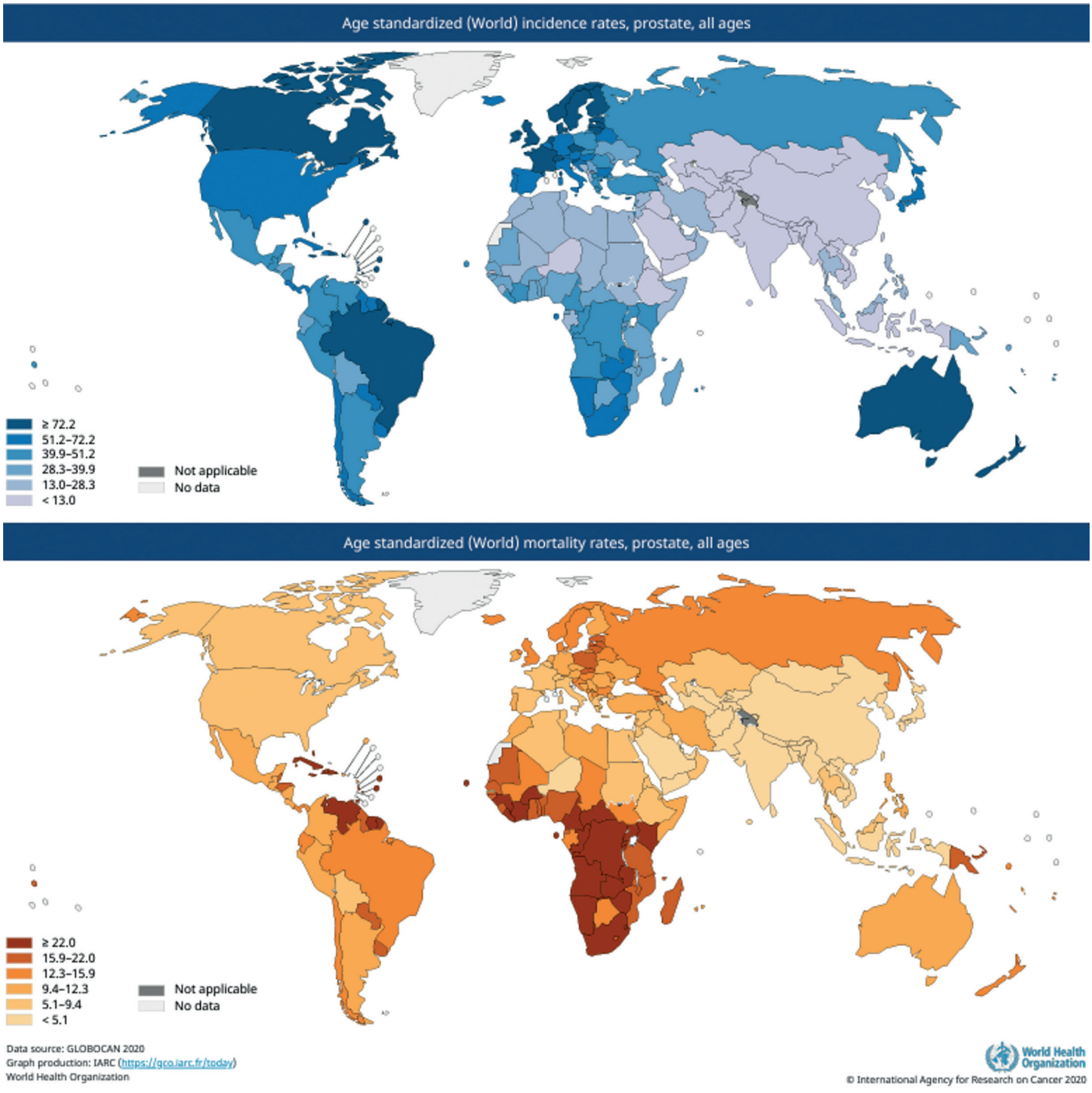

Figure 2. Global prevalence of prostate cancer diagnosis and global prostate cancer mortality rates[5].

Treatment

There are various treatments available for prostate cancer depending on the type and stage of the cancer. In some cases, watchful waiting or active surveillance will be prescribed by the clinician. Although both these strategies are used to avoid unnecessary treatments, the terms are often confused but have fundamental differences.

Watchful waiting is prescribed for men who harbour other health conditions which may eliminate the benefit derived from classic treatment strategies, or in cases where the cancer is expected to remain asymptomatic throughout the individual's lifetime. This intends to control symptoms rather than treating the cancer. In contrast, active surveillance describes a strategy suitable for men with slow-growing cancers which have not spread beyond the prostate (localised prostate cancer) and for those who would benefit from classic prostate cancer treatments if they were deemed necessary, the aim of which will be to remove the cancer. Active surveillance consists of more hospital visits than watchful waiting to receive MRIs, biopsies, and PSA testing[1].

Where intervention is required, there are various treatment options, which will be determined by the type of stage of the cancer.

TREATMENT	DESCRIPTION
Surgery	Radical prostatectomy (RP) is suitable for treating localised prostate cancer, and in some cases, recurrent prostate cancer. This involves removing the entire prostate gland. This surgery is usually keyhole surgery (robot-assisted or by hand), but in cases of more invasive cancer, open surgery may be required.
Radiotherapy	There are various types of radio therapy (RT) available depending on the type and stage of the cancer. Examples include Intensity-modulated radiotherapy (IMRT), Volumetric modulated arc therapy (VMAT) and Stereotactic ablative radiotherapy (SABR).
Hormone Therapy	Like RT, there are a number of forms of hormone therapy which can be selected. These treatments act by interrupting/inhibiting normal hormonal pathways with the intent of blocking the proliferation of cancer cells.

Prostate-specific Antigen

Prostate-specific antigen (PSA) is a major protease in semen, produced by the prostate ductal and acinar epithelium before being secreted into the lumen, where it functions to cleave semenogelins into smaller polypeptides resulting in the liquification of semen[6]. Intact PSA enters the circulation and is rapidly bound to protease inhibitors, however, a proportion of PSA that is inactivated in the lumen circulates as free PSA.

The transcription of this protease is positively regulated by the androgen receptor (AR), a steroid hormone receptor that binds as a homodimer to specific DNA sequences known as the androgen-responsive elements (AREs). PSA is expressed in prostate cancer cells where its level of expression per cell is lower than that of normal prostate epithelium, in other words, it is the increase in cell number as a result of cancer which causes an increase in PSA level, not an increase in transcription[6]. In addition, prostate cancer causes a disruption of the basal cell layer and basement membrane. These features result in a loss of glandular architecture which allows PSA increased access to the peripheral circulation[6].

Normal PSA levels vary with age. Men aged between 50-69 are expected to have a PSA level of <3ng/ml. Therefore, a PSA concentration of more than 3ng/ml may be indicative of prostate cancer. The difficulty with PSA monitoring for prostate cancer arises due to the associated high false positive rate. Elevated PSA concentration may also be indicative of an enlarged prostate, prostatitis, or a urinary tract infection. Research has shown that 3 out of 4 men who display elevated PSA levels will not have prostate cancer. Furthermore, data shows that 1 in every 7 men who have prostate cancer will maintain normal PSA levels[7]. For these reasons, PSA screening alone is not enough to diagnose prostate cancer, and some countries are limiting recommendations related to PSA-based prostate cancer diagnosis. Other countries are maintaining their recommendations in relation to PSA testing but are adding to the guidelines to support the inclusion of additional criteria to make an accurate diagnosis[6].

Non-cancerous causes of elevated PSA

As previously discussed, elevated levels of PSA are not always indicative of prostate cancer. In older men, benign prostatic hyperplasia, or enlarged prostate, is a common reason for elevated PSA[8]. Prostatitis, defined as inflammation of the prostate, can also cause a rise in PSA concentration. This is thought to be due to altered permeability of the neighbouring vasculature and hypervascularity. Patients suffering from acute prostatitis who receive appropriate treatment can expect their PSA levels to return to normal after around 1-3 months, however, those suffering from chronic prostatitis have a less definitive return to homeostasis[9]. Antibiotics have been used as a primary strategy in an effort to reduce the frequency of unnecessary biopsies. While this approach may be useful for those patients suffering from bacterial prostatitis, many of these cases of prostatitis arise form another origin. Additionally, this strategy does not consider the possibility of a comorbidity of prostatitis and prostate cancer. Asymptomatic prostatitis can also make this policy problematic as around 32% of men harbour this condition, one which causes an elevation in serum PSA concentration[10].

Other causes of elevated PSA include urinary tract infections, recent sexual activity, natural increase due to ageing, and injury to the area surrounding the prostate, namely the groin area. Additionally, one study investigated the effects of bicycle riding on PSA levels in healthy men with an average age of 55 years old. This investigation found that a bicycle ride of over 55km caused a marked PSA elevation of 9.5%[11]. For these reasons, patients who require PSA testing are asked to refrain from physical and sexual activity for up to 48 hours prior to their appointment.

Mechanisms of altered PSA concentrations

PSA concentrations have been shown to decrease in response to treatment and increase when stimulated by recurrent cancer. Androgen Deprivation Therapy (ADT) is commonly used as a treatment for advanced prostate cancer. ADT functions to inhibit the production of PSA mRNA and ultimately PSA transcription[12]. However, PSA is not a growth factor that directly affects prostate cancer proliferation.

There are three proposed mechanisms for the increase in PSA concentration is response to prostate cancer[12]:

1. When basal cells are eliminated during prostate cancer, the ductal structure is broken down and PSA can more freely enter the blood stream.
2. Some mechanisms work to increase androgen receptor activity such as, AR amplification, increased AR protein or the actions of several AR coactivators.
3. The increased number of cells resultant of the prostate cancer tumour express PSA in addition to that produced by healthy prostate cells, driving the increase in PSA concentration.

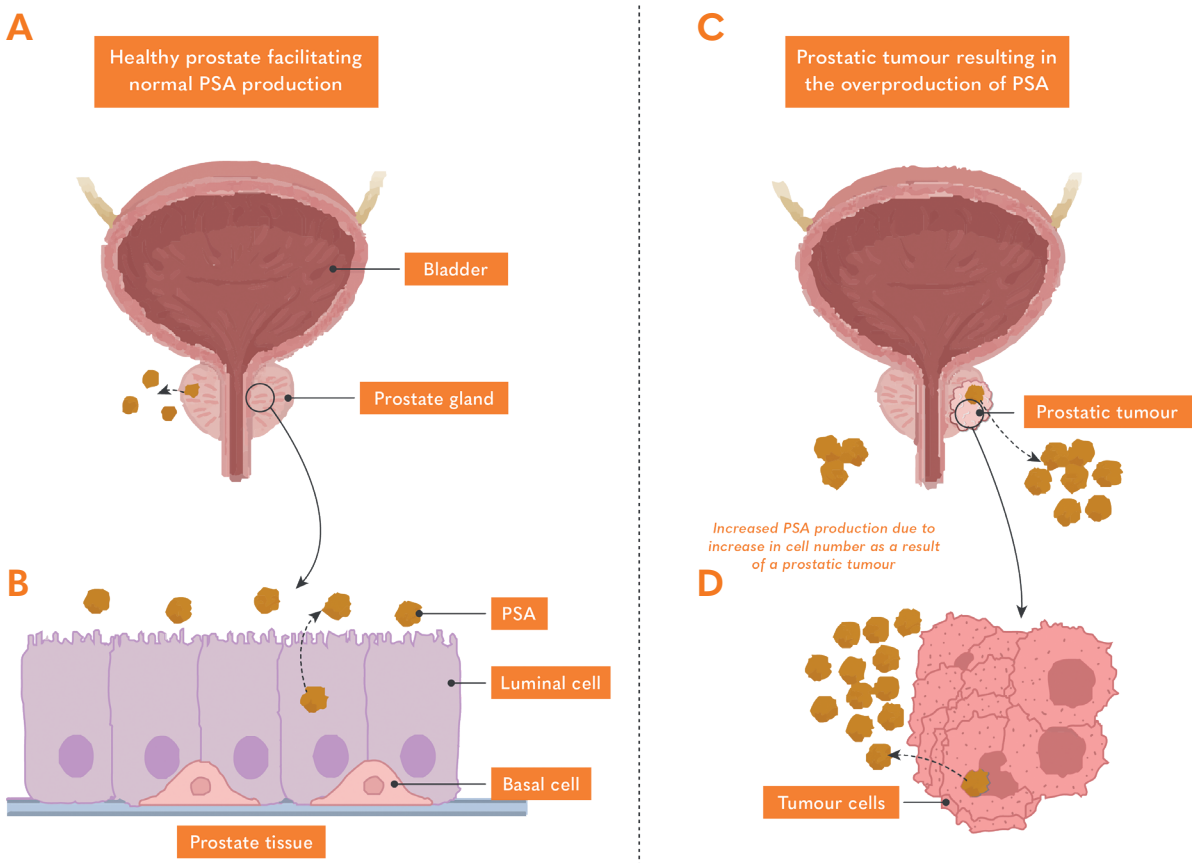

Figure 3. (A) Healthy prostate gland secreting healthy levels of PSA. (B) Illustration of the luminal cells of the prostate gland secreting healthy levels of PSA. (C) Prostate gland displaying a prostatic tumour and overproduction of PSA (D) Illustration of prostatic tumour cells and the overproduction of PSA as a result of the increased cell number.

Ultra-low PSA levels

PSA concentration for the diagnosis of prostate cancer is accompanied by a high level of inaccuracy. However, it is undeniable that there is a link between PSA levels and prostate cancer. Therefore, it is still considered to have utility in risk stratification and diagnosis when used in combination with other known factors.

PSA is also useful in monitoring prostate cancer patients after they have received treatment. When the patient is considered to be cancer free, their PSA levels should drop to within the normal range, or in cases of radical prostatectomy, PSA levels should be essentially undetectable.

PSA levels post-radiotherapy can be expected to return to nadir within 12-18 months, however, a spike in PSA concentration post-radiotherapy has been reported in some cases. This should not be considered as recurrent cancer, but these patients should be monitored particularly closely. PSA concentrations that rise above 2.0ng/ml post-radiotherapy should be tested for recurrent cancer. In addition, it is commonly the rate of increase of PSA concentration that is considered to be indicative of biochemical recurrence. Patients in remission are monitored closely and their PSA concentrations determined over time. This data is then used to calculate the PSA doubling time. A doubling time of less than 12 month should be investigated further as this is indicative of biochemical recurrence[13].

PSA concentrations in patients who have undergone radical prostatectomy (RP) should be almost undetectable (<0.1ng/ml). In fact, only recently, through the advent of more sensitive test procedures, have we been able to monitor ultra-low PSA levels. RP is a surgery that removes the entire prostate gland from the patient. As PSA levels are governed almost entirely by this gland, only trace levels of PSA should be present in the patient's blood. These traces are considered ultra-low levels of PSA. Any increase in PSA should be regarded as reason for investigating biochemical recurrence[13].

Guidelines for Ultra-low PSA testing

Throughout the world, different countries and healthcare systems provide diverging advice on ultra-low PSA monitoring. In the table below some of these guidelines are detailed:

GUIDELINES	DESCRIPTION
American Urology Association[14]	PSA concentrations of >0.2ng/ml, followed by a subsequent confirmatory >0.2ng/ml result should be considered biochemical recurrence. However, a cut-off of 0.4ng/ml may better predict metastatic relapse.
European Association of Urology[9]	A detectable PSA indicating relapse should be differentiated from a clinically meaningful relapse. PSA thresholds that predict further metastasises are: Post-RP = >0.4ng/ml Post-RT = nadir + 2ng/ml
Prostate Cancer Foundation[1]	Post-RP = PSA 0.2ng/ml is indicative of biochemical recurrence Post-RT = PSA nadir + 2ng/ml is indicative of biochemical recurrence

Randox Acusera Ultra-low PSA control

To aid in the quantitative determination and monitoring of ultra-low PSA levels of post-therapy prostate cancer patients, Randox introduces its new Ultra-low PSA Control. This control has been optimised for use on Roche systems but is suitable for use on a variety of other platforms, providing the only control for the measurement of ultra-low levels of PSA on the market.

Features & Benefits

- Impressive 30-day stability at +2°C to +8°C minimising waste
- Liquid ready-to-use control ensuring minimal sample preparation
- Manufactured using human serum providing a matrix similar to the patient sample
- Target values for specific instruments are available
- Clinically relevant concentration - Typical value = 0.055ng/ml

(This product is for Research Use Only)

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Conclusions

PSA-based testing for the diagnosis of prostate cancer has advantages and disadvantages. When used in combination with other factors and tests, PSA concentration can provide valuable insight into the disease state of prostate cancer patients. Monitoring of ultra-low PSA levels post-RP and post-RT is a useful method of determining biochemical recurrence, however the guidelines and cut-off values vary internationally.

Like all biomarker analysis, IQC is a crucial part of the process. The introduction of the Randox Ultra-low PSA control to the market provides laboratories with a control at clinically relevant ultra-low concentrations to improve the confidence in and accuracy of the results to aid in the monitoring of post-therapy PSA levels and to identify cases of biochemical recurrence.

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