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Stratifying Individuals at Risk of Prostate Cancer Using a Novel Biomarker-Based Predictive Algorithm

Mary Jo Kurth[1], Joanne Watt[1], Laura Mooney[1], Allister Irvine[1], John V. Lamont[1], Peter Fitzgerald[1] and Mark W. Ruddock[1,2]*

[1]*Randox Laboratories Ltd., Randox Health, 55 Diamond Road, Crumlin, County Antrim, BT29 4QY, Northern Ireland, UK*

[2]*Randox Health GB Ltd., 143-149 Great Portland Street, Marylebone, London, W1W 6QN, UK*

Abstract

In the United Kingdom (UK), prostate cancer (PCa) is a significant health concern, with over 50,000 new cases reported annually. Prostate cancer now accounts for almost 26% of all new cancers in UK males. In 2023, PCa accounted for almost 13% of all cancer deaths, making PCa the second most common cause of cancer death in males. The high mortality rate is often attributed to late-stage diagnoses, rendering the disease incurable in many patients. The aim of this study was to evaluate, in an independent retrospective patient cohort, a biomarker-based prostate cancer risk score (PCRS) for prostate health screening.

Materials and methods: Two hundred and ninety-two anonymized male clients, who had attended a Randox Health Clinic within the UK for health screening (2019-2023), were selected and their serum sample was evaluated using a novel biomarker-based algorithm (tPSA, EGF, IL-8, and MCP-1) to stratify/triage individuals at risk of prostate disease and deliver an individual PCRS.

Results: Three hundred and twenty-four serum samples were obtained from n = 292 clients (median age 49 years). Using a PCRS cut-off 0.0538 (PCRS > 0.0538 positive risk), clients were divided into one of the following 4 groups based on their PCRS [PCRS = c + m1 (EGF) + m2 (log10 IL-8) + m3 (log10 MCP-1) + m4 (log10 tPSA); where c and m1 through m4 are constants]: Group 1 (n = 282/324 (87.0%)) (low risk): tPSA < 4 ng/ml and PCRS < cut-off; Group 2 (n = 28/324 (8.6%)): tPSA < 4 ng/ml and PCRS > cut-off (low-moderate risk); Group 3 (n = 4/324 (1.2%)): tPSA > 4 ng/ml and PCRS < cut-off (moderate risk); Group 4 (n = 10/324 (3.1%)), tPSA > 4 ng/ml and PCRS > cut-off (high risk).

Conclusions: Application of the PCRS for prostate health screening was shown previously to outperform tPSA alone. Using this novel biomarker-based algorithm is a useful tool to stratify/triage individuals at risk of prostate disease as demonstrated in the current study. If the biomarker-based algorithm were to be deployed in primary care, clinicians would have additional information on how they could manage their patients; refer or defer. Screening asymptomatic individuals and monitoring an individual's PCRS would potentially reduce the number of unnecessary referrals to secondary care for invasive biopsies while potentially detecting patients at risk of disease, earlier.

Keyword

Prostate cancer, Stratifying risk, tPSA, EGF, IL-8, MCP-1, Algorithm, Triage

Introduction

Over 50,000 men in the UK are diagnosed annually with prostate cancer (PCa), at an economic cost of over £800 million [1]. Prostate cancer is now one of the most common cancers reported in men [2]. By 2038-2040, it is estimated that this figure will increase to over 85,100 new cases each year, underscoring the importance of proactive surveillance for early detection and effective treatment [3].

The prostate specific antigen (PSA) test, which is used to refer individuals to secondary care for further investigation, has significant limitations: (a) the test is not diagnostic, (b) PSA

***Corresponding author:** Mark W. Ruddock, Randox Laboratories Ltd., Randox Health, 55 Diamond Road, Crumlin, County Antrim, BT29 4QY, Northern Ireland, UK, Tel: +44 (0) 28 9442 2413

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levels can be raised by factors other than cancer e.g., benign prostate enlargement, (c) PSA levels increase with age, and (d) routine testing for PSA is not recommended for most men [4], as PSA has a false positive rate of approximately 70%, and false negative rate of 20% [5].

Identification of PCa clinical risk factors have not been conclusive, however, it is generally accepted that age, family history and genetics, trouble urinating, frequent urination, decreased force of urination, difficulty starting or stopping urine stream, lower back or bone pain, lethargy, erectile dysfunction, visible hematuria, blood in semen, pain or discomfort in the pelvic area, and being overweight, are important clinical considerations for effective patient management [6-8].

Individuals who present with an elevated PSA are normally referred to secondary care for further investigations; however, the gold standard for diagnosing PCa remains histological assessment of the prostate (transperineal ultrasound-guided biopsy of the prostate) [9]. Biopsy of the prostate is not without risk (e.g., bruising, bleeding, serious infection, and trouble urinating) [10,11]. Moreover, it is important to acknowledge that not all individuals with an elevated PSA and a prostate imaging-reporting and data score (PI-RADS) > 2 have a positive biopsy diagnosis for PCa [12]. PI-RADS are used to standardize interpretation of prostate MRI, improve diagnosis, and reduce unnecessary biopsies [12]. However, > 70% of patients with an elevated PSA level (> 4 ng/ml) who are referred to secondary care for further investigation, have a negative prostate biopsy result [13]. Furthermore, a negative biopsy does not always indicate that there is no cancer, and a repeat biopsy may be required [5,14]. Thus, these results underscore the complexity involved in the pathophysiology of PCa and the diagnostic need for careful consideration and clinical interpretation of both patient history (clinical risk factors), diagnostic test results and imaging (biomarker/PI-RAD risk score). Application of an individual's prostate cancer risk score (PCRS), based on biomarker combinations, could help support clinical decision making and potentially stratify/triage patients who are at potential risk of PCa, into low, medium, or high-risk categories.

As the field of PCa diagnosis and risk stratification evolves, ongoing research and updated guidelines, such as those provided by the National Institute for Health and Care Excellence (NICE), play a critical role in improving diagnostic accuracy and patient outcomes. New and evolving tests and biomarker-based combination models for the early detection and stratification of individuals at risk of PCa are currently being investigated e.g., Stockholm-3 risk-based model, the 4k score, the Prostate Cancer Prevention Trial, and the Irish Prostate Cancer Risk Calculator [15-19].

Previously we described the clinical utility of a novel combination of biomarkers (EGF, MCP-1, IL-8 and tPSA), and their use in a biomarker-based algorithm to stratify potential risk of PCa based on an individual's PCRS [20]. The novel biomarker combination was compared to tPSA alone, and the algorithm was shown to provide improved diagnostic utility, sensitivity and specificity [20]. The current study describes the use of the biomarker-based algorithm in an independent, retrospective, cohort of males who attended a Randox Health Clinic for a wellness check. To reduce the potential for health inequality between genders i.e., females are offered cervical smear tests and mammograms for early detection of cancer; is it now time to introduce annual prostate health screening using the PCRS for all asymptomatic males ≥ 50 years of age?

Materials and Methods

Sample population

This is a retrospective study involving n = 292 individual males who attended a Randox Health Clinic for a Randox Health Signature Panel (Health Wellness Checkup) between January 2019 and August 2023. In this study, client data that contained the biomarkers of interest used in the algorithm (tPSA, EGF, IL-8, and MCP-1) (324/435 (74.5%)) were selected for prostate health investigation. All individual data was anonymized. Consent was obtained digitally through Randox's online platform. Venous blood was collected and processed, and the biomarker analysis was undertaken by Randox Clinical Laboratory Services (RCLS), (Randox Science Park, 30 Randalstown Road, Antrim, BT41 4FL, Northern Ireland, UK) (ISO17025). In total, n = 324 serum samples were analyzed. Some individuals visited the clinic on more than one occasion. Client age at presentation ranged from 18 to 79 years (Table 1). At the time of sampling, clinical information and client prostate health outcomes were unknown.

Sample analysis

Individual serum samples were analyzed using Biochip Array Technology on an Evidence Investigator analyzer (Randox Laboratories Ltd, Crumlin, UK) [21]. The limit of detection (LOD) for the analytes were: tPSA (0.045 ng/ml), EGF (2.5 pg/ml), IL-8 (2.3 pg/ml), and MCP-1 (25.5 pg/ml). The biomarkers that reported below the LOD were recorded at 90% of the LOD [22].

Application of the prostate cancer risk score (PCRS)

All individuals, irrespective of their tPSA result, were screened for PCa risk using the novel prostate cancer risk

Table 1: Age of individuals at time of sample collection by mean ± SD, median, range, and number (n).

	Mean ± SD	Median (Range)	n
All	48.6 ± 11.9	49.0 (18-79)	324
Group 1	47.5 ± 11.5	48.0 (18-78)	282
Group 2	52.9 ± 12.7	53.0 (28-79)	28
Group 3	65.0 ± 4.80	63.5 (61-72)	4
Group 4	60.6 ± 8.60	60.0 (43-73)	10

score (PCRS), as described previously [20]:

Prostate Cancer Risk Score Logistic Regression Equation

$$PCRS = c + m1\left(EGF\right) + m2\left(\log_{10} IL - 8\right) + m3\left(\log_{10} MCP - 1\right) + m4\left(\log_{10} tPSA\right)$$

Where *c* = -8.92652, *m1* = 0.01002, *m2* = -1.52428, *m3* = 3.95772, *m4* = 1.31471, and the cut-off for the biomarker-based predictive algorithm = 0.05385012.

Individuals who had a tPSA < 4 ng/ml and a PCRS < the assigned cut off (0.05385012), were designated low risk of PCa and were assigned to Group 1. Individuals with a tPSA < 4 ng/ml and a PCRS > the cut-off, were designated low-moderate risk and assigned to Group 2 (these individuals would require further clinical investigation to determine why the PCRS identified them in the absence of a positive tPSA i.e., a tPSA > 4 ng/ml). Individuals with a tPSA > 4 ng/ml, and a PCRS < the cut-off, were designated moderate risk and assigned to Group 3 (it should be noted that these patients would require further investigation, based on their presentation symptoms and age, and would likely receive a referral for further investigations). Individuals who had a tPSA > 4 ng/ml and a PCRS > the cut off were designated high risk and assigned to Group 4.

Statistical analyses

All statistical analyses and visualisations were undertaken using R, version 4.3.1. Calculating the PCRS has been described previously [20]. Briefly, biomarker output results were inputted into the logistic regression equation for each individual, as shown previously. Individuals were then assigned to their respective Group (1-4; low to high risk) based on their tPSA result and PCRS. Data that was not normally distributed was transformed using log10.

Results

Patient demographics

The age of the individuals involved in the study are shown in Table 1.

Prostate Cancer Risk Score (PCRS)

In total, n = 324 individual samples were included in the prostate health analysis; the concentration of tPSA (ng/ml), EGF (pg/ml), IL-8 (pg/ml), and MCP-1 (pg/ml), were measured and the value (output from the analyzer) for each individual biomarker was used in the PCRS algorithm to calculate an individual's risk score. Individuals were then assigned to one of the 4 groups, as follows: n = 282/324 (87%) samples were assigned to Group 1 (low risk); n = 28/324 (8.6%) samples were assigned to Group 2 (low-moderate risk); n = 4/324 (1.2%) samples were assigned to Group 3 (moderate risk); and n = 10/324 (3.1%) samples were assigned to Group 4 (high risk) (Figure 1).

Group 1: tPSA < 4 ng/ml and PCRS < cut-off (green-low risk); Group 2: tPSA < 4 ng/ml and PCRS > cut-off (yellow-low-moderate risk); Group 3: tPSA > 4 ng/ml and PCRS < cut-off (amber-moderate risk); Group 4, tPSA > 4 ng/ml and PCRS > cut-off (red-high risk).

Follow up on individual history based on prostate cancer risk score (PCRS)

Individuals were assigned to the different risk groups, based on their tPSA and PCRS, Group 1 through Group 4. Clinical history and presentation symptoms were investigated retrospectively.

A detailed individual clinical history was recorded at the time of venous sampling, and any prostate-related symptoms were noted e.g., nocturia, poor urine flow, urgency, pelvic or pubic pain, benign prostate enlargement, penis or testes problems, urinary dribbling, and any family history of cancer.

Group 1 (tPSA < 4 ng/ml and PCRS < cut-off tPSA; low risk)

Group 1 individuals (n = 282) were designated low risk, and thus were excluded from further analysis.

Group 2 (tPSA < 4 ng/ml and PCRS > cut-off; low-moderate risk)

Twenty-eight individual samples with a tPSA < 4 ng/ml were identified as low-moderate risk based on their PCRS (PCRS > cut-off). The breakdown of the clinical characteristics for these individual samples are presented in Figure 2 and are detailed in Table 2.

Group 3 (tPSA > 4 ng/ml and PCRS < cut-off; moderate risk)

Group 3 individuals (n = 4) were designated moderate risk and their clinical characteristics are detailed in Table 3.

Group 4 (tPSA > 4 ng/ml and PCRS > cut-off; high risk)

Group 4 individuals (n = 10) were designated high risk; two individuals were diagnosed with PCa, and the remaining individuals in the group have prostate-related issues and are currently under the care of a urologist (Table 3). Three individuals in this group are currently on watch and wait protocols.

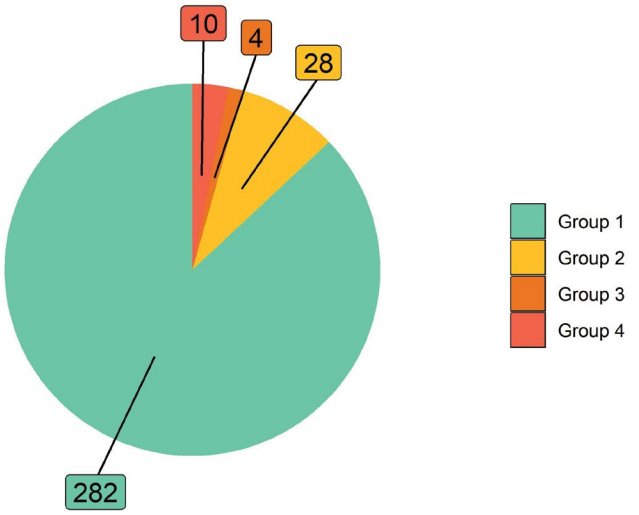

Figure 1: Group 1: tPSA < 4 ng/ml and PCRS < cut-off (green-low risk); Group 2: tPSA < 4 ng/ml and PCRS > cut-off yellow-low-moderate risk); Group 3: tPSA > 4 ng/ml and PCRS < cut-off (amber-moderate risk); Group 4, tPSA > 4 ng/ml and PCRS > cut-off (red-high risk).

Table 2: Clinical characteristics for individual samples identified by the PCRS in the absence of an elevated tPSA.

Group	Age	tPSA (ng/ml)	Clinical characteristics
Group 2	45	0.97	Family history of cancer
Group 2	56	1.84	Family history of cancer
Group 2	53	0.96	Family history of cancer
Group 2	72	1.34	Poor urine flow, urgent need to urinate, urinating more frequently at night
	73	1.9	
Group 2	28	0.61	Penis or testes problems: lumps, pain, other, urinating more frequently
Group 2	54	0.96	Urinating more frequently
Group 2	63	3.97	Benign prostate enlargement, family history of cancer
Group 2	62	1.95	Urinating more frequently
Group 2	60	3.24	Poor urine flow, urinating more frequently, family history of cancer
Group 2	79	0.93	Benign prostate enlargement
Group 2	49	0.67	Poor urine flow
Group 2	50	1.06	Family history of cancer
Group 2	61	3.77	Family history of cancer
Group 2	38	1.09	Family history of cancer
Group 2	53	1.15	None
Group 2	48	0.82	Family history of cancer
Group 2	50	0.92	Family history of cancer
	50	0.94	
Group 2	73	0.37	Poor urine flow, urgent need to urinate, urinating more frequently at night
Group 2	36	0.75	Family history of cancer
Group 2	56	2.41	Family history of cancer
	57	3.53	
Group 2	54	3.46	Family history of cancer
Group 2	39	0.43	Penis or testes problems, other
Group 2	30	0.88	Side pain
Group 2	40	0.85	Family history of cancer
Group 2	53	1.37	Family history of cancer

Table 3: Clinical characteristics for individual samples identified by the PCRS and placed in Groups 3 and 4.

Group	Age	tPSA (ng/ml)	Clinical characteristics
Group 3	72	4.06	Normal
Group 3	61	4.48	BPE Repeat testing after 2 years
Group 3	63	4.31	
Group 3	63	4.33	Prostate examined, no signs of cancer
Group 4	55	4.27	Prostate cancer
Group 4	64	236	Prostate cancer Stage 4
Group 4	59	4.22	Nocturia Advised to arrange prostate examination with NHS GP
Group 4	58	4.74	Under the care of a consultant urologist Diagnosed with BPE Continued monitoring (watch and wait) Repeat test after 6 months
Group 4	58	5.77	
Group 4	72	5.35	Under the care of a consultant urologist Diagnosed with BPE Continued monitoring (watch and wait)
Group 4	43	4.56	Pelvic and pubic pain, urinary dribbling Advised to arrange assessment with consultant urologist
Group 4	61	4.23	Under the care of a consultant urologist Consultant urologist satisfied that no further action
Group 4	73	7.29	History of recurrent UTI's and urological problems
Group 4	63	4.64	Under the care of a consultant urologist Continued monitoring (watch and wait)

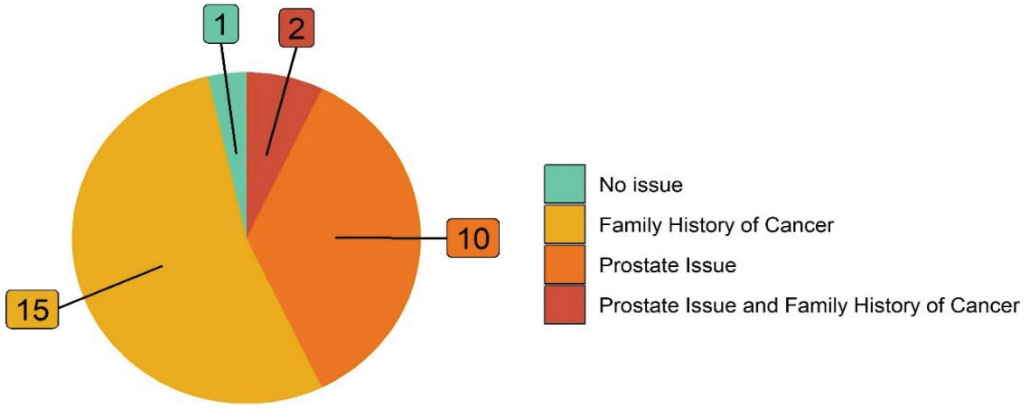

Figure 2: Individuals assigned to Group 2 (tPSA < 4 ng/ml and PCRS > cut off; low-moderate risk), based on their PCRS, by clinical risk factors. Of the n = 28 samples in Group 2, 1/28 (3.6%) had no prostate-related issues and no family history of cancer; 15/28 (53.6%) had no prostate-related issues but a family history of cancer; 10/28 (35.7%) had prostate-related issues but no family history of cancer; 2/28 (7.1%) had prostate-related issues and a family history of cancer; as reported at the time of sampling.

Discussion

A national screening programme for prostate health in the UK does not exist. Moreover, current tests e.g., PSA, do not reduce the number of deaths from PCa. Indeed, almost one in seven men with PCa may have a normal PSA [23]. Therefore, a simple PSA test would be ineffective if the individuals were asymptomatic, and the PSA level was within normal range (standardized for age). In contrast, there are screening programmes in place for females for early detection of both cervical (smear test) and breast cancer (mammograms).

However, despite the numerous studies that have been published detailing the use of biomarkers for the diagnosis of PCa, PSA remains the biomarker of choice that directs urologists once a diagnosis is made (observe versus treat and identify individuals with aggressive disease). The current study proposes a disruptive approach; application of a prostate cancer risk score (PCRS), incorporating tPSA and three independent biomarkers (EGF, IL-8 and MCP-1) used in a single biomarker-based algorithm, to stratify risk of PCa into one of four categories; (1) low risk, (2) low-moderate risk, (3) moderate risk, and (4) high risk of PCa.

Of the n = 324 individual samples that were included in the study, n = 282 were designated low risk (Group 1) and were excluded from further investigation. A total of n = 28 individuals with a tPSA < 4 ng/ml were identified as low-moderate risk (Group 2) based on their PCRS (PCRS > cut-off). These individuals would require further clinical investigation to determine why the PCRS identified them in the absence of an elevated tPSA. PSA levels are not always indicative of PCa grade and stage since it has already been shown that men with normal PSA levels may have PCa (1 in 7 men) or a fast-growing cancer (1 in 50 men) [23]. There was n = 4 individuals in Group 3, moderate risk i.e. elevated PSA and low PCRS. It is noteworthy that when these four individuals were followed up, they had undergone urological investigations; three of these individuals did not have PCa, and one individual had a normal PSA based on age (our cut-off for PSA was set at 4 ng/ml). In the highest PCa risk category, Group 4, where tPSA > 4 ng/ml and PCRS > cut-off there were 10 individuals. Two of these individuals had PCa and the remaining eight individuals had prostate-related issues. Interestingly, these remaining individuals are currently under the care of a urologist.

The PCRS, based on the novel biomarker combination, would allow general practitioners (GPs) in primary care, to make more informed management decisions, and more importantly, the decision regarding secondary referral for further investigation; this is a different and valuable approach to managing individuals that present with a raised PSA level (4-10 ng/ml). Low risk patients would be monitored in primary care without referral, whereas high risk patients would be red flagged for referral to secondary care for further investigations. This is not commonly proposed and has positive implications with respect to community-based screening for PCa. GPs then could monitor low-moderate and moderate risk individuals every 3-12 months and refer if a change in an individuals' PCRS is observed. However, the GP will use their own clinical judgment, in combination with the PCRS, to decide if an individual in any of the risk categories should be referred for further investigation.

Conclusion

Prostate cancer risk stratification and diagnosis are multifaceted processes that involve various clinical indicators and diagnostic procedures. As the incidence of PCa continues to rise, it is imperative that healthcare professionals remain vigilant in identifying and managing individuals at risk while also being mindful of the challenges associated with false positives in diagnosis. By offering the PCRS as a potential screening tool in primary care, both for symptomatic and asymptomatic individuals, the reduction in the number of unnecessary referrals to secondary care will free up more resources for patients that have been identified as high risk. Furthermore, armed with this additional information, clinicians can make the decision to refer or defer. In addition, by closely monitoring any change in PCRS, the clinician can make more informed decisions on an individual's care and clinical pathway.

Study Limitations

A detailed clinical history was not available for all individuals. It was assumed that all individuals that had a tPSA < 4 ng/ml and a PCRS < cut-off did not have PCa.

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Conflict of Interest

MJK, JW, LM, AI, JL and MWR are employees of Randox Laboratories Ltd but hold no shares in the company. PF is the Managing Director and owner of Randox Laboratories Ltd.

Authors Contribution

MJK and MWR wrote the manuscript. JW, AI, LM, JL, and PF assisted with reviewing and editing the manuscript. JW compiled the data, undertook the analyses, and produced the figures.

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