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THE VALUE OF MAGNETIC RESONANCE IMAGING AND GENETIC URINARY BIOMARKERS IN THE DIAGNOSIS OF CLINICALLY SIGNIFICANT PROSTATE CANCER

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MAGNETINIO REZONANSO TOMOGRAFIJOS TYRIMO IR GENETINIŲ ŠLAPIMO BIOŽYMENŲ VERTĖ DIAGNOZUOJANT KLINIŠKAI REIKŠMINGĄ PROSTATOS VĖŽĮ

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CONTENTS

ABBREVIATIONS

ADC	–	apparent diffusion coefficient
AI	–	artificial intelligence
AUC	–	area under the curve
BMI	–	body mass index
BPH	–	benign prostatic hyperplasia
bpMRI	–	biparametric magnetic resonance imaging
BW	–	band width
CI	–	confidence intervals
CisPCa	–	clinically insignificant prostate cancer defined as having a Gleason score = 6
CsPCa	–	clinically significant prostate cancer defined as having a Gleason score ≥ 7
ctDNA	–	circulating tumor DNA
DCE	–	dynamic contrast-enhanced imaging
DRE	–	digital rectal examination
DWI	–	diffusion-weighted imaging
EAU	–	European Association of Urology
ERG	–	Erythroblast transformation specific related gene
ERSPCRC	–	European Randomized Study of Screening for Prostate Cancer Risk Calculator
ESTRO	–	European Society for Radiotherapy and Oncology
FOV	–	field of view
GS	–	Gleason score
GUT	–	genetic urinary test
IGF-1	–	insulin-like growth factor-1
ISUP	–	International Society of Urological Pathology
MDT	–	multidisciplinary team
mpMRI	–	multiparametric magnetic resonance imaging
MPS2	–	MyProstateScore 2
non-csPCa	–	non-clinically significant prostate cancer that comprises negative biopsy and Gleason score = 6
PACS	–	picture archiving and communication system
PB	–	prostate biopsy
PBCG-RC	–	Prostate Biopsy Collaborative Group Risk Calculator
PCa	–	prostate cancer
PCA3	–	prostate cancer antigen 3
PCPTRC2	–	prostate cancer prevention trial risk calculator version 2.0
PHI	–	Prostate Health Index
PIRADS	–	prostate imaging reporting and data system v.2.1
PSA	–	prostate specific antigen
PSMA PET/CT	–	prostate-specific membrane antigen positron emission tomography/computed tomography
PZ	–	peripheral zone
RPCRC-MRI	–	Rotterdam Prostate Cancer Risk Calculator
SD	–	standard deviation
SIOG	–	International Society of Geriatric Oncology

SPDEF	–	SAM-pointed domain-containing erythroblast transformation specific transcription factor
T:E	–	fusion of TMPRSS2 and ERG genes
TE	–	echo time
TMPRSS2	–	androgen-regulated transmembrane serine protease 2
TR	–	repetition time
TRUS	–	transrectal ultrasound-guided
TZ	–	transition zone
US	–	ultrasound
vs.	–	in Latin – *versus*
WHO	–	World Health Organization

INTRODUCTION

Prostate cancer (PCa) remains one of the most commonly diagnosed malignancies worldwide. It is the leading cause of cancer-related morbidity and mortality in men [1]. The clinical spectrum of PCa ranges from asymptomatic disease to aggressive, clinically significant changes. Identifying and accurately diagnosing clinically significant prostate cancer (csPCa) – defined as cancer with a Gleason score $\geq 3 + 4$ – is critical to ensure proper treatment. It is also important to minimize the risks of overdiagnosis and overtreatment of low-risk disease [2].

Typically PCa detection has been based primarily on prostate-specific antigen (PSA) testing, digital rectal examination (DRE), and systematic transrectal ultrasound (TRUS)-guided biopsy. Now it was revealed that these methods demonstrate limitations in both sensitivity and specificity, also are related to missed diagnoses and unnecessary biopsies. In recent years, alternative diagnostic tools such as multiparametric magnetic resonance imaging (mpMRI) and genetic urinary biomarkers have been acknowledged as promising non-invasive approaches for PCa diagnostic [3]. MpMRI has been recognized as a valid method in visualizing and localizing clinically significant lesions, assisting targeted biopsies and reducing unnecessary prostate biopsies. It has become one of the main tools in PCa diagnostic, especially in biopsy-naïve patients [4].

Genetic urinary biomarkers are also being investigated widely in PCa diagnostics. These biomarkers are usually collected after prostate massage and can provide likelihood of csPCa. The main examples include Prostate Cancer Antigen 3 (PCA3) and TMPRSS2:ERG gene fusion (T:E), each delivering unique diagnostic value. When used in combination with known risk factors and mpMRI results, genetic urinary biomarkers are able to improve diagnostic accuracy even further and potentially reduce the number of unnecessary invasive procedures [5].

Risk calculators provide personalized risk prediction scores and are increasingly used in PCa diagnostic protocols. Prostate Cancer Prevention Trial Risk Calculator version 2.0 (PCPTRC2) includes clinical variables such as PSA, age, family history, and DRE findings to predict the risk of both overall and high-grade PCa. [6] The other calculator that is widely applied among European populations is the European randomized study of screening for prostate cancer risk calculator (ERSPCRC). This calculator uses PSA, prostate volume, and prior biopsy results aiding in further treatment planning decisions [6]. Besides mentioned clinical calculators, biomarker-based tools like the 4Kscore and Prostate Health Index (PHI) have shown significant

added value in detecting csPCa. The 4Kscore combines four kallikrein markers with clinical data to assess high-grade cancer risk [7]. Another tool – PHI – combines total, free, and proPSA for improved specificity compared to PSA alone [8]. Recent studies suggest that combining these calculators with mpMRI or genetic urinary biomarkers such as PCA3 or T:E can further improve csPCa diagnostic and reduce unnecessary biopsies [9]. Despite these advancements, there is no approved diagnostic protocol for biopsy-naïve patients. Therefore, comparative studies of mpMRI, genetic urinary biomarkers, and risk calculators are crucial to improve early detection strategies for csPCa.

The aim of the study

The aim of this study was to determine and compare the multiparametric magnetic resonance imaging, genetic urinary biomarkers, the prostate cancer risk calculator and their combinations diagnostic performance in the identification of clinically significant prostate cancer (Gleason $\geq 3 + 4$).

The objectives of the study

1. To determine the sensitivity and specificity of multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in biopsy naïve patients.
2. To estimate the role of genetic urinary testing in diagnosing clinically significant prostate cancer in biopsy naïve patients.
3. To evaluate the added value of the Prostate Cancer Prevention Trial Risk Calculator v.2.0 with and without the inclusion of urinary biomarkers in detecting clinically significant prostate cancer in biopsy naïve patients.
4. To analyse the value of different diagnostic methods combinations in diagnosing clinically significant prostate cancer in biopsy naïve patients and to provide diagnostic recommendations for the early diagnosis of clinically significant prostate cancer.

The novelty of the study

To our knowledge this is the first study that examined the value of mpMRI and genetic urinary biomarkers (PCA3 and T:E) combination in detecting csPCa among biopsy naïve patients. In clinical practice, there are currently no approved diagnostic protocols for detecting suspected PCa

before the first prostate biopsy. Several previous studies have explored the association between mpMRI and PCA3 in detecting csPCa. For instance, Fenstermaker et al. analysed 187 biopsy-naïve men who underwent both mpMRI and PCA3 testing, demonstrating an association between PCA3 scores, MRI suspicion, and cancer detection on MRI-targeted biopsy (AUC = 0.67, 95% CI: 0.59–0.76) [10]. Similarly, Porpiglia et al. retrospectively reviewed 120 biopsy-naïve patients and found that mpMRI provided greater predictive accuracy for csPCa than PCA3 (AUC = 0.78, $p < 0.01$) [11]. The 2019 San Francisco consensus statement proposed a research direction emphasizing the clinical utility of genetic biomarkers in PCa diagnostics. [12] The statement clearly defined the added value of diagnostic tests and biomarkers, which our study aims to assess and validate by using MRI, genetic biomarkers, and their combinations. However, the novelty of our study is characterized by its prospective design, larger cohort, and expanded focus. Unlike prior research, our study not only evaluates mpMRI and PCA3 but also incorporates T:E biomarker testing, PCPTRC2 calculated PCa risk and assesses the diagnostic value of different test combinations. By integrating multiple diagnostic approaches, our study aims to provide a more comprehensive and clinically applicable strategy for improving early csPCa detection in biopsy-naïve patients.

Several cancer screening programs have been introduced in Lithuania, but the early detection program for PCa remains one of the most criticized. It is often viewed as poorly justified, mainly because screening tends to detect many cases of early, clinically insignificant PCa (cisPCa) cases that do not require treatment. A study conducted in 2013 demonstrated that low-risk patients have the same mortality rate as individuals in a healthy control group. Conversely, high-risk patients, particularly those with advanced PCa, showed significantly higher mortality rates compared to the general population. [13] These findings suggest that low-risk patients should not undergo treatment or additional invasive diagnostic procedures, but should instead be placed under active surveillance.

1. LITERATURE REVIEW

1.1. Epidemiology and incidence of prostate cancer

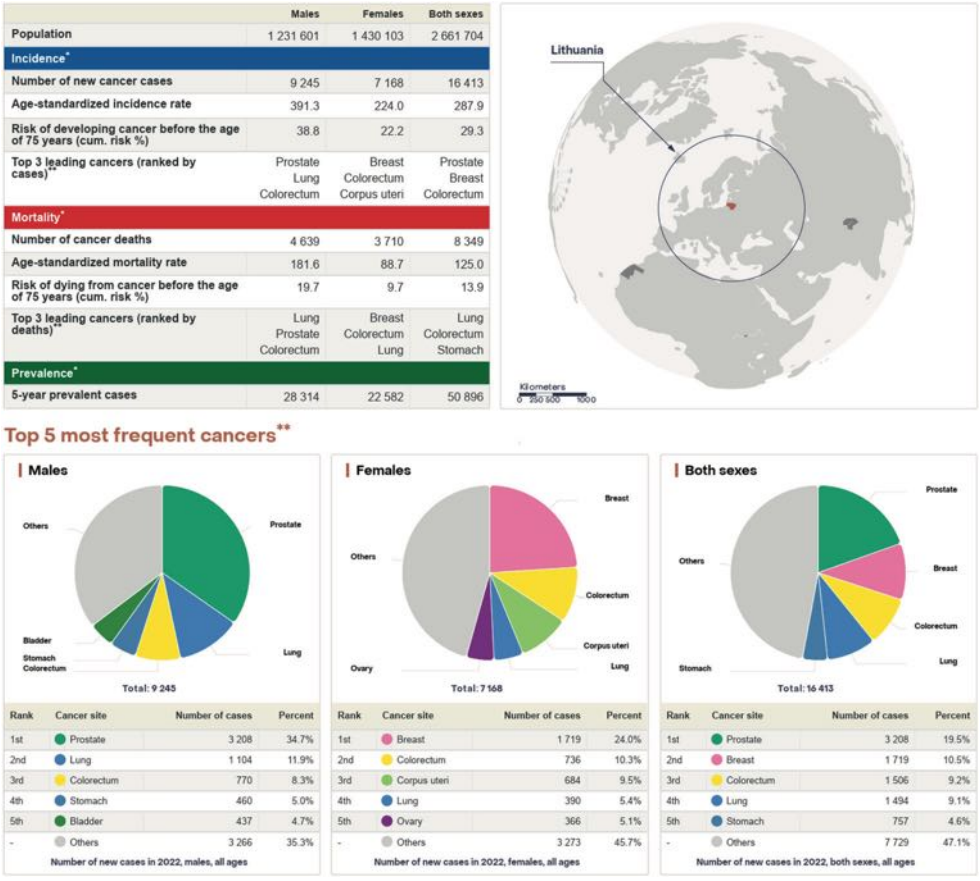
Prostate cancer (PCa) is the second most commonly diagnosed malignancy worldwide. It is the fifth cause of cancer-related mortality among men and accounts for approximately 1.4 million new cases and over 375 000 deaths annually as of data of 2022. [14] The global impact of PCa varies greatly among different countries, with the highest incidence rates reported in North America, Western Europe, and Oceania. This pattern is likely reflecting a combination of different factors, including genetic predisposition, dietary patterns, and the PSA screening. In contrast, lower incidence rates observed in parts of Asia and Africa may be resulting not only from genetic and environmental differences but rather from underdiagnosis due to limited access to screening and healthcare facilities.[15]

In Lithuania, prostate cancer is the leading malignancy among men, accounting for 34.7 % of all new male cancer diagnoses as of data of in 2022. In the same year there were also 545 deaths from this cancer registered, representing about 6.5% of all cancer-related deaths in Lithuania [14]. This pattern reflects both the longstanding national PSA screening programme and persistent challenges in prostate-cancer awareness and access to treatment.

The introduction of PSA screening has significantly influenced PCa epidemiology. While the detection rates of localized disease increased, it was accompanied by certain limitations. During the past years it was noted the rising numbers of overdiagnosis and overtreatment of clinically insignificant tumours. This outcome raised questions about whether it is an acceptable tool for a PCa screening [16]. Furthermore, there are notable differences in PCa outcomes across different regions and socioeconomic groups. For example, early detection of PCa by PSA screening demonstrated lower mortality rates in high-income countries. However, men in low- and middle-income countries often experience various difficulties to access early diagnosis and treatment. This often lead to diagnosing later-stage disease and higher mortality rates [17].

Multiple factors such as healthcare infrastructure limitations, lack of routine screening programs, cultural differences, and economic barriers all contribute to PCa epidemiology [18]. Understanding this highlights the need for creating strategies to improve healthcare infrastructure, primarily focusing on improving access to early diagnostic of PCa [19]. Continued epidemiological research and prevention strategies are essential for reducing the global

burden of PCa, enhancing patient outcomes, and optimizing resource allocation.



	Males	Females	Both sexes
Population	1 231 601	1 430 103	2 661 704
Incidence*			
Number of new cancer cases	9 245	7 168	16 413
Age-standardized incidence rate	391.3	224.0	287.9
Risk of developing cancer before the age of 75 years (cum. risk %)	38.8	22.2	29.3
Top 3 leading cancers (ranked by cases)**	Prostate Lung Colorectum	Breast Colorectum Corpus uteri	Prostate Breast Colorectum
Mortality*			
Number of cancer deaths	4 639	3 710	8 349
Age-standardized mortality rate	181.6	88.7	125.0
Risk of dying from cancer before the age of 75 years (cum. risk %)	19.7	9.7	13.9
Top 3 leading cancers (ranked by deaths)**	Lung Prostate Colorectum	Breast Colorectum Lung	Lung Colorectum Stomach
Prevalence*			
5-year prevalent cases	28 314	22 582	50 896

Rank	Cancer site	Number of cases	Percent
1st	Prostate	3 208	34.7%
2nd	Lung	1 104	11.9%
3rd	Colorectum	770	8.3%
4th	Stomach	460	5.0%
5th	Bladder	437	4.7%
-	Others	3 266	35.3%

Number of new cases in 2022, males, all ages

Rank	Cancer site	Number of cases	Percent
1st	Breast	1 719	24.0%
2nd	Colorectum	736	10.3%
3rd	Corpus uteri	684	9.5%
4th	Lung	390	5.4%
5th	Ovary	366	5.1%
-	Others	3 273	45.7%

Number of new cases in 2022, females, all ages

Rank	Cancer site	Number of cases	Percent
1st	Prostate	3 208	19.5%
2nd	Breast	1 719	10.5%
3rd	Colorectum	1 506	9.2%
4th	Lung	1 494	9.1%
5th	Stomach	757	4.6%
-	Others	7 729	47.1%

Number of new cases in 2022, both sexes, all ages

Fig. 1.1.1. *Number of new cancer cases in 2022 in Lithuania (Source: Globocan 2022) [14]*

This figure is adapted from a review by GLOBOCAN, 2022.

1.2. Aetiology and risk factors of prostate cancer

Prostate cancer is influenced by a mix of genetic and environmental factors, making it a complex disease with a number of possible causes. Age is by far the most significant risk factor – incidence rate rise significant in men over 50 and are most commonly diagnosed among 70 year of age. This pattern is likely due to a combination of factors: accumulated genetic changes over time, shifts in hormone levels that come with aging, and longer exposure to environmental triggers that may contribute to cancer development [19]. A man's family history is also a factor to be considered. In cases of men with a

close relative – like a father or brother – who had been diagnosed with PCa – are two to three times more likely to develop the disease themselves, which shows a strong inherited risk [20].

Growing knowledge in genetics continues to reveal how inherited factors contribute in increased PCa risk. Through large-scale studies of genetic variation across populations, researchers have identified over a hundred gene variants – specifically, single nucleotide polymorphisms – that appear more often in men who develop the disease. These findings support the idea that PCa doesn't stem from one single gene but rather from the combined effect of many [21]. Another key finding is the fusion between the TMPRSS2 gene and the ERG gene. This rearrangement can lead to an overactive ERG gene, which may interfere with normal cell functions and create conditions that allow cancer to grow [22]. The rearrangement can lead to an overactive ERG gene, which may interfere with normal cell functions and create conditions that allow cancer cells to grow [23].

There is a wide range of environmental and lifestyle factors that influence potential PCa risk and disease progression. First of all, it is known that dietary patterns play an important role. Researches have shown, that a high intake of red and processed meats, saturated fats, and high-fat dairy products increased PCa risk. This effect is possible due to the pro-inflammatory process, oxidative stress, and hormonal alterations [24]. In contrast, Mediterranean-style diets which are filled with fruits, vegetables, legumes, and omega-3 fatty acids may have a protective effect through their antioxidant, anti-inflammatory, and anti-proliferative properties [25].

Obesity is another well-recognized risk factor for higher risk related to PCa. Higher body mass index (BMI) has been associated with a likelihood of developing advanced-stage disease, as well as with increased mortality. The underlying mechanisms may include insulin resistance, chronic inflammation, and increased levels of circulating hormones such as insulin-like growth factor-1 (IGF-1) and sex steroids [26]. Additionally, physical inactivity, has been shown to be as an independent factor elevating PCa risk [27].

Environmental exposures, especially endocrine-disrupting chemicals and industrial toxins, also should be taken into consideration when evaluating the risk of PCa development. Studies have identified a potential association between exposure to pesticides, heavy metals, and petroleum derivatives and increased PCa incidence. This effect is especially well seen among agricultural workers and industrial laborers. Carcinogenic effects may be elaborated through genotoxic mechanisms or hormonal disruption, although further research is needed to confirm the dose-response relationships [28].

1.3. Diagnosis of prostate cancer

Prostate cancer diagnostic typically starts with standard clinical evaluation along with novel diagnostic technologies. Initial diagnostic typically involves collecting clinical data, performing a DRE and a PSA blood testing. PSA is a protein produced by prostate cells and while high levels may be related to PCa, they can also be caused by benign conditions like prostatitis or benign prostatic hyperplasia (BPH). If any suspicious findings are detected, further non-invasive diagnostic methods, including magnetic resonance imaging (MRI) or transrectal ultrasound (TRUS), are used. Finally, if suspicion of the PCa remain after non-invasive diagnostic methods applied, a prostate biopsy usually is the next used method. In most cases it is guided by imaging, to collect tissue samples for histological examination to confirm or deny the presence of PCa [29].

In recent years, genetic testing has become increasingly important part of PCa diagnostics and management. Urine-based tests usually involve specific biomarkers like PCA3, TMPRSS2:ERG fusion and other testing. These tests analyse gene expression in urine and are useful for detecting biomarkers associated with PCa. Urine biomarker testing offer a non-invasive way to assess cancer risk and reduce unnecessary biopsies. Similarly, blood-based genetic tests are designed to find circulating tumour DNA or mutations in genes like BRCA1**,** BRCA2**,** and ATM **–** all of have been linked to higher PCa risk and more aggressive disease. Together, these tests provide more than just PCa risk estimation – they also help in guiding treatment decisions, especially in cases where active surveillance *vs.* more aggressive intervention is being considered [30, 31].

Risk calculators have become one of the key tools for assessing the PCa risk. These models involve some of clinical parameters such as age, PSA level, DRE findings, prostate volume, and family history and provide an individual's risk of PCa diagnosis. One of the mostly used tools is the Prostate Cancer Trial Risk Calculator 2.0 (PCTRC2)**,** which was developed as part of the Prostate Cancer Prevention Trial. It's been updated to improve predictions and is easy to access by using online platforms. These advantages make a calculator a valuable practical option during routine clinical work. Other well-known calculators, such as the Rotterdam Prostate Cancer Risk Calculator (RPCRC-MRI) and the Prostate Biopsy Collaborative Group Risk Calculator (PBCG-RC), have also shown promising results in identifying cases that are more likely to be aggressive. When MRI findings are added into these calculators, their accuracy enhance even further, therefore helping clinicians better determine who should undergo biopsy and who may safely avoid it [32, 33].

Once cancer is confirmed, it is graded using the Gleason scoring system. This grading system evaluates tumour aggressiveness and determine how far it has spread. This includes determining whether the cancer is confined to the prostate, has spread to nearby tissues, or has metastasized to distant organs [34].

1.4. Prostate cancer screening

Prostate cancer screening primarily aims to find potential malignant changes early – when treatment is most likely to be effective – which can ultimately improve patient outcomes and reduce death rates. In clinical practice, the two main tools used are PSA testing and DRE [35] Although PSA testing shows advances in early PCa detection, it is related to several limitations. It has low specificity, therefore often provides false-positive results. This overdiagnosis can lead to a number of unnecessary procedures, including biopsies and treatments that carry their own risks, including infection, haemorrhage, urinary incontinence, and erectile dysfunction [36]. In contrast, the DRE can help reveal palpable abnormalities, but its low sensitivity prohibits it being used as a solely diagnostic method. Instead, it is most valuable when combined with PSA and patient's clinical history [37].

Improving the accuracy of screening accuracy and reducing the number of unnecessary biopsies has led to the growing use of MRI technique, especially multiparametric MRI (mpMRI), in clinical practice. Unlike relying solely on PSA levels, mpMRI is being used to better detection of clinically significant tumours. What is more, when combining traditional PSA screening with mpMRI results, it is possible effectively categorize patients by risk and make more informed decisions about whether a biopsy is necessary. Research indicates that using mpMRI as an assessment tool for men with raised PSA levels not only minimizes the number of unnecessary biopsies but also increases the detection of csPCa [38].

In prostate biopsy-naïve patients with suspected PCa, the European Association of Urology (EAU) guidelines advises performing mpMRI before any biopsy is considered. This strategy not only improves the detection of cancers that are clinically important but also helps to avoid unnecessary biopsies and the overdiagnosis of low-risk tumours. For example, the PRECISION trial showed that following an mpMRI with a targeted biopsy of suspicious lesions leads to a higher detection rate of csPCa while reducing the number of insignificant cancers found compared to the conventional systematic transrectal ultrasound-guided approach [39].

For patients with a negative mpMRI and low clinical suspicion (e.g., PSA density < 0.15 ng/mL/cm³), the guidelines suggest that a biopsy may be safely avoided after discussing the options with the patient. If a biopsy is still indicated, a trans perineal method is generally preferred because it is related to lower risk of infection. The EAU guidelines also highlights the importance of a thorough discussion with the patients about the benefits and potential harms of early PCa detection, taking into account factors such as age, family history, and any other health issues [40, 41].

1.5. Clinically significant *vs.* clinically insignificant prostate cancer

The distinction between clinically significant prostate cancer (csPCa) and clinically insignificant prostate cancer (cisPCa) is one of the most important issues in PCa management. csPCa is typically defined as cancer with a Gleason score of 7 or higher (ISUP Grade Group ≥ 2), a tumour volume greater than 0.5 mL, or evidence of extra prostatic extension. These features are associated with an increased risk of disease progression, metastasis, and prostate cancer-specific mortality. In contrast, cisPCa include tumours with a Gleason score of 6, low tumour volume, and disease confined to the prostate, which are unlikely to impact a patient's lifespan [42].

With the expansion of PSA-based screening programs, concerns about overdiagnosis and overtreatment of indolent tumours have grown significantly. Studies have shown that many of these low-risk cancers would never become clinically relevant during a patient's lifetime. However, definitive treatments such as surgery or radiotherapy often lead to significant side effects, including urinary incontinence and erectile dysfunction [43]. As a result, guidelines from major organizations like the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) now recommend active surveillance for men with low-risk disease. Active surveillance strategies involve careful monitoring through PSA testing, DRE, mpMRI, and repeat biopsies, with treatments reserved only for cases where disease progression is evident [29, 42].

On the other hand, for patients with csPCa, active treatment is recommended to prevent metastasis and improve long-term survival. Radical prostatectomy, radiation therapy, or a combination of therapies are commonly used techniques depending on the extent of disease at diagnosis. [44] Identifying the difference between csPCa and cisPCa remains one of the most important challenges in modern PCa management. Advances in imaging, such as mpMRI and genetic biomarker tests development are critical to

achieving the balance between avoiding overtreatment and ensuring timely, effective intervention when needed.

1.6. Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) has become one of the main tools in the diagnosis and management of PCa. Multiparametric MRI (mpMRI) integrates several imaging techniques – T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging – to distinguish clinically significant changes from benign conditions. For example, T2-weighted imaging provides detailed anatomical features of the prostate and its surroundings, which is especially useful for localizing tumours in the peripheral zone [45]. DWI examines how water molecules move within tissue. A reduction in this movement is commonly observed in malignant lesions due to their high cellular density. Quantitative measures like the apparent diffusion coefficient (ADC) derived from DWI, further help in differentiating high-grade tumours from less aggressive disease [46]. DCE imaging adds further functional assessment by mapping tissue vascularity and perfusion patterns, with malignant lesions often showing rapid contrast uptake and washout – a reflection of angiogenesis [47]. Studies have shown that mpMRI significantly enhances the detection and localization of csPCa. This improvement not only helps in risk stratification but also allows to avoid unnecessary biopsies by identifying patients who might not require invasive procedures [45, 47]. Additionally, a simplified approach, known as biparametric magnetic resonance imaging (bpMRI), which omits DCE component, has emerged as a potential alternative in selected cases. bpMRI maintains high diagnostic accuracy while offering benefits like reduced scan time and lower overall cost of the procedure [46]. MRI also plays a critical role in staging PCa by evaluating extracapsular extension, seminal vesicle invasion, and lymph node involvement – factors essential for effective treatment planning [45].

Sensitivity and specificity studies has shown that mpMRI has a higher sensitivity in detecting PCa, largely because it incorporates DCE imaging, that highlights tissue vascularization. In contrast, bpMRI tends to have slightly lower sensitivity while maintaining a similar level of specificity. In practical terms, mpMRI is superior in clinically significant changes detection, especially in cases where findings are ambiguous. Although bpMRI shows well overall performance, its slightly lower detection rates can be a limitation in some situations. Both techniques use the prostate imaging reporting and data system version 2.1 (PIRADS v2.1) to classify lesion, but the additional data provided by mpMRI can help to reduce inter-reader variability. A study

by Tamada et al. found that three different readers had significantly higher diagnostic sensitivity with mpMRI compared to bpMRI and the results were statistically significant ($P < 0.001$). The study also revealed that bpMRI offered significantly higher diagnostic specificity ($P < 0.001$) [48]. For biopsy guidance, MRI remains the gold standard for targeting areas of concern [49]. While bpMRI is very effective overall, it may sometimes be considered as insufficient for guiding biopsies in complex cases. On the other hand, bpMRI is growing in popularity for initial screening and active surveillance. Its non-invasive nature, lower cost, and absence of contrast-related adverse effects make it an attractive option – especially in resource-limited settings where long scan times or contrast agents may not be feasible [49]. A systematic review and meta-analysis by Bass et al. found that bpMRI has test accuracies comparable to mpMRI in detecting PCa, making it a strong alternative in many clinical scenarios [50]. bpMRI not only reduce overall healthcare costs but also means less discomfort for the patient. Without the risk of contrast-induced nephropathy and with faster scan times, patients are more likely to repeat the imaging in the future if needed. Additionally, bpMRI helps radiology departments to admit more patients, making prostate MRI more available for larger group of patients. As noted in a narrative review by Greenberg et al., the major advantage of bpMRI is its affordability, which makes it a practical option in many clinical settings [51]. On the other hand, mpMRI is associated with higher cost, longer scan time, and contrast-related risks, which may limit its widespread application. A study by Caglic et al. concluded that diagnostic performance of bpMRI and mpMRI was comparable for detection of extracapsular extension, however, mpMRI was superior for seminal vesicle invasion detection and improved inter-reader agreement [52].

Artificial intelligence integration in both mpMRI and bpMRI could enhance diagnostic accuracy and reduce inter-reader variability. Hybrid imaging approaches that combine elements of bpMRI with novel imaging biomarkers may further improve diagnostic accuracy. Personalized imaging protocols based on individual risk stratification could help balance diagnostic accuracy, cost-effectiveness, and patient safety. A review by Belue et al. reported that AI models achieved a pooled area under the curve (AUC) of 0.86 for detecting csPCa, indicating promising diagnostic performance [53].

1.7. PIRADS system and structured reporting

The prostate imaging reporting and data system version 2.1 (PIRADS v2.1) is a structured guide used to evaluate prostate lesions on mpMRI. Its purpose is to bring consistency to image interpretation and reporting for the

detection of clinically significant changes in the prostate. PIRADS uses a scoring system from 1 to 5 to describe the likelihood of clinically significant cancer, with each score linked to specific imaging features [54].

The peripheral zone, which constitutes approximately 70% of the glandular prostate tissue and is located at the outer part of the prostate. This zone is primarily assessed using diffusion-weighted imaging (DWI) as the dominant sequence. This is because prostate cancers in the peripheral zone typically demonstrate restricted diffusion, appearing as areas of high signal intensity on high b-value DWI and low signal intensity on apparent diffusion coefficient (ADC) maps (Fig. 1.7.1). In contrast, the transitional zone surrounds the urethra and is mostly associated with benign prostatic hyperplasia (BPH). For lesions in the transitional zone, PIRADS v2.1 designates T2-weighted imaging as the dominant sequence due to the distinct appearance of prostate cancer in this area. Cancerous lesions typically present as hypointense areas on T2WI against the heterogeneous background of BPH nodules (Fig. 1.7.2).

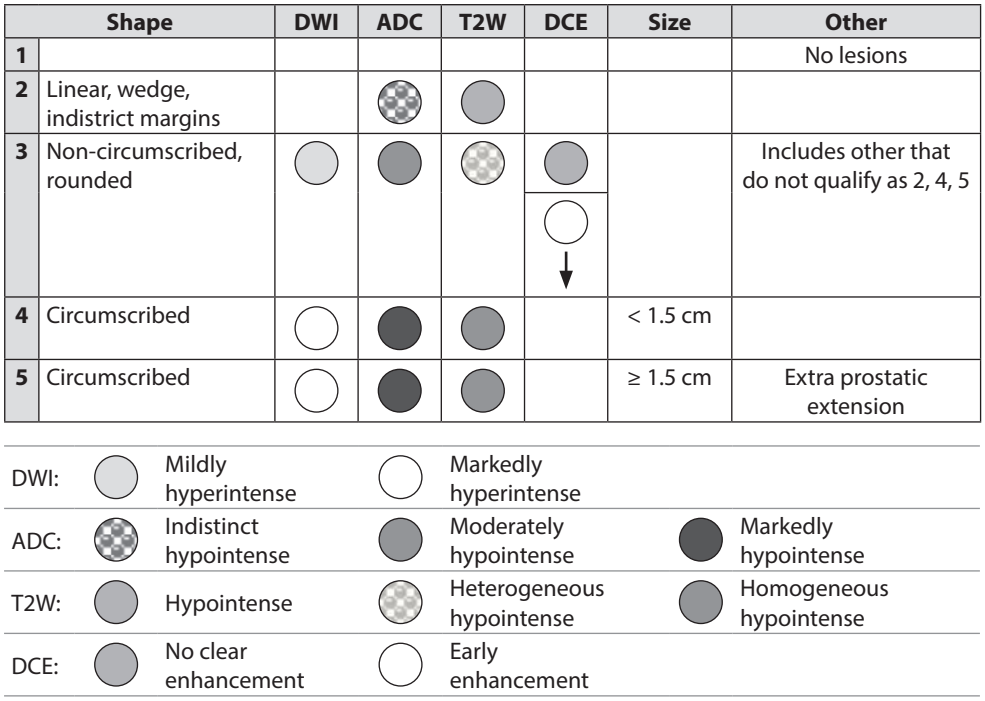


***Fig. 1.7.1**. Prostate Imaging Reporting and Data System (PIRADS): 2015, v2.1. Evaluation of peripheral zone lesions*

DWI – diffusion weighted imaging; ADC – apparent diffusion coefficient; T2W – T2 weighted imaging; DCE – dynamic contrast enhancement.

	Shape	T2W	DWI	ADC	Size	Other
1						No lesions
2	Linear, wedge, indistrict margins					
3	Non-circumscribed, rounded					Includes other that do not qualify as 2, 4, 5
4	Circumscribed				< 1.5 cm	
5	Circumscribed				≥ 1.5 cm	Extra prostatic extension

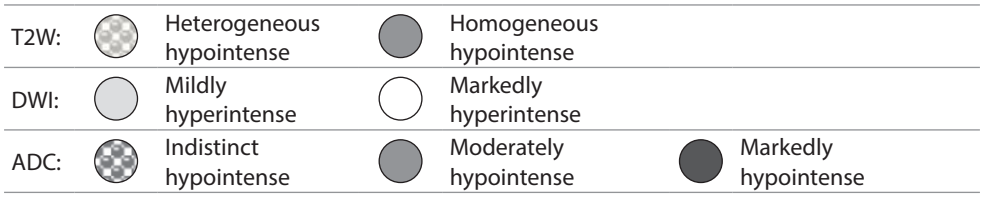


Fig. 1.7.2. *Prostate Imaging Reporting and Data System (PIRADS): 2015, v2.1. Evaluation of transitional zone lesions*

T2W – T2 weighted imaging; DWI – diffusion weighted imaging; ADC – apparent diffusion coefficient.

A PIRADS 1 indicates a very low likelihood of csPCa. Typically, this category includes cases where prostate in mpMRI appears completely normal, or when the findings are consistent with benign conditions. For instance, homogeneous hyperintensity on T2-weighted imaging (T2WI) in the peripheral zone (PZ) or diffuse hypointensity in the transition zone (TZ) is often seen in normal tissue. Similarly, in the TZ, a diffuse low signal, often due to benign prostatic hyperplasia, would also suggest a PIRADS 1 changes.

PIRADS 2 points to a low likelihood of csPCa. Changes in this category include patchy or diffuse areas of mild T2 hypointensity without any distinct focal lesion in the PZ. In the TZ, typical changes would be a well-circumscribed, rounded nodules that are typical of benign prostatic hyperplasia with no significant diffusion restriction or contrast enhancement [55].

PIRADS 3 is an intermediate category, indicating that mpMRI findings are not clearly benign or malignant, therefore further evaluation is needed. In the PZ, these lesions usually appear as areas of moderate hypointensity on T2WI or might show slight diffusion restriction on DWI. In the TZ, lesions that fall into this category often have an uneven signal or blurry margins on

T2WI, but without significant diffusion restriction or suspicious enhancement.

PIRADS 4 suggest a high likelihood of csPCa. In the PZ, PI-RADS 4 lesions tend to be distinct, marked hypointense on T2WI with moderate to severe diffusion restriction, often reflected by low apparent diffusion coefficient (ADC) values. In the TZ, a lesion categorized as PI-RADS 4 typically appears as nodule with ill-defined margins and moderate diffusion restriction, which raises concerns about malignancy.

PIRADS 5 indicates a very high probability of csPCa. In the PZ, this includes lesions with severe diffusion restriction and significant enhancement patterns on DCE imaging. In the TZ, PIRADS 5 lesions present as large, invasive nodules with extra prostatic extension or significant diffusion restriction. The size of the lesion also plays a key role in differentiation between PIRADS 4 and PIRADS 5 lesions. Lesions that exhibit all PI-RADS 4 features but are larger than 1.5 cm of size should be classified as PIRADS 5 [56, 57] (Table 1.7.1).

Table 1.7.1. *PIRADS v2.1 system and representative MRI pictures.*

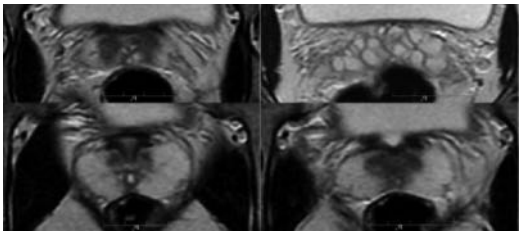
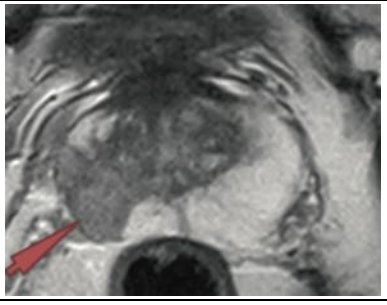
PIRADS	Definition	Representative figure
PIRADS 1	Normal prostate gland in T2W axial plane. In the upper section – T2W MRI images in different levels, upper right – seminal vesicles, upper left – prostate apex, lower right – midgland, lower left – prostate base.	
PIRADS 2	Hypointense lesion in the PZ on the right, on T2W with ill-defined contour and no mass effect on the adjacent normal prostate tissue (red arrow), referred as prostatitis.	

Table 1.7.1. *Continued*

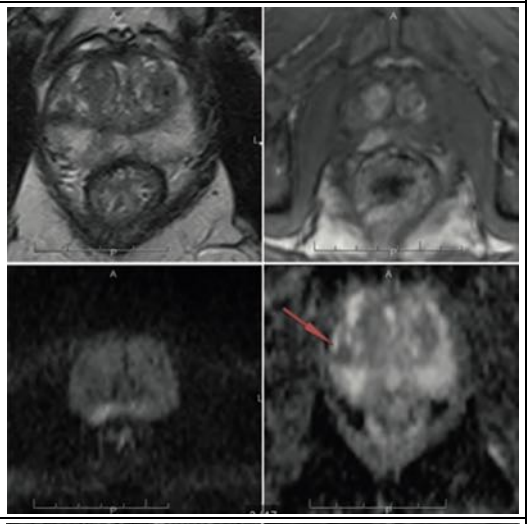
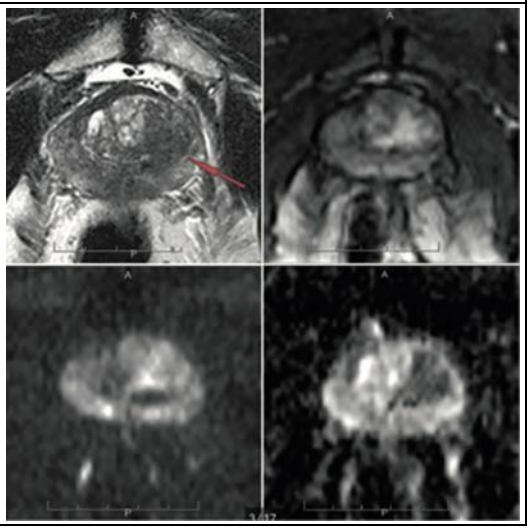
PIRADS	Definition	Representative figure
PIRADS 3 PZ	Lesion in the PZ on the right (red arrow). Upper part: on the right – hypointense lesion in T2W, on the left – no signs of early contrast enhancement in DCE; lower part: on the left – mildly hyperintense lesion in DWI, right lower image – hypointense lesion in ADC map.	
PIRADS 3 TZ	Lesion in the TZ on the left (red arrow). Upper part: on the left – hypointense lesion in T2W, on the right – early contrast enhancement in DCE; lower part: on the left – mildly hyperintense lesion in DWI, right lower image – hypointense lesion in ADC map.	

Table 1.7.1. *Continued*

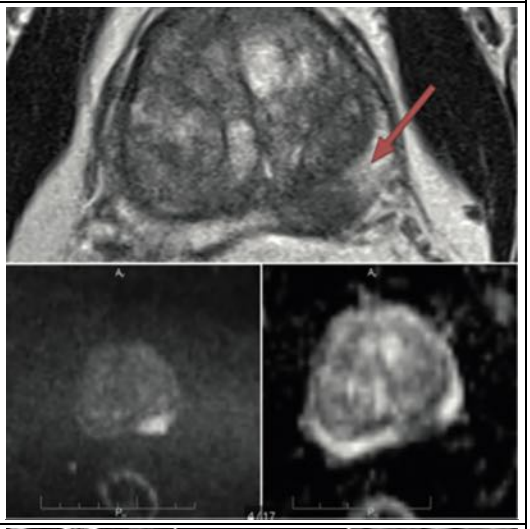
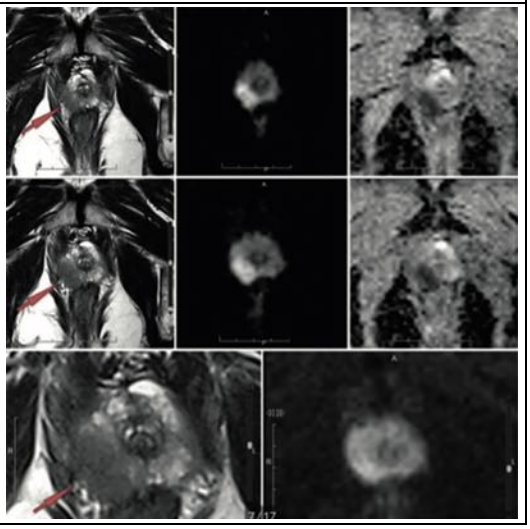
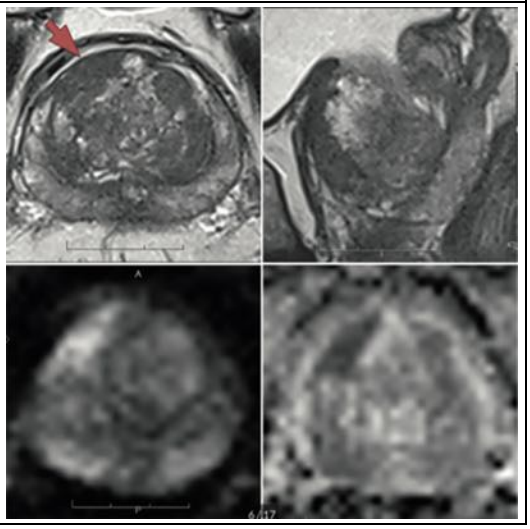
PIRADS	Definition	Representative figure
PIRADS 4 PZ	Lesion in posterior medial part of PZ on the left (red arrow). Upper image – hypointense lesion in T2W, left lower image – hyperintense lesion in DWI, right lower image – hypointense lesion in ADC map (< 1.5 cm of size).	
PIRADS 5 PZ	Lesion in PZ on the right (red arrows). Images on the left – hypointense lesion in T2W images, with signs of periprostatic fat infiltration, in the middle part – hyperintense lesion in DWI and on the right – hypointense lesion in ADC map (> 1.5 cm of size).	

Table 1.7.1. *Continued*

PIRADS	Definition	Representative figure
PIRADS 5 TZ	Lesion in anterior part of TZ on the right (red arrow). Upper images – hypointense lesion in T2W axial and sagital images, lower part: on the left - hyperintense lesion in DWI, on the right - hypointense lesion in ADC map (> 1.5 cm).	

T2W – T2 weighted imaging; MRI – magnetic resonance imaging; DCE – dynamic contrast enhancement; DWI – diffusion weighted imaging; ADC – apparent diffusion coefficient; PZ – peripheral zone; TZ – transition zone.
These MRI pictures were added from Clinic hospital of Barcelona (Barcelona, Spain) PACS server by dr. Carlos Nicolau.

1.8. Genetic urinary testing

Urinary genetic testing has changed the diagnostic pathway for PCa, mainly because of its non-invasive approach to detect csPCa. Two of the most researched urinary biomarkers, Prostate Cancer Antigen 3 (PCA3) and the TMPRSS2:ERG fusion (T:E)**,** are well known for their value in enhancing csPCa diagnostic. PCA3, a prostate-specific non-coding RNA highly overexpressed in prostate tissue and can be quantified in urine. This is particularly effective in reducing false positive results associated with PSA testing. The T:E**,** resulting from the fusion of the androgen-regulated TMPRSS2 gene with the ETS transcription factor ERG, is found in approximately 50% of PCa cases and is associated with tumorigenesis and disease progression. These biomarkers not only improve the detection of PCa but also adds significant value in risk stratification by identifying clinically significant forms of the PCa. Recent studies have showed the value of PCA3 and T:E combination in urinary assays, providing superior accuracy in predicting biopsy outcomes and reducing unnecessary procedures [58, 59]. The combination of PCA3 and T:E has been shown to be applicable to urine samples collected prior to DRE.

However, improved diagnostic performance has been observed with samples collected after the DRE. An example of such a GUT result, which was used in our research, is presented in Fig. 1.8.1 [60].

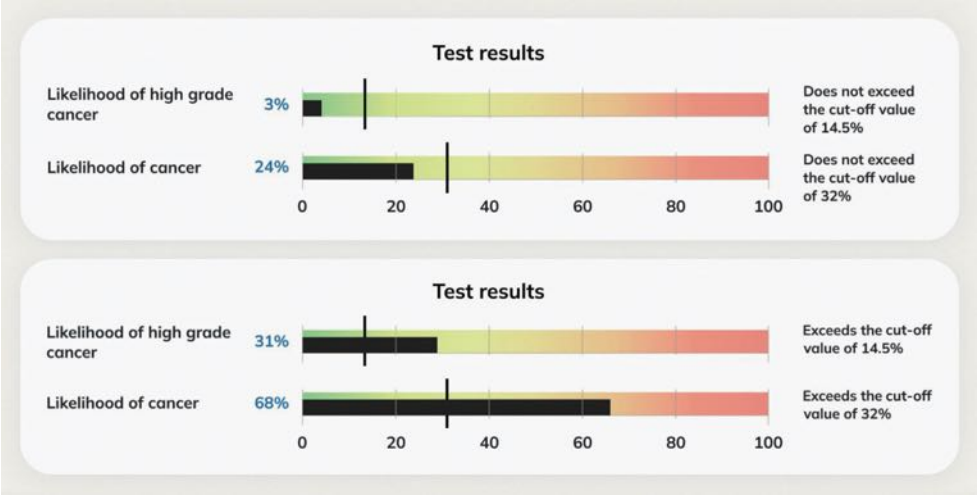


Fig. 1.8.1. *Typical GUT test results provided after post-DRE urine collection and investigation [65]*

PCa risk and csPCa risk are provided in percent (%). This figure is adapted from an article by DIAGNOLITA https://www.diagnolita.lt/en/samples-of-diagnolitas-test-results/

In addition to PCA3 and T:E, other urinary biomarkers are also being explored for their diagnostic potential. For example, the MyProstateScore 2 (MPS2) test, which represents a significant step forward in non-invasive PCa diagnostics. According to Tosoian et al., MPS2 not only incorporates established biomarkers like PCA3 and the T:E fusion but also integrates an additional 15 novel biomarkers, with PSA used for normalization [61]. This expanded biomarker panel enhances the diagnostic precision for csPCa. Moreover, the test is available in two versions, and the post-DRE variant has demonstrated superior diagnostic indicators compared to the non-DRE version. These advances in the MPS2 test may lead to improved risk stratification and a reduction in unnecessary biopsies, ultimately supporting more personalized treatment strategies for patients. Another genetic urinary test – SelectMDx – evaluates the expression of two genes, HOXC6 and DLX1, which are associated with PCa aggressiveness. SelectMDx has shown better results than PCA3 in certain cases, which may be useful in screening programs. However, SelectMDX, as well as MPS2 test and the GUT used in our research, are using post-DRE urine. After performing a DRE, the test sample contains a higher number of tumour-associated genetic material, which can

enhance both the sensitivity and specificity of these assays. However, while DRE itself is useful, there are several disadvantages related to post-DRE based urine biomarker tests. The DRE can be uncomfortable for some patients and usually require additional time before test could be performed, therefore inclusion of these post DRE urinary biomarker tests in screening programs could be limited.

Another promising test, ExoDx Prostate (IntelliScore), analyses exosomal RNA levels of ERG, PCA3, and SPDEF (SAM-pointed domain-containing erythroblast transformation specific transcription factor), offering a non-invasive, pre-DRE risk assessment for csPCa. Studies have demonstrated that ExoDx shows better results than both PSA and PCA3 in predicting Gleason score ≥ 7 cancers, with improved specificity and sensitivity [62–64].

1.9. Prostate cancer risk calculators

Prostate cancer risk calculators have become essential in today's clinical practice. These tools bring together clinical, demographic, and biomarker data to estimate an individual's personalized risk estimate. The prostate cancer crevention trial risk calculator version 2.0 (PCPTRC2) is one of the most popular calculator used for PCa risk prediction. It incorporates factors like age, race, family history, PSA levels, DRE findings, and prior biopsy results. PCPTRC2 not only predicts a patient's overall risk for PCa but also estimates the likelihood of developing a more aggressive, high-grade disease. Research has demonstrated that PCPTRC2 is highly effective in stratifying patients based on their risk. This helps clinicians reduce the number of unnecessary biopsies, especially in men with low predicted risk, without compromising the detection of csPCa [66, 67]. An typical online interface of PCPTRC2 illustrating the estimated probabilities of high-grade cancer, low-grade cancer, and negative biopsy findings based on patient characteristics is showed in Fig. 1.9.1.

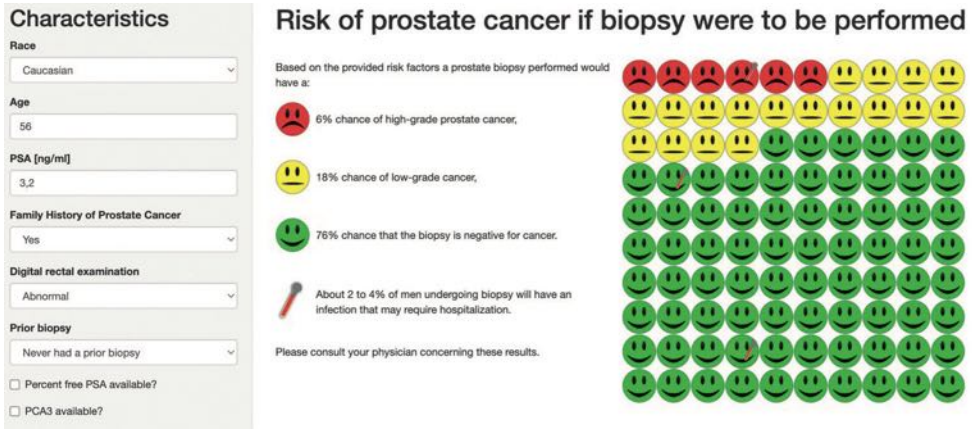


Fig. 1.9.1. *An typical online interface of Prostate Cancer Prevention Trial Risk Calculator version 2.0 (PCPTRC2) illustrating the estimated probabilities of high-grade cancer, low-grade cancer, and negative biopsy findings based on patient characteristics [75]*

This figure is adapted from a PCPTRC2 calculator available online https://riskcalc.org/PCPTRC/

The PCPTRC2 calculator was developed using data from the Prostate Cancer Prevention Trial (PCPT). It uses a multivariable logistic regression model based on data from over 5 500 men who underwent prostate biopsy regardless of PSA levels or DRE findings. This approach minimized verification bias and provided more understanding of prostate cancer risk factors [68]. One of the key advantages of PCPTRC2 is its accessibility and ease of use in clinical settings. It can be applied at easily, without needing specialized tests during routine urological assessment [68]. However, the calculator does have some limitations. The model does not include newest diagnostic tools like mpMRI or molecular biomarkers such as PCA3, PHI, or 4Kscore, which are now increasingly used to improve risk assessment [69]. Another matter is that the model was developed using data from a U.S. based population, which means its accuracy may be lower when applied to patients from other countries or different ethnic backgrounds [70].

When compared to other risk calculators, such as the European randomized study of screening for prostate cancer (ERSPC) risk calculator, PCPTRC2 advantages become clearly seen. The ERSPC calculator mainly relies on PSA levels and DRE findings, and in some versions it also incorporates prostate volume. While both calculators are effective in identifying clinically significant disease, PCPTRC2 increase the effectiveness even further by including race and family history in its assessment. This more comprehensive approach helps address the disparities in PCa incidence and

outcomes seen in different populations. In areas with a mix of racial backgrounds, this additional information can make PCPTRC2 particularly useful for providing a more accurate risk prediction [71].

Other risk calculators, like the SelectMDx and the Prostate Health Index (PHI), take a slightly different approach by including biomarker data in their assessments. For example, SelectMDx evaluates the expression of HOXC6 and DLX1 in urine – two genes that have been linked to more aggressive forms of PCa. PHI combines total PSA, free PSA and proPSA into one risk score. Studies suggest that these biomarker-based test are more sensitive in detecting high-grade cancers compared to traditional models, like PCPTRC2 [64]. However, these advanced tools depend on specialized laboratory procedures, which may not be available or affordable in all clinical settings. In contrast, a basic version PCPTRC2 relies solely on clinical data that is mostly readily available, making it a more practical choice for everyday clinical practice [72].

Researchers are currently exploring how adding biomarkers like PCA3 and T:E to risk calculators can enhance their accuracy. Evidence suggest that combining these biomarkers with traditional clinical data, the overall prediction of csPCa risk improves. For example, including PCA3 and T:E results in PCPTRC2 not only helps to identify men who are more likely to have csPCa but also aids in making better biopsy decisions and minimizing overdiagnosis for less aggressive forms of the disease [73, 74].

1.10. Prostate biopsy and histological tissue examination

Prostate biopsy remains the gold standard for the final diagnosis of prostate cancer, with improving techniques for better diagnostic accuracy. The traditional approach involves systematic transrectal ultrasound (TRUS) – guided biopsy, typically obtaining 10–12 cores from various regions of the prostate [76]. However, systematic sampling alone may miss clinically significant lesions or overdiagnose indolent disease. To address these limitations, the integration of mpMRI into the diagnostic algorithm has become recognized tool in prostate cancer diagnostic. To this day, there are three main types of MRI-targeted biopsy known: cognitive fusion**,** software-based MRI/US fusion, and in-bore MRI-guided biopsy. Cognitive targeted biopsy technique combines mpMRI findings with real-time transrectal ultrasound (TRUS) guidance and relies on the clinician's anatomical expertise to target lesions without the need for software-based fusion systems. Studies have demonstrated that cognitive targeting provides a practical and cost-effective alternative with acceptable diagnostic performance, especially in resource-limited settings [77]. In contrast, software-based MRI/US fusion biopsy uses specialized

platforms to fuse pre-acquired MRI images onto real-time ultrasound, improving lesion targeting accuracy and reducing inter-operator variability [78]. Finally, in-bore MRI-guided biopsy, which is considered the most precise method, involves real-time sampling under direct MRI visualization. Although it offers high spatial resolution and superior lesion targeting, it is less cost-effective, more time-consuming, and limited to centres with advanced imaging techniques [79]. Several studies have demonstrated that combining systematic and targeted biopsies is associated with higher detection rates of csPCa than these methods alone [80]. As evidence and expertise in prostate cancer diagnostic grows, international guidelines – such as the EAU-ESTRO-SIOG 2023 update – now strongly recommend the use of mpMRI before the first biopsy and consider the incorporation of biomarkers and risk calculators to further personalize diagnostic pathways [76].

Regardless of the technique used, next step after prostate biopsy is histopathological evaluation of the prostate tissue. Nowadays, it is commonly supported by digital software tools, which allows for tumour grading according to the Gleason scoring system. The Gleason scoring system is the gold standard in the histopathological assessment of prostate adenocarcinoma, providing critical insights into tumour aggressiveness and guiding clinical management decisions. Developed by Donald Gleason in the 1960s, this system evaluates the architectural patterns of prostate cancer cells in haematoxylin and eosin-stained biopsy specimens, as well as assigning grades based on their resemblance to normal glandular structures [81].

Each tumour is assigned two grades: the primary grade represents the most prevalent histological pattern, and the secondary grade corresponds to the second most common pattern. Grades range from 1 (well-differentiated) to 5 (poorly differentiated), with the sum of these two grades constituting the Gleason score, ranging from 2 to 10. However, in common practice, grades 1 and 2 are rarely used, therefore 6 (3 + 3) is the lowest assigned score [82].

A Gleason score of 6 indicates a well-differentiated, less aggressive tumour, while scores of 8 to 10 are associated with poorly differentiated, highly aggressive cancers. Importantly, a score of 7 can be subdivided into 3 + 4 and 4 + 3, with the latter indicating a higher proportion of the more aggressive pattern 4 and a worse prognosis.

Recognizing the need to improve prognostic accuracy, the International Society of Urological Pathology (ISUP) introduced a revised grading framework in 2014, later adopted by the World Health Organization (WHO) in 2016. This system categorizes PCa into five Grade Groups to better reflect prognostic differences [83]:

- Grade Group 1: Gleason score ≤ 6 (3 + 3);
- Grade Group 2: Gleason score 7 (3 + 4);
- Grade Group 3: Gleason score 7 (4 + 3);
- Grade Group 4: Gleason score 8 (4 + 4, 3 + 5, or 5 + 3);
- Grade Group 5: Gleason scores 9–10 (4 + 5, 5 + 4, or 5 + 5).

This updated classification enhances prognostic accuracy and aids in clinical decision-making by providing a more information for interpretation of tumour aggressiveness. In clinical practice, the Gleason score, along with other parameters such as prostate-specific antigen (PSA) levels and tumour staging, plays a pivotal role in risk stratification and treatment planning for PCa patients [84].

1.11. The role of multidisciplinary team in management of patients with prostate cancer

The management of PCa in today's clinical practice often means bringing together a team of specialists – urologists, oncologists, radiologists, pathologists, and other dedicated specialists – to work as a multidisciplinary team (MDT) unit. This collaborative approach ensures that the different expert opinions make an impact in each treatment decision and ultimately lead to better clinical outcomes and increased patient satisfaction [85].

Research shows that the involvement of MDT enhances adherence to clinical guidelines and often leads to more optimized treatment pathways. For instance, a systematic review revealed that MDT discussions tend to result in more accurate cancer staging and more suitable treatment choices, which eventually improve patient prognoses [86]. MDTs also play a crucial role in addressing the complex needs of PCa patients, including psychosocial support, management treatments side effects, and incorporating patient preferences into the care plan [87]. Another benefit of the MDT approach is the increase use of advanced diagnostic and treatment methods. Integrating tools like mpMRI into MDT discussions has proven to enhance the accuracy of PCa diagnosis and staging. This allows for more tailored treatment strategies that match the specific needs of each patient [88]. While coordinating a group of specialists and managing the necessary resources can be challenging, the MDT model remains a cornerstone of today's PCa management. It continues

to evolve by incorporating new evidence in research and technologies to optimize patient care [89].

1.12. Further diagnostic strategies for prostate cancer

In recent years, further more sophisticated diagnostic strategies for PCa have improved significantly, aiming to improve the detection of csPCa. Beyond the widely use of mpMRI and its implementation into international guidelines, several novel approaches have emerged. Among these are advanced imaging modalities such as prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT), which has demonstrated superior sensitivity and specificity in detecting both primary and recurrent prostate cancer, especially when combined with mpMRI [90, 91]. PSMA PET/CT is a highly sensitive imaging technique that uses a radiotracer targeting PSMA, a cell surface protein overexpressed in most prostate cancer cells. After intravenous injection of the radiotracer – commonly 68Ga-PSMA-11 or 18F-DCFPyL – the PET scan detects areas of high radiotracer uptake, which typically correspond to cancerous lesions. Alongside, CT provides detailed anatomical localization. PSMA PET/CT has proven particularly effective not only in identifying primary tumours but also in detecting lymph node involvement and distant metastases, even at low PSA levels. This hybrid approach enhances lesion detection, guides targeted biopsies, and supports more precise staging and treatment planning.

Furthermore, artificial intelligence (AI) and machine learning models are being increasingly applied to imaging data analysing. There are growing evidence that AI-assisted diagnostics can match or even exceed human performance in lesion detection and classification [92]. The integration of these new diagnostic tools into everyday clinical practice offers the potential for a more accurate PCa detection. AI tools can also contribute to workflow efficiency by streamlining image analysis, prioritizing high-risk cases, and supporting clinical decision-making suing integrated predictive models. Some platforms even combine imaging data with clinical variables (e.g., PSA levels, biopsy history) to offer real-time risk assessments or biopsy recommendations [93]. These AI based tools are particularly promising for enhancing precision medicine approaches in PCa management and their integration marks an important step forward and represents a critical area of ongoing research and development.

2. METHODS

2.1. Ethics

The investigation was approved by the regional Bioethical Commission, Decision no. BE-2-116, dated 2020-09-28) (Appendix 1). All patients signed an informed consent form before inclusion.

2.2. Study population and design

In this single-centre prospective study, 246 patients were consecutively enrolled between January 2022 and August 2024 at the Hospital of Lithuanian University of Health Sciences Kauno klinikos in Kaunas, Lithuania. The study population consisted of men scheduled for an initial prostate biopsy due to an elevated total PSA level, defined in this study as greater than 2 ng/mL but less than 25 ng/mL, or the presence of abnormal findings on DRE.

Of the initially recruited cohort, two patients ultimately did not undergo prostate biopsy for personal reasons. An additional seven participants were excluded due to unsuccessful purification of urinary test samples. Moreover, 29 patients did not meet the age criteria, as the PCPTRC2 is designed to estimate the risk of csPCa only in individuals aged 55 to 90 years, in accordance with the tool's established guidelines. After applying these exclusion criteria, the final study population comprised 208 men who subsequently underwent genetic urinary testing following DRE, as well as mpMRI (Fig. 2.2.1).

The genetic urine testing protocol employed in this study involved the detection and quantification of the urinary biomarkers PCA3 and T:E using a validated molecular assay. This process required the collection of first-void urine samples immediately following a DRE, followed by sample stabilization and biomarker quantification through advanced molecular diagnostic techniques.

Following these diagnostic assessments, patients with mpMRI-identified lesions categorized as PIRADS 3, 4, or 5 underwent both targeted cognitive fusion ultrasound (US)-guided prostate biopsy and systematic prostate biopsy. In cases where mpMRI findings were classified as PIRADS 1 or 2, only systematic US-guided biopsy was performed, as per the study protocol.

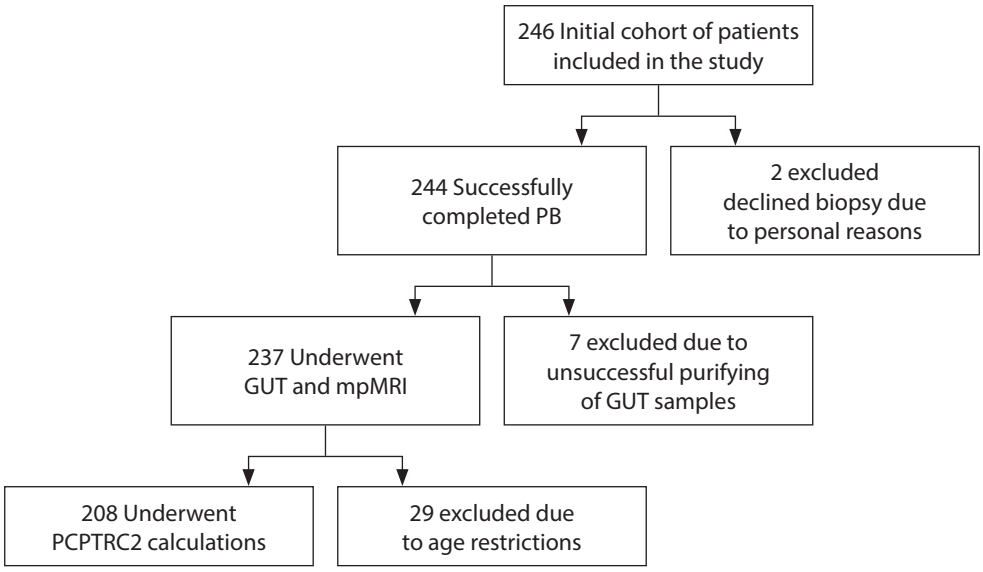


Fig. 2.2.1. *Study cohort flowchart: patient selection and data processing*

PB – prostate biopsy; GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0.

After histological tissues examination further assessment depended on the presence or absence of csPCa. If csPCa was detected patients received suitable treatment, if csPCa was not detected patients were referred to active surveillance. All patients meeting the initial study criteria completed a survey about disease-related symptoms, medications, past illnesses, interventions, and family history. The information in the survey was coded to ensure anonymity. Patients' diagnostic algorithm is showed in Fig. 2.2.2.

This thesis benefited from the use of AI-assisted tools, including OpenAI's ChatGPT, which was used to improve clarity and structure in the early drafts [94]. While all ideas, analysis, and original research presented in this thesis are original, AI tools were used to assist with literature search and language style. Any suggestions generated by the AI were carefully reviewed to ensure they met academic standards and maintained the integrity of the work [95].

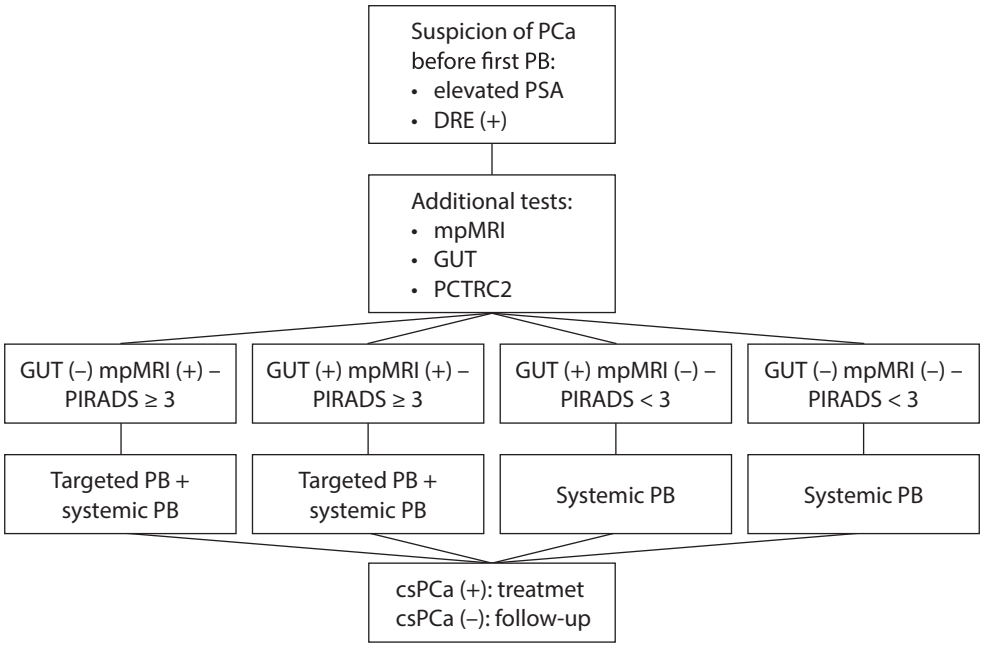


Fig. 2.2.2. *Patients' diagnostic algorithm flow chart*

PCa – prostate cancer; mpMRI – multiparametric magnetic resonance imaging; GUT – genetic urinary test; PIRADS – Prostate – Imaging Reporting and Data System v.2.1; PB – prostate biopsy; csPCa – clinically significant prostate cancer.

2.3. Inclusion end exclusion criteria of the study population

The inclusion criteria were as follows:

- Male patients presenting with suspected prostate pathology during their first-ever urological examination were included in the study:
  1. Following the evaluation of clinical parameters (PSA level > 2 and < 25, DRE suspicion), the urologist has recommended a prostate biopsy.
  2. The patient has never undergone a prostate biopsy before.
- Additionally, general health criteria were assessed:
  3. The patient is capable of cooperating during the study.
  4. The individual is 18 years or older and has agreed to participate in the biomedical study (has signed the informed consent form).

The exclusion criteria were as follows:

1. Contraindications for undergoing MRI, such as severe claustrophobia, allergy to contrast agents, or incompatible metallic implants in the body.
2. Severe chronic illnesses (metastatic cancer, severe cardiovascular disease, dementia).
3. Prior history of prostate biopsy.

2.4. Diagnostic methods

2.4.1. Prostate mpMRI examination

All patients underwent prostate mpMRI with an intravenous contrast agent. The mpMRI's were performed based on clinical availability using either a 1.5 Tesla or 3 Tesla magnetic resonance imaging scanner (manufactured by "Siemens" or "Philips"), and the images were stored digitally for comparative analysis. The applied PCa mpMRI protocol included pre-examination fasting for 4–6 hours and micro-enema before MRI scanning in order to minimize sensitivity from air in the bowel. Upon arrival to the study, the patient filled out standard MRI consent form (Appendix 2). The person was informed about the progress of the investigation. mpMRI was performed using a standardized protocol that included T1, T2, DWI and DCE (Table 2.4.1). All patients were scanned in three different planes. The sequences planning of mpMRI of the prostate was identical in all cases. Sagittal sequence was oriented perpendicular to the anal canal, coronal sequence – parallel to the anal canal and axial sequence – cantered on the prostate, ensuring coverage of both hips (Fig. 2.4.1.1).

Table 2.4.1.1. *The protocol of mpMRI for the detection and evaluation of prostate cancer before prostate biopsy*

Multiparametric MRI for prostate
Patient fasted overnight
Micro-enema before mpMRI
Patient placed in the supine position in an MR scanner
MRI scan: T2 sag T2 ax – perpendicular to the prostate base T2 cor – perpendicular to the axial images T2 DWI/ADC – the same as T2W inclination, high b value (≥ 800 mm^2/s) T1 ax + contrast – the same as T2W inclination

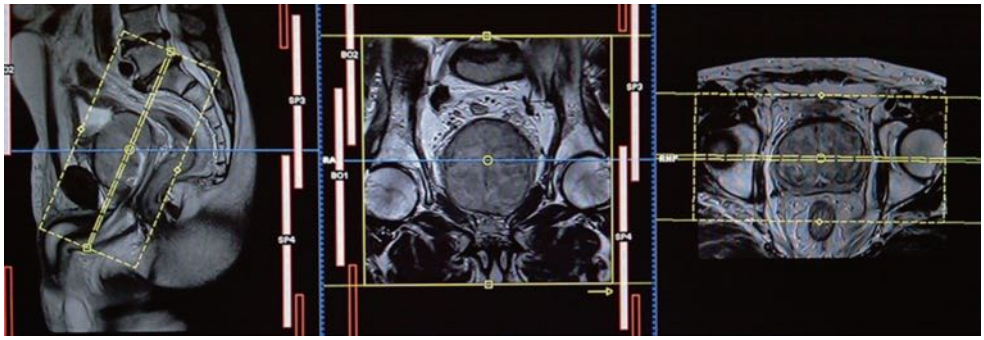


Fig. 2.4.1.1. *The sequences planning of mpPMRI of the prostate*

Left image – sagittal sequence, middle image – coronal sequence, right image – axial sequence.
These MRI pictures were added from Hospital of Lithuanian University of Health Sciences Kauno klinikos approved prostate mpMRI diagnostic protocol, prepared by Jūratė Kemėšienė.

2.4.1.1. Diffusion imaging and ADC mapping quantification in prostate mpMRI

Typical mpMRI protocol parameters ar 1.5 T and 3 T are summarized in Tables 2.4.1.1.1 and 2.4.1.1.2, respectively. During the diffusion (DWI) sequence, the software automatically generated an ADC (apparent diffusion coefficient) map, from which numerical diffusion values were measured. Radiologist manually marked the regions of interest (ROIs) on consecutive ADC map tumour slices (b value = 1000 mm²/s). The average ADC of the rectal mass was determined by selecting three different regions within the tumour across the images. These regions were identified as restricted areas on the ADC map that aligned with their isotropic DWI, enabling the calculation the average ADC value. T2W sequences were utilized to identify the primary tumour and lymph nodes. Each ROI was defined according to the maximum cross-sectional area of the tumour on the ADC map, effectively minimizing the T2W shine-through effect.

Table 2.4.1.1.1. *Typical mpMRI protocol parameters at 1.5 T*

Parameter	T1 ax	T2 sag	T2 cor	T2 ax	DWI ax	DCE ax
TR (ms)	5500	6700	6500	6400	3700	4.36
TE (ms)	50	108	146	146	73	1.76
Flip angle (°)	130	160	160	160	–	12
Freq FOV (mm; phase FOV)	200	200	200	200	200	260
Matrix size	256	320	320	320	100	192
# Slices/thickness (mm)	19/3	19 /3	15/3	19/3	19/3	22/3
Gap (%)	10	20	20	20	20	–
Voxel size (mm)	0.6 × 0.6 × 3	0.6 × 0.6 × 3	0.6 × 0.6 × 3	0.6 × 0.6 × 3	2 × 2 × 3	1.4 × 1.4 × 3
Averages/NEX	5	2	2	2	b50 – 4 b400 – 7 b800 – 18	–
Phase enc dir	R ≫ L	H ≫ F	R ≫ L	R ≫ L	R ≫ L	R ≫ L
≅ BW (Hz/Px)	200	200	200	200	1428	300
b values (s/mm^2; directions)	–	–	–	–	b50 b400 b800 b1400 (calc.)	–
Measurements	1	1	1	1	1	40
≅ Time	3:40	2:22	3:07	3:26	4:33	3:10

TR – repetition time; TE – echo time; FOV – field of view; NEX – number of excitations; BW – band width; DWI – diffusion-weighted imaging; DCE – dynamic contrast enhanced imaging.

Table 2.4.1.1.2. *Typical mpMRI protocol parameters at 3 T*

Parameter	T1 ax	T2 sag	T2 cor	T2 ax	DWI ax	DCE ax
TR (ms)	4000	5590	5000	5660	3200	3.62
TE (ms)	15	101	101	104	63	1.27
Flip angle (°)	130	160	160	160	–	14
Freq FOV (mm; phase FOV)	180	180	192	192	256	192
Matrix size	256	320	320	320	128	224
# Slices/thickness(mm)	19/3	19/3	15/3	19/3	19/3	26/3
Gap (%)	10	20	20	20	20	–
Voxel size (mm)	0.6 × 0.6 × 3	0.6 × 0.6 × 3	0.6 × 0.6 × 3	0.6 × 0.6 × 3	2 × 2 × 3	0.9 × 0.9 × 3
Averages/NEX	5	2	2	2	b50 – 3 b400 – 8 b800 – 12	–
Phase enc dir	R ≫ L	H ≫ F	R ≫ L	R ≫ L	R ≫ L	R ≫ L
≅ BW (Hz/Px)	200	200	200	200	1502	490
b values (s/mm^2; directions)	–	–	–	–	b50 b400 b 800 b1400 (calc.)	–
Measurements	1	1	1	1	1	45
≅ Time	2:40	2:31	2:15	2:33	4:50	2:50

TR – repetition time; TE – echo time; FOV – field of view; NEX – number of excitations; BW – band width; DWI – diffusion-weighted imaging; DCE – dynamic contrast enhanced imaging.

2.4.1.2. Contrast protocol and diagnostic consensus in prostate mpMRI interpretation

A single dose of (0.2 mg/kg) IV gadolinium-based contrast media (Magnevist Bayer Schering Pharma, Berlin Germany) was injected into an arm vein at 2 ml/s. One radiology technologist conducted the examination, and a radiologist supervised the procedure. MRI images were evaluated on the picture archiving and communication system (PACS, Syngovia, Siemens Healthineers) workstation by 2 radiologists with 7-year and 4-year experience in PCa imaging. A final diagnosis was made after the consensus between 2 radiologists was achieved. All changes in the prostate were described using the international PIRADS v2.1. classification of prostate focal lesions. Visible PIRADS 3, 4 and 5 lesions were marked in typical prostate map (Appendix 3) to guide prostate biopsy.

2.4.2. Genetic urinary biomarkers testing

The GUT used in our research (© Diagnolita) employed RT-qPCR to quantify two RNA biomarkers, PCA3 and T:E, in the initial fraction of urine, with normalization against prostate-specific PSA mRNA. Urine collection and immediate stabilization were achieved using Colli-Pee 20 mL devices (Novosanis) prefilled with 10 mL of proprietary stabilization medium (© Diagnolita). Samples were transferred to the Diagnolita laboratory for analysis. RNA was extracted from whole urine, capturing RNA from both exosomes and cells. The quantification process involved reverse transcription (RT), followed by pre-amplification of the target sequences and quantitative PCR (qPCR). Biomarker quantities were combined with clinical parameters such as PSA density and patient's age. The test results allowed for predicting the likelihood of a positive prostate biopsy and assessing the risk of csPCa. The GUT score was positive or negative depending on whether the threshold of the test was exceeded. Originally, the threshold of the GUT was set to achieve a sensitivity of nearly 90% based solely on the results of systematic biopsy [60, 96].

The post-DRE urine test was conducted at the laboratory of JSC "Diagnolita", which holds a license from the State Accreditation Service for Health Care Activities under the Ministry of Health (License No. 4013). JSC "Diagnolita" laboratory is accredited according to the recognized quality control standard LST EN ISO 15189:2023. JSC "Diagnolita" received coded urine samples, and no personal information about the patients was disclosed.

2.4.3. Prostate risk calculator

In this study three different PCPTRC2 versions were used to evaluate the risk of csPCa in patient cohort [75]. Firstly, a basic version of PCPTRC2 was employed. This version of the calculator involved several clinical and demographic variables known to influence PCa risk, including patient's race, age, PSA level (ng/mL), family history of PCa, DRE result, and prior biopsy. Using these parameters, the calculator generated an individualized probability estimate of high-grade prostate cancer, which was then used for all subsequent calculations. As there was no predefined cut-off for PCPTRC2 we chose the cut-off of 6% to match the sensitivity of mpMRI. This allowed us to compare saved biopsy numbers at a similar sensitivity level.

Later, the study incorporated updated PCPTRC2 models that integrate urinary biomarkers to improve risk prediction accuracy. The PCPTRC2 models included PCA3 alone or in combination with T:E. Originally, PCPTRC2 integrated biomarkers by calculating their values based on copy numbers determined through the MyProstateScore 2 (MPS2) test. The MPS2 test combines serum PSA, urine T:E, and PCA3 to predict a patient's risk for having PCa detected by standard biopsy after DRE. [97] In this study, instead of the MPS2 test urinary biomarker values of PCA3 and the PCA3 and T:E combination, obtained through the Diagnolita urinary test, were incorporated in PCTRC2 [60, 98].

The output of PCPTRC2 presents estimated probabilities for each biopsy outcome category. Therefore, clinicians can interpret these probabilities to determine the necessity of a prostate biopsy. For instance, a higher estimated risk of high-grade cancer may prompt a recommendation for biopsy, while a lower risk might support continued monitoring. By providing individualized risk assessments, it supports informed discussions about the potential benefits and harms of proceeding with a prostate biopsy [68].

2.4.4. Prostate biopsy

All patients underwent a transrectal ultrasound-guided core needle biopsy of the prostate, performed in accordance with standardized urological practice guidelines and a protocol approved at the Urology Clinic of Hospital of Lithuanian University of Health Sciences Kauno klinikos. Prior to the procedure, patients received a single oral dose of Fosfomycin trometamol 3 g (powder for oral solution) approximately three hours in advance. This antibiotic prophylaxis has demonstrated efficacy in reducing post-biopsy infectious complications and is widely recommended in current urological protocols [99].

Patients were instructed to void the bladder and ensure bowel evacuation prior to arrival. Upon arrival, the purpose, procedure details and potential risks of the biopsy were discussed in detail. Patients were given the opportunity to ask questions, which were answered by the attending physician. Informed consent was then obtained by signing a standardized consent form titled “Transrektalinė stulpinė prostatos biopsija” (“Transrectal Core Prostate Biopsy”) (Appendix 4).

The cognitive targeted prostate biopsy technique was a method used to perform prostate biopsies. This type of biopsy is performed by combining cognitive fusion with traditional ultrasound guidance. It involves the integration of information from pre-procedural imaging, such as mpMRI, with real-time US during the biopsy procedure. This approach enables targeted and efficient sampling of suspicious areas while minimizing dependence on automated systems, which may not always be accessible in standard clinical practice.

The biopsy was performed with the patient positioned in the left lateral decubitus position. Local anaesthesia was administered via rectal application of Cathejell L gel, a combination of lidocaine hydrochloride (local anaesthetic) and chlorhexidine dihydrochloride (antiseptic), to minimize patient discomfort during probe insertion and tissue sampling. A transrectal ultrasound (TRUS) probe was inserted through the rectum, and real-time imaging was used to assess the prostate gland. Prostate volume and the volume of the transitional zone were measured using standard ellipsoid volume calculation formulas. This anatomical data supported targeted and systematic sampling.

Tissue samples were obtained using an 18-gauge core biopsy needle. Each core measured approximately 15–22 mm in length. Two targeted biopsy cores were obtained from lesions with a PIRADS score of 3 or higher, as identified on pre-biopsy mpMRI. These lesions were marked on a standardized prostate sector map (Appendix 3) prior to the procedure. In addition to targeted sampling, a systematic 10-core biopsy protocol was performed. Five cores were obtained from each of the right and left prostatic lobes, distributed evenly from the apex to the base, to ensure comprehensive sampling and reduce the likelihood of underdiagnosing clinically significant prostate cancer.

Following the procedure, patients were monitored briefly and discharged with instructions for post-biopsy care. A second single dose of Fosfomycin 3 g was administered 24 hours post-biopsy, consistent with antimicrobial prophylaxis recommendations. No further antibiotic therapy was prescribed, in line with evidence of infectious complications prevention in low-risk patients [100].

Following the biopsy procedure, the obtained prostate tissue samples were fixed in formalin to preserve cellular structure and prevent degradation. The samples were then embedded in paraffin, allowing for stable sectioning and microscopic analysis. Tissue was sectioned, stained, and prepared for pathological evaluation. Special software was used to assess the histological origin and grade of cellular changes. The Gleason score, a well-established prognostic marker, was used to evaluate the degree of tumour differentiation and to categorize the aggressiveness of the prostate cancer.

2.5. Statistical analysis

All calculations were performed using R v.4.3.2. A P-value ≤ 0.05 was considered indicative of statistical significance. The normality of the data was estimated with Shapiro-Wilk test. The comparisons of continuous parameter values between groups were performed using a two-sided Student's t-test for normally distributed data and a two-sided Wilcoxon rank sum test otherwise. Analogously, categorical parameter counts were compared with two-sided Fisher's exact test.

Descriptive statistics were used to describe patients' characteristics. The GUT findings were categorized as positive or negative depending on whether the predicted csPCa risk exceeded the predefined threshold. The mpMRI results were considered positive if reported as PIRADS 3–5 and negative if PIRADS 1–2. To evaluate the performance of using both tests together, positive cases required at least one positive result from either GUT or mpMRI.

Combined systematic and targeted biopsy results were used to allocate a patient to clinically significant (GS $\geq$ 7) prostate cancer (csPCa) or non-clinically significant prostate cancer (non-csPCa) groups. The highest Gleason score identified by either the systematic or targeted biopsy was used for the assignment. All calculated sensitivity, specificity and, missed csPCa, saved biopsies, and saved unnecessary biopsies numbers were based on the aforementioned grouping of patients. 95% confidence intervals (CI) for sensitivity and specificity were calculated with an exact binomial test using binom.test function from R stats package. The sensitivity and specificity values were contrasted with the McNemar test using sesp.mcnemar function from R package DTComPair v.1.2.2. The comparisons were made only among complete cases for both compared models.

To assess the predictive capability of different PCPTRC2 models, we calculated the area under the receiver operating characteristic curve (AUC) for three versions: the original PCPTRC2, the updated version incorporating PCA3, and the model including both PCA3 and T:E. To compare AUC

values, a one-sided DeLong test was performed, with the alternative hypothesis stating that the AUC values of PCPTRC2 models incorporating one or both biomarkers would be higher than the PCPTRC2 version without biomarkers. The approach was supported by existing literature demonstrating biomarker-enhanced AUC performance [73, 101]. Given the importance of high sensitivity in diagnosing csPCa, we examined the portion of the ROC curve ranging from 75% to 100% sensitivity, aligning with methodologies from previous studies [102]. The AUC values, partial AUC values, their 95% confidence intervals, and comparison test results were computed using functions from the R package pROC v.1.18.5.

3. RESULTS

3.1. Characteristics of the study population

3.1.1. Summary of patient characteristics, diagnostic test results, and biopsy outcomes in the study cohort

A total of 208 men were included in the analysis, with patient characteristics, mpMRI, GUT, PCPTRC2, and biopsy outcomes summarized in Table 3.1.1.1. The median age of the participants was 63 years, with a range of 43 to 87 years, and the mean PSA level was 6.3 ng/mL and PSA density averaged 0.15 ng/mL. The mean prostate volume was 51.2 and digital rectal examination (DRE) was suspicious in 51.4% of cases. A positive family history of prostate cancer was reported in 13.5%. According to GUT scoring, 67.8% of patients (141 cases) were classified as GUT positive, 28.8% (60 cases) as GUT negative, and in 3.4% (7 cases) GUT evaluation was not available. The mean predicted risk for clinically significant prostate cancer (csPCa) based on the GUT model was 26.1%. Multiparametric MRI (mpMRI) findings revealed that 81.7% of patients (170 cases) had a PIRADS score of ≥ 3, while 18.3% (38 cases) had a PIRADS score of < 3. The mean predicted csPCa risk according to the PRCTPRC2 model was 11.6%. Biopsy outcomes demonstrated that 53.8% of patients (112 cases) had clinically significant prostate cancer (Gleason score ≥ 7), while 46.2% (96 cases) had negative findings or Gleason score < 7. Combined GUT and mpMRI analysis showed that 63.2% of patients (127 cases) were GUT positive and mpMRI positive, 10.9% (22 cases) were GUT negative and mpMRI negative, 7% (14 cases) were GUT positive but mpMRI negative, and 18.9% (38 cases) were GUT negative but mpMRI positive (Figs. 3.1.1.1 and 3.1.1.2).

Table 3.1.1.1. *Patients' characteristics*

Parameter		**Value**
Number of cases, n		208
Age (years)	Mean ± SD	62.9 ± 7.2
	Median	63
	Range	43–87
Total PSA (ng/mL)	Mean ± SD	6.3 ± 2.9
	Median	5.5
	Range	2.7–19.1

Table 3.1.1.1. *Continued*

Parameter		Value
PSA density (ng/mL/mL)	Mean ± SD	0.15 ± 0.11
	Median	0.12
	Range	0.04–0.79
Prostate volume	Mean ± SD	51.2 ± 22.1
	Median	44.8
	Range	13.5–129.1
DRE suspicious, n (%)	Yes	107 (51.4)
	No	101 (48.6)
Family history, n (%)	Yes	28 (13.5)
	No	180 (86.5)
GUT score, n (%)	Negative	60 (28.8)
	Positive	141 (67.8)
	NA	7 (3.4)
GUT predicted risk for csPCa (%)	Mean ± SD	26.1 ± 18.7
	Median	23
	Range	1–86.9
mpMRI, n (%)	PIRADS < 3	38 (18.3)
	PIRADS ≥ 3	170 (81.7)
PRCTPRC2 csPCa risk (%)	Mean ± SD	11.6 ± 5.9
	Median	10
	Range	4–41
Biopsy outcomes, n (%)	Negative and GS < 7	96 (46.2)
	GS ≥ 7	112 (53.8)
GUT score and mpMRI PIRADS score, n (%)	GUT positive, mpMRI positive	127 (63.2)
	GUT negative, mpMRI negative	22 (10.9)
	GUT positive, mpMRI negative	14 (7)
	GUT negative, mpMRI positive	38 (18.9)

n – number; SD – standard deviation; PSA – prostate-specific antigen; PSAD – PSA density; DRE – digital rectal examination; GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PIRADS – prostate imaging reporting and data system v.2.1; PCPTRC2 –prostate cancer prevention trial risk calculator version 2.0.

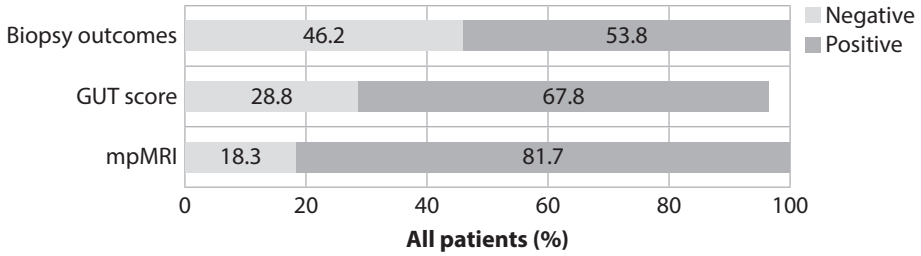


Fig. 3.1.1.1. *Comparison of positive and negative results across biopsy, GUT score, and mpMRI findings*

Biopsy results were classified as negative when histopathological findings were negative or GS < 7, positive – when GS ≥ 7. mpMRI was considered negative for PIRADS scores < 3, positive – for PIRADS scores ≥ 3.
GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; GS – Gleason score; PIRADS – prostate imaging reporting and data system v2.1.

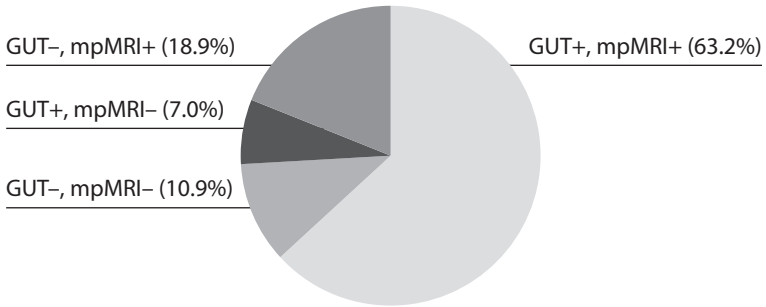


Fig. 3.1.1.2. *Distribution of combined GUT and mpMRI findings among all patients*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging.

3.1.2. Patient cohort characteristics and comparative analysis of diagnostic markers in prostate cancer subgroups

Out of the total patients cohort, 165 patients (79.3%) were diagnosed with PCa, including 112 cases (53.8%) of csPCa and 53 cases (25.5%) of cisPCa, while 43 patients (20.7%) showed no evidence of malignancy. The median age across the cohort was 63 years, ranging from 43 to 87 years, and the mean PSA level was 6.3 ng/mL. Total PSA levels differed significantly between two groups, with a higher mean in csPCa patients (6.7 ng/mL) compared to the negative PCa group (5.3 ng/mL), reaching statistical significance ($P = 0.015$). PSA density also showed a strong association with clinically significant disease, with csPCa patients presenting a higher mean value (0.16 ng/mL/mL) compared to 0.11 ng/mL/mL in the negative PCa group ($P < 0.001$). A positive GUT score was observed in 82.1% of csPCa

cases (92 out of 112), significantly more frequent than in the negative PCa group and cisPCa groups, where only 55.8% and 45.2% had a positive GUT score, respectively ($P < 0.001$). Similarly, the GUT model's predicted risk for csPCa was markedly higher in patients with csPCa, with a median risk of 28.7%, compared to 5.7% and 23.4% in the negative PCa group and cisPCa group, respectively ($P < 0.001$). mpMRI findings aligned with this pattern, as 93.8% of csPCa patients had a PIRADS score of 3 or greater, significantly more than the 60.5% observed in the negative PCa group and 73.6% observed in cisPCa group ($P < 0.001$). When combining the GUT score with mpMRI findings, 76.8% of csPCa patients were positive on both, while only 0.9% were negative on both, further supporting the synergistic diagnostic value of these tools ($P < 0.001$). In contrast, 1.9% of cisPCa patients in the negative group were negative on both assessments and 11.5% of negative PCa patients were positive in both tests – GUT and mpMRI (Fig. 3.1.2.1). The distribution of patients based on biopsy-confirmed histopathological outcomes is detailed in Table 3.1.2.1.

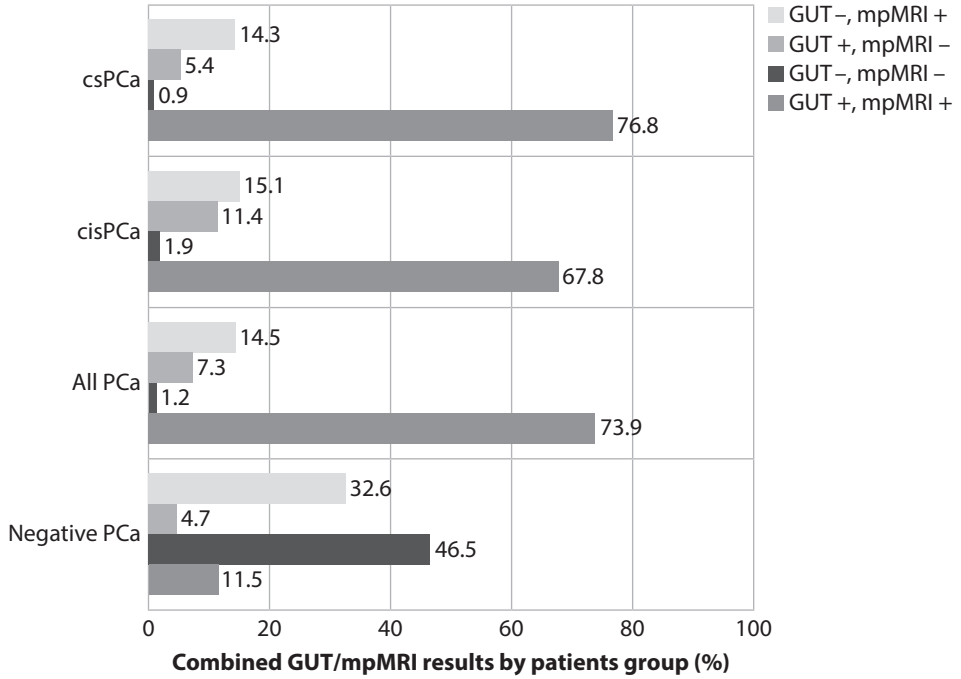


Fig. 3.1.2.1. *Distribution of combined GUT and mpMRI findings across histopathological groups*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; csPCa – clinically significant prostate cancer, cisPCa – clinically insignificant prostate cancer.

Table 3.1.2.1. *Stratification of patients' characteristics on the basis of prostatic biopsy results*

Parameter		**Negative PCa**	**All PCa**	**cisPCa**	**csPCa**	***P*-value**
Number of cases, n (%)		43 (20.7)	165 (79.3)	53 (25.5)	112 (53.8)	
Age (years)	Mean ± SD	61 ± 7.2	62.3 ± 7.2	62.3 ± 7.3	63.4 ± 7.1	
	Median	62	63	63	63	**0.245**
	Range	43–73	50–87	51–82	50–87	
Total PSA (ng/mL)	Mean ± SD	**5.3 ± 1.5**	6.2 ± 2.8	6.5 ± 2.6	**6.7 ± 3.0**	
	Median	5.3	5.6	5.6	5.7	**0.015**
	Range	3.2–10.9	2.7–18.4	2.9–18.1	3–19.1	
PSA density (ng/mL/mL)	Mean ± SD	**0.11 ± 0.09**	0.15 ± 0.11	0.14 ± 0.11	**0.16 ± 0.11**	
	Median	0.09	0.13	0.11	0.14	**< 0.001**
	Range	0.04–0.52	0.04–0.79	0.04–0.76	0.05–0.79	
GUT score, n (%)	Negative	18 (41.9)	43 (26.3)	26 (49.5)	17 (15,2)	
	Positive	**24 (55.8)**	116 (70.3)	**24 (45.3)**	**92 (82.1)**	**< 0.001**
	Not evaluated	1 (2.3)	6 (3.7)	3 (5.7)	3 (2.7)	

Table 3.1.2.1. *Continued*

Parameter		Negative PCa	All PCa	cisPCa	csPCa	*P*-value
GUT predicted risk for csPCa (%)	Mean ± SD	**9.2 ± 9.1**	24.9 ± 19.4	**27.8 ± 18.1**	**30.8 ± 17.5**	**< 0.001**
	Median	5.7	21.6	23.4	28.7	
	Range	1–35.4	1–86.9	1–72.8	3.3–86.9	
mpMRI PIRADS score, n (%)	PIRADS < 3	16 (37.2)	21 (12.7)	14 (28.2)	7 (6.2)	**< 0.001**
	PIRADS ≥ 3	**26 (60.5)**	144 (87.3)	**39 (73.6)**	**105 (93.8)**	
GUT score and mpMRI PIRADS score	GUT positive, mpMRI positive	**5 (11.5)**	122 (73.9)	**36 (67.8)**	**86 (76.8)**	**< 0.001**
	GUT negative, mpMRI negative	**20 (46.5)**	2 (1.2)	1 (1.9)	**1 (0.9)**	
	GUT positive, mpMRI negative	**2 (4.7)**	12 (7.3)	6 (11.4)	**6 (5.4)**	
	GUT negative, mpMRI positive	**14 (32.6)**	24 (14.5)	**8 (15.1)**	**16 (14.3)**	
	Not evaluated	2 (4.7)	5 (3.1)	2 (3.8)	3 (2.6)	

Statistically significant differences are highlighted in bold.
n – number; SD – standard deviation; PSA – prostate-specific antigen; PSAD – PSA density; DRE – digital rectal examination; GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PIRADS –prostate imaging reporting and data system v.2.0; PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; cisPCa – clinically insignificant prostate cancer.

3.1.3. Stratification of patients by clinically significant prostate cancer status and comparative analysis of diagnostic parameters

For further calculations patients were stratified into two groups: clinically significant prostate cancer (csPCa) and non-clinically significant prostate cancer (non-csPCa), based on histopathological findings. csPCa was defined as the presence of tumours with a Gleason score of 7 or higher, corresponding to ISUP Grade Group 2 or greater. Non-csPCa included tumors with a Gleason score of 6 (ISUP Grade Group 1) as well as cases where no malignancy was detected upon biopsy. Total PSA levels were significantly higher in the csPCa group (6.7 ng/mL) compared to the non-csPCa group (5.8 ng/mL, $P = 0.013$). PSA density was also significantly greater in csPCa patients (0.16 ng/mL/mL) than in non-csPCa patients (0.13 ± 0.11 ng/mL/mL, $P < 0.001$). A positive GUT score was observed in a significantly higher proportion of csPCa cases – 92 out of 112 (82.1%) – compared to 49 out of 96 (51%) in the non-csPCa group ($P < 0.001$). Additionally, the GUT model's predicted risk for csPCa was notably higher in the csPCa group, with a median value of 28.7% *vs.* 12.8% in the non-csPCa group ($P < 0.001$) and the PCPTRC2 predicted risk for csPCa was also significantly higher in the csPCa group, with median value of 10% *vs.* 11% in non-csPCa group ($P = 0.031$) (Fig. 3.1.3.1). A positive mpMRI result, defined as PIRADS ≥ 3, was reported in 93.8% of csPCa cases, significantly more frequent than the 67.7% seen in the non-csPCa group. Combined analysis of GUT scores and mpMRI findings indicated that the majority of csPCa patients (78.9%) were GUT positive and mpMRI positive, significantly more than in the non-csPCa group (44.6%), while GUT negative and mpMRI negative findings were significantly more common among non-csPCa patients (22.8% *vs.* 0.9%, $P < 0.001$) (Fig. 3.1.3.2). The distribution of patients based on biopsy-confirmed histopathological outcomes (csPCa *vs.* non-csPCa) is presented in Table 3.1.3.1. Seven cases were referred as PIRADS 3 lesions and the same stratification of subjects is reported in Table 3.1.3.2.

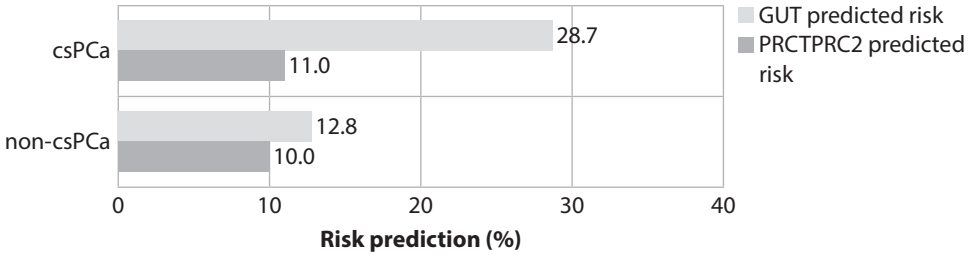


Fig. 3.1.3.1. *Comparison of GUT and PRCT PRC2 predicted risk in non-csPCa vs. csPCa*

GUT – genetic urinary test; PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

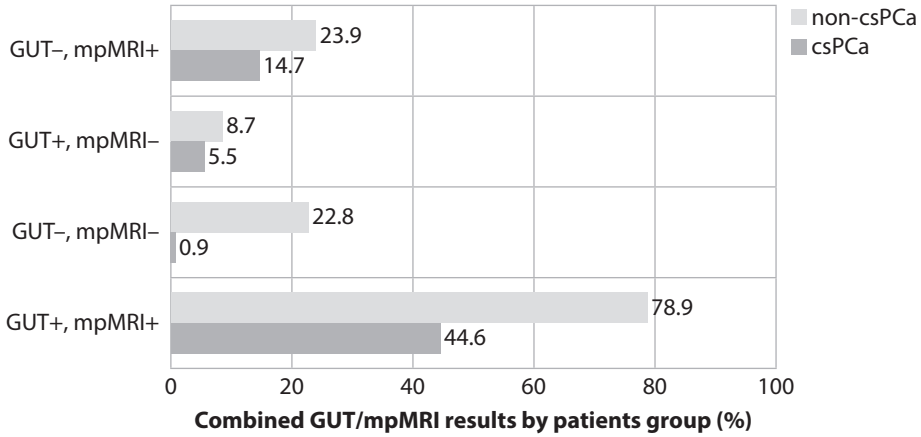


Fig. 3.1.3.2. *Distribution of combined GUT and mpMRI findings across histopathological groups*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

Table 3.1.3.1. *Stratification of patients' characteristics on the basis of prostatic biopsy results*

Parameter		**non-csPCa**	**csPCa**	***P*-value**
Number of cases, n (%)		96 (46.2)	112 (53.8)	
Age (years)	Mean ± SD	62.3 ± 7.3	63.4 ± 7.1	0.267
	Median	63	63	
	Range	43–82	50–87	
Total PSA (ng/mL)	Mean ± SD	5.8 ± 2.7	6.7 ± 3.0	0.013
	Median	5.2	5.7	
	Range	2.7–18.7	3.0–19.1	
PSA density (ng/mL/mL)	Mean ± SD	0.13 ± 0.11	0.16 ± 0.11	**< 0.001**
	Median	0.1	0.14	
	Range	0.04–0.73	0.05–0.79	
Prostate volume	Mean ± SD	56.2 ± 26.4	46.9 ± 16.6	**0.041**
	Median	48.4	43.4	
	Range	13.7–129.1	13.5–92.0	
DRE suspicious, n (%)	Yes	44 (45.8)	63 (56.2)	0.164
	No	52 (54.2)	49 (43.8)	
Family history, n (%)	Yes	14 (14.6)	14 (12.5)	0.688
	No	82 (85.4)	98 (87.5)	
GUT score, n (%)	Negative	43 (44.8)	17 (15.2)	**< 0.001**
	Positive	49 (51.0)	92 (82.1)	
	Not evaluated	4 (4.2)	3 (2.7)	
GUT predicted risk for csPCa (%)	Mean ± SD	20.7 ± 18.6	30.8 ± 17.5	**< 0.001**
	Median	12.8	28.7	
	Range	1.0–72.8	3.3–86.9	
mpMRI PIRADS score, n (%)	PIRADS < 3	31 (32.3)	7 (6.2)	**< 0.001**
	PIRADS ≥ 3	65 (67.7)	105 (93.8)	
PRCTPRC2 csPCa risk (%)	Mean ± SD	10.8 ± 5.7	12.3 ± 6.0	**0.031**
	Median	10	11	
	Range	4–35	4–41	

Table 3.1.3.1. *Continued*

Parameter		non-csPCa	csPCa	*P*-value
GUT score and mpMRI PIRADS score, n (%)	GUT positive, mpMRI positive	41 (44.6)	86 (78.9)	**< 0.001**
	GUT negative, mpMRI negative	21 (22.8)	1 (0.9)	
	GUT positive, mpMRI negative	8 (8.7)	6 (5.5)	
	GUT negative, mpMRI positive	22 (23.9)	16 (14.7)	
	Not evaluated	4 (4.2)	3 (2.7)	

Statistically significant differences are highlighted in bold.
n – number; SD – standard deviation; PSA – prostate-specific antigen; PSAD – PSA density; DRE – digital rectal examination; GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PIRADS – prostate imaging reporting and data system v.2.0, PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

Table 3.1.3.2. *Patient characteristics of a subgroup with PIRADS = 3 stratified on the basis of prostatic biopsy results*

Parameter		non-csPCa	csPCa	*P*-value
Number of cases, n (%)		3 (42.9)	4 (57.1)	
Age (years)	Mean ± SD	61.7 ± 4.9	63.5 ± 8.1	0.727
	Median	64	61.5	
	Range	56–65	56–75	
Total PSA (ng/mL)	Mean ± SD	7.4 ± 2.9	10 ± 4.4	0.629
	Median	6	10	
	Range	5.481–10.66	5.4–14.52	
PSA density (ng/mL/mL)	Mean ± SD	0.16 ± 0.07	0.23 ± 0.18	1
	Median	0.17	0.16	
	Range	0.08–0.23	0.11–0.5	
Prostate volume	Mean ± SD	50.5 ± 19.4	51.8 ± 23.7	1
	Median	47.1	49.5	
	Range	33.1–71.4	29–79	
DRE suspicious, n (%)	Yes	1 (33.3)	2 (50)	1
	No	2 (66.7)	2 (50)	
Family history, n (%)	Yes	1 (33.3)	1 (25)	1
	No	2 (66.7)	3 (75)	

Table 3.1.3.2. *Continued*

Parameter		non-csPCa	csPCa	*P*-value
GUT score, n (%)	Negative	2 (66.7)	0 (0)	0.143
	Positive	1 (33.3)	4 (100)	
	Not evaluated	0 (0)	0 (0)	
GUT predicted risk for csPCa (%)	Mean ± SD	11.6 ± 8.5	29.8 ± 20.9	0.229
	Median	11	20.4	
	Range	3.4–20.3	17.4–61.2	
PRCTPRC2 csPCa risk (%)	Mean ± SD	13 ± 1	15 ± 7	1
	Median	13	14.5	
	Range	12–14	9–22	
GUT negative, mpMRI positive		22 (23.9)	16 (14.7)	

n – number; SD – standard deviation; PSA – prostate-specific antigen; PSAD – PSA density; DRE – digital rectal examination; GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PIRADS – prostate imaging reporting and data system; PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

3.2. Comparative diagnostic performance of mpMRI, GUT, PCPTRC2 and their combinations in detecting clinically significant prostate cancer

Among the individual tests, GUT demonstrated the lowest sensitivity, at 84.4% (76.2–90.6)**,** indicating that approximately 15.6% of csPCa cases could be missed if relying solely on this modality. In contrast, both PCPTRC2 and mpMRI exhibited significantly higher and nearly identical sensitivities of 93.9% (87.3–97.7) and 93.8% (87.5–97.5), respectively (Table 3.2.1, Fig. 3.2.1). However, the greatest diagnostic performance was observed with combined approaches. The integration of mpMRI and PCPTRC2 achieved a sensitivity of 99.0% (94.5–100), while mpMRI combined with GUT slightly exceeded this, reaching 99.1% (95.0–100). Finally, the combination of all three modalities – mpMRI, GUT, and PCPTRC2 – achieved 100% sensitivity (96.2–100) and was the most sensitive combination for csPCa detection.

Table 3.2.1. *Sensitivity comparisons for prediction of csPCa with 95% CI given in brackets*

Model	csPCa, n	Sensitivity, %	*P*-value *vs.* PCPTRC2	*P*-value *vs.* mpMRI	*P*-value *vs.* GUT
PCPTRC2	99	93.9 (87.3–97.7)	NA	1	0.071
mpMRI	112	93.8 (87.5–97.5)	1	NA	0.033
GUT	109	84.4 (76.2–90.6)	0.071	0.033	NA
mpMRI & PCPTRC2	99	99.0 (94.5–100)	0.025	0.025	0.001
mpMRI & GUT	109	99.1 (95.0–100)	0.059	0.014	< 0.001
mpMRI & PCPTRC2 & GUT	96	100 (96.2–100)	0.014	0.014	< 0.001

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer.

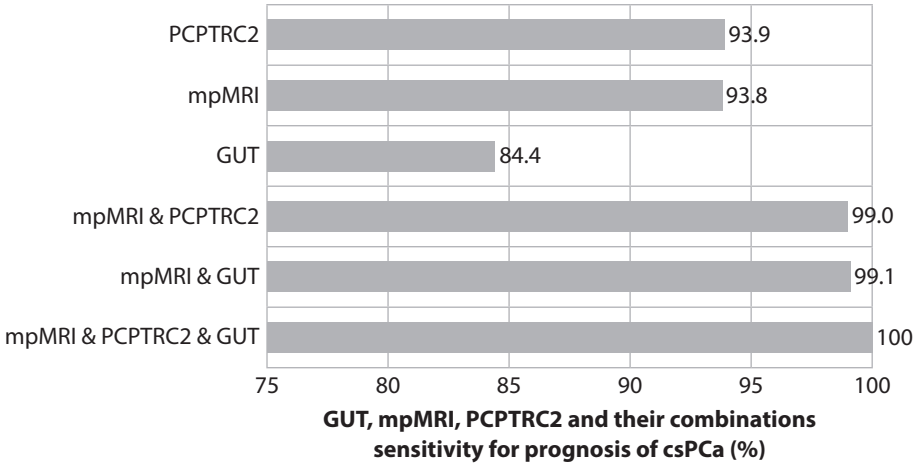


Fig. 3.2.1. *Sensitivity of GUT, mpMRI, PCPTRC2, and their combinations for prognosis of csPCa (n = 208)*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer.

According to the data presented in Table 3.2.2 and Fig. 3.2.2, GUT test achieved the highest specificity, measured at 46.7% (36.3–57.4), indicating a comparatively better ability to correctly rule out csPCa in patients who do not have the disease. GUT was also significantly superior to both the PCPTRC2 model (11.0%, $P < 0.001$) and mpMRI (32.3%, $P = 0.011$). However, mpMRI with a specificity of 32.3%, and PCPTRC2 with a specificity of 11.0% both

demonstrated the lowest specificity among the individual, reflecting limited discriminatory power when used in isolation.

Table 3.2.2. *Specificity comparisons for prediction of csPCa with 95% CI given in brackets*

Model	non-csPCa, n	Sensitivity, %	*P*-value *vs.* PCPTRC2	*P*-value *vs.* mpMRI	*P*-value *vs.* GUT
PCPTRC2	82	11.0 (5.1–19.8)	NA	0.028	< 0.001
mpMRI	96	32.3 (23.1–42.6)	0.028	NA	0.011
GUT	92	46.7 (36.3–57.4)	< 0.001	0.011	NA
mpMRI & PCPTRC2	82	2.4 (0.3–8.5)	0.008	< 0.001	< 0.001
mpMRI & GUT	93	25.0 (16.6–35.1)	0.251	0.058	< 0.001
mpMRI & PCPTRC2 & GUT	79	2.5 (0.3–8.8)	0.008	< 0.001	< 0.001

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer; NA – not applicable.

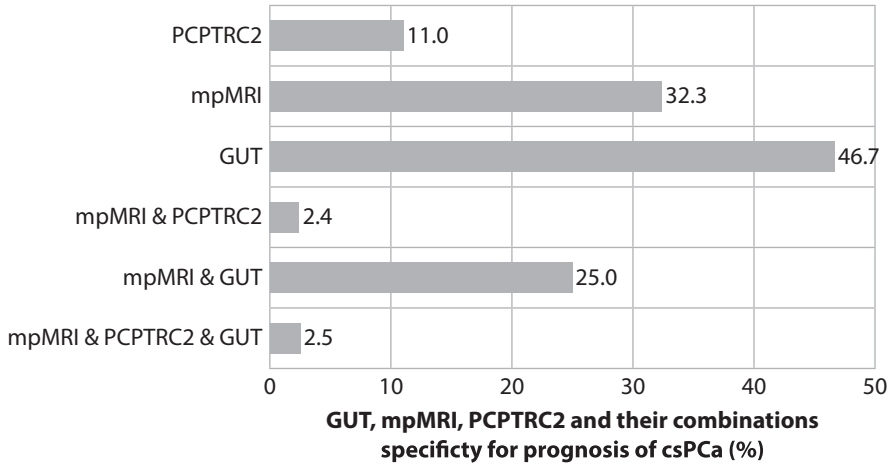


Fig. 3.2.2. *Specificity of GUT, mpMRI, PCPTRC2, and their combinations for prognosis of csPCa (n = 208)*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 –prostate cancer prevention trial risk calculator version 2.0; csPCa –clinically significant prostate cancer.

Interestingly, all of the combination of diagnostic modalities resulted in markedly reduced specificity – mpMRI and PCPTRC2 2.4% ((0.3–8.5), mpMRI & GUT 25.0% (16.6–35.1) and mpMRI and GUT and PCPTRC2 2.5% (0.3–8.8).

Fig. 3.2.3 illustrates the trade-off between sensitivity and specificity, with the area under the curve (AUC) serving as a summary measure of overall diagnostic performance. mpMRI demonstrated the highest diagnostic accuracy among the three diagnostic methods, with an AUC of 0.72 and the GUT followed closely with an AUC of 0.69. In contrast, the PCPTRC2 model showed the lowest AUC (0.59).

The summarized comparison of sensitivity and specificity of diagnostic models for csPCa detection is presented in Fig. 3.2.4.

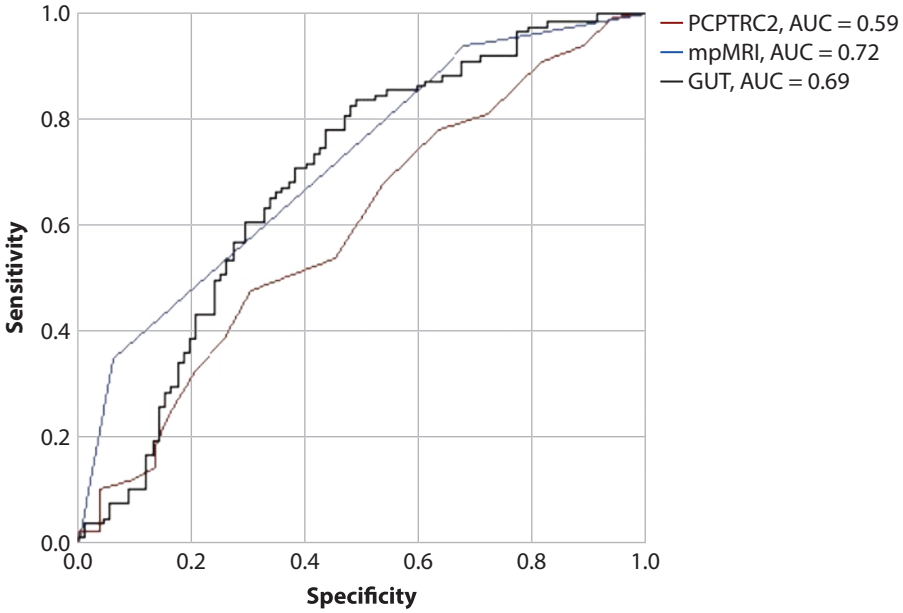


Fig. 3.2.3. *ROC curves and AUC of mpMRI, GUT, and PCPTRC2 for predicting csPCa*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer.

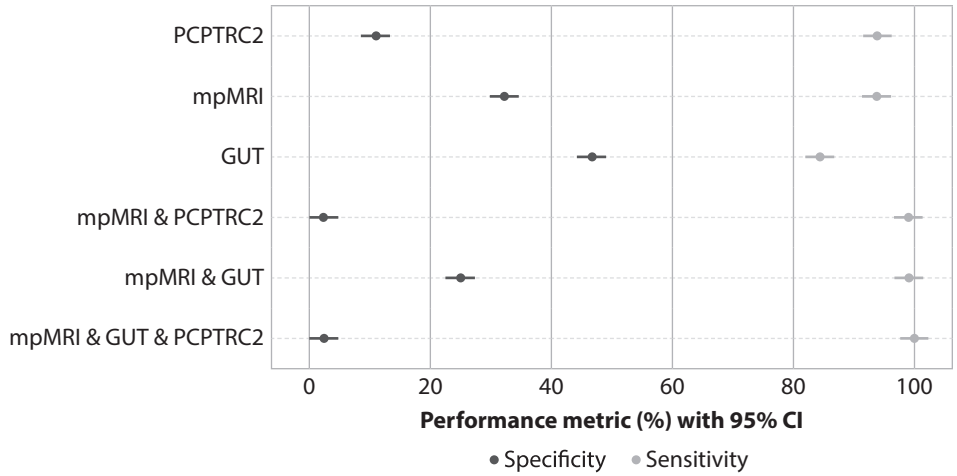


Fig. 3.2.4. *Comparison of sensitivity and specificity of diagnostic models for csPCa detection*

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

In patients with PIRADS ≤ 2, the GUT risk was significantly higher in csPCa compared to non-csPCa ($P = 0.004$), suggesting that the GUT test may enhance diagnostic sensitivity even in cases with low-suspicion imaging. For PIRADS 3 lesions, no statistically significant difference was observed between csPCa and non-csPCa groups ($P = 0.171$). In contrast, among patients with PIRADS ≥ 4, the GUT risk probability was again significantly higher in the csPCa group compared to the non-csPCa group ($P = 0.037$) (Fig. 3.2.5).

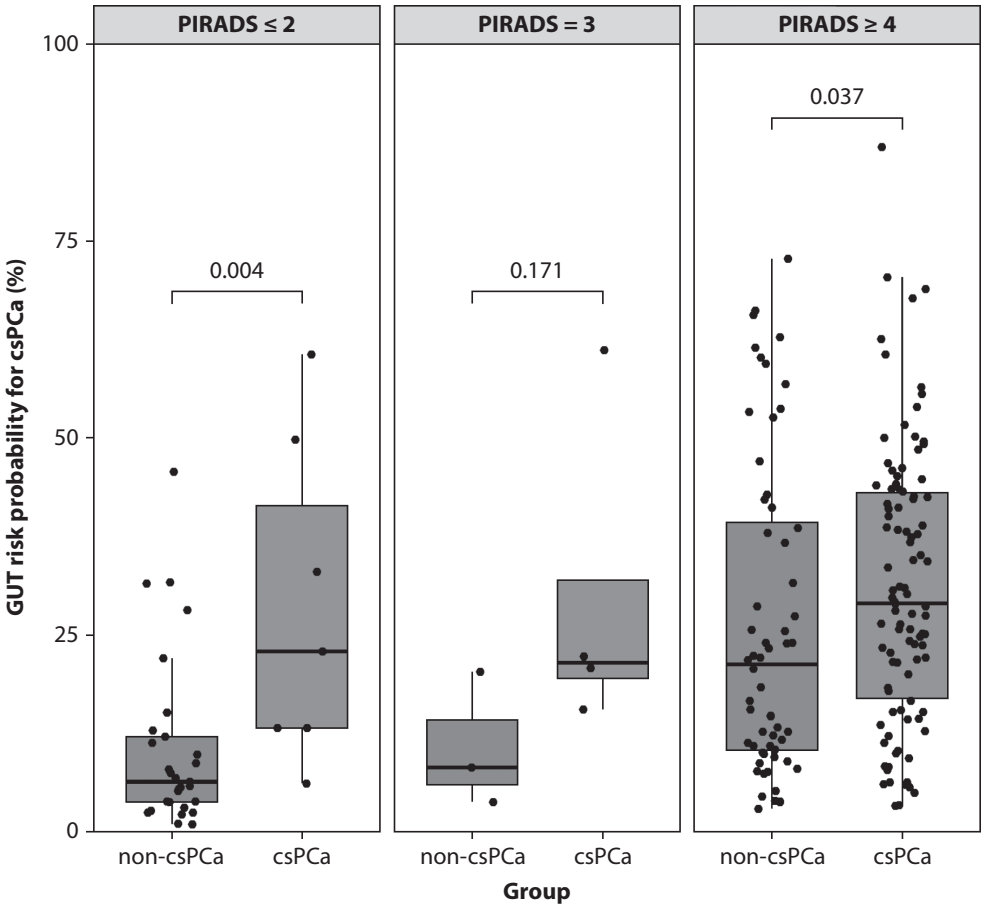


Fig. 3.2.5. *GUT risk probabilities stratified by mpMRI PIRADS scores and biopsy results*

GUT – genetic urinary test; mpMRI –multiparametric magnetic resonance imaging; csPCa – clinically significant prostate cancer; non-csPCa – non-clinically significant prostate cancer.

3.3. The performance of prostate cancer prevention trial risk calculator v.2.0 in prostate cancer detection in biopsy naïve patients

PCPTRC2 achieved a sensitivity of 93.9% (95% CI: 87.3–97.7), comparable to mpMRI (93.8%) and superior to the GUT test (84.4%), though the difference did not reach statistical significance (P = 0.071) (Table 3.2.1). However, as illustrated in table 3.2.2, its specificity was notably low at 11.0% (95% CI: 5.1–19.8), significantly inferior to both mpMRI (32.3%, P = 0.028) and GUT (46.7%, P < 0.001). Nevertheless, when combined with mpMRI, the model's sensitivity increased to 99.0%, with a further drop in specificity

(2.4%), indicating that integration with imaging may enhance detection but at the cost of more false positives.

In the prediction of PCa *vs.* no PCa, we examined three different versions of the PCPTRC2 risk calculator. The original PCPTRC2 had an AUC of 59.6%, while the updated version with PCA3 increased this to 76.2%, and the version with both PCA3 and T:E further improved it to 79.5%. The updated calculators showed significantly higher sensitivity compared to the original ($P = 0.001$ and $P < 0.001$, respectively) (Table 3.3.1, Fig. 3.3.1). When assessing csPCa against no PCa or non-csPCa, no significant differences were found between the original and updated versions ($P > 0.05$) (Table 3.3.2). Given that high sensitivity is crucial for diagnosing csPCa [102], we focused on the ROC curve portion between 75% and 100% sensitivity [14], mirroring the approach taken in a previous study focused on PCa prediction [103]. For csPCa prognosis, the updated PCPTRC2 with PCA3 had a partial AUC of 7.8%, while the version including both PCA3 and T:E achieved 8.6%. The latter demonstrated significantly higher performance ($P = 0.043$) (Table 3.3.3, Fig. 3.3.2).

Table 3.3.1. *AUC comparisons for predicting PCa with 95% CI are given in brackets*

Model	AUC with CI, %	*P*-value *vs.* PCPTRC2
PCPTRC2	59.6 (50.2–69.1)	NA
PCPTRC2 including PCA3	76.2 (68.3–84.1)	0.001
PCPTRC2 including PCA3+T:E	79.5 (71.9–87.1)	< 0.001

Systematic and targeted biopsy results were used in the post-DRE urine dataset. Maximum valid PCA3 and/or T:E scores were imputed in cases where the calculated biomarker scores exceeded the values allowed by the calculator. AUC comparisons were performed for cases where calculator results were valid after imputation (n = 209).
PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCA3 – prostate cancer antigen 3; T:E – fusion of TMPRSS2 and ERG gene.

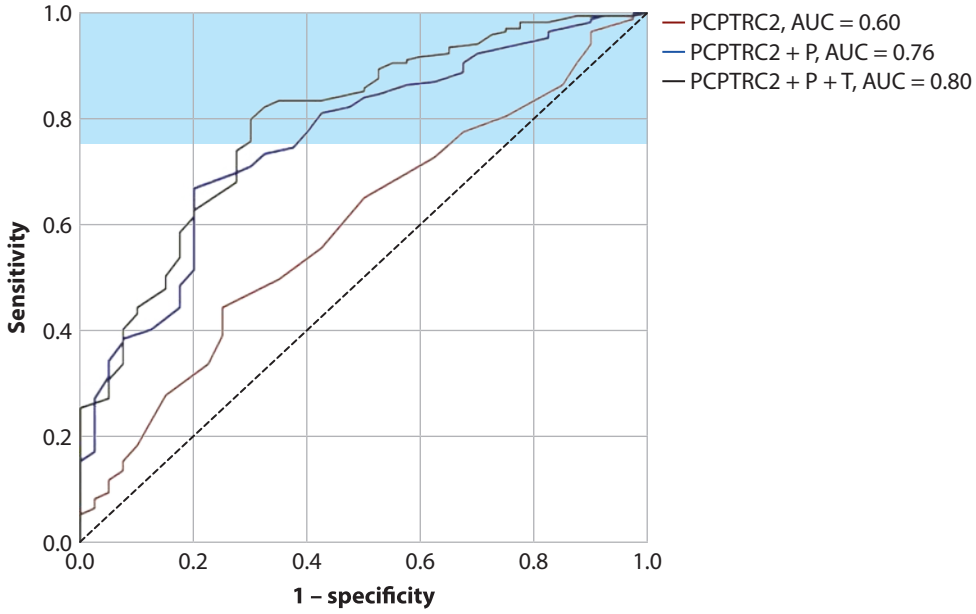


Fig. 3.3.1. *ROC curves and AUC of various PCa risk calculators for predicting PCa*

PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCPTRC2 + P – PCPTRC2 version including PCA3 scores; PCPTRC2 + P + T – PCPTRC2 version including PCA3 and TMPRSS2:ERG scores.
The blue shaded area indicates a sensitivity range of 75% to 100% that was used for partial AUC calculations.

Table 3.3.2. *AUC comparisons for predicting csPCa with 95% CI are given in brackets*

Model	AUC with CI, %	*P*-value *vs.* PCPTRC2
PCPTRC2	61.6 (53.9–69.3)	NA
PCPTRC2 including PCA3	64.9 (57.3–72.6)	0.150
PCPTRC2 including PCA3 + T:E	67.8 (60.3–75.3)	0.058

Systematic and targeted biopsy results were used in the post-DRE urine dataset. Maximum valid PCA3 and/or T:E scores were imputed in cases where the calculated biomarker scores exceeded the values allowed by the calculator. AUC comparisons were performed for cases where calculator results were valid after imputation (n = 209).
PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCA3 – prostate cancer antigen 3; T:E – fusion of TMPRSS2 and ERG gene.

Table 3.3.3. *Partial AUC (1–0.75 sensitivity) comparisons for predicting csPCa with 95% CI, given in brackets*

Model	Partial AUC with CI, %	*P*-value *vs.* PCPTRC2
PCPTRC2	5.8 (3.7–8.5)	NA
PCPTRC2 including PCA3	7.8 (5.4–10.7)	0.063
PCPTRC2 including PCA3 + T:E	8.6 (5.7–11.8)	0.043

PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCA3 –prostate cancer antigen 3; T:E – fusion of TMPRSS2 and ERG gene.

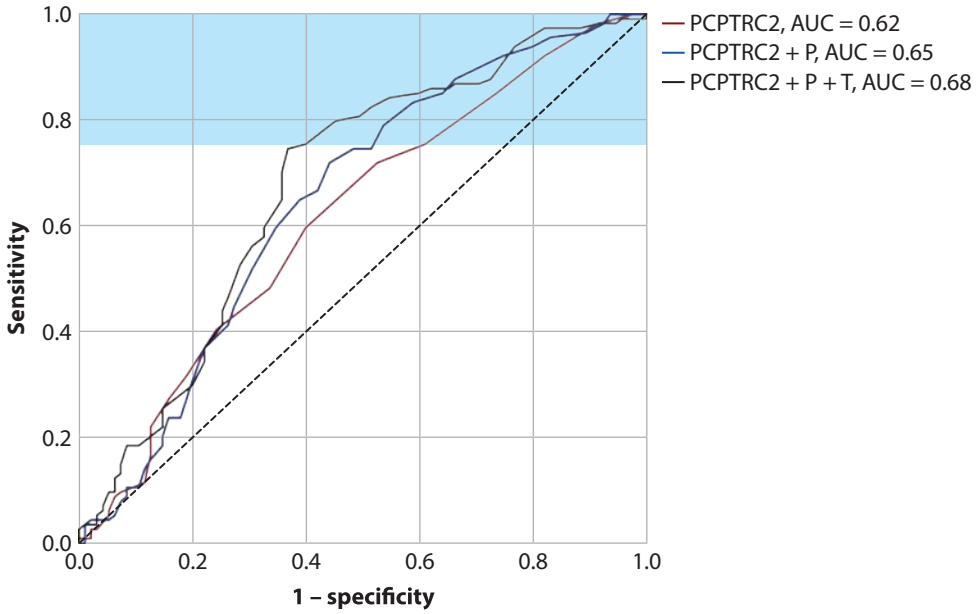


Fig. 3.3.2. *ROC curves and AUC of various PCa risk calculators for predicting csPCa*

PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCPTRC2 + P – PCPTRC2 version including PCA3 scores; PCPTRC2 + P + T – PCPTRC2 version including PCA3 and TMPRSS2:ERG scores.
The blue shaded area indicates a sensitivity range of 75% to 100% that was used for partial AUC calculations.

Table 3.3.4 presents the average predictions of different versions of the PCPTRC2 calculator, including the basic version and those that incorporate urinary biomarkers, in comparison to biopsy results. In the basic PCPTRC2 version, the average probability of detecting any PCa was 30%, with csPCa at 11% and non-csPCa at 19%. Negative biopsy results were predicted at 70% on average. The addition of PCA3 to the PCPTRC2 model increased the average likelihood of detecting PCa to 51%, csPCa to 20%, and non-csPCa

to 30%, while negative biopsy results decreased to 49%. Incorporating both PCA3 and T:E further enhanced average predicted detection rates, with PCa reaching 55%, csPCa at 25%, and non-csPCa remaining at 30%, alongside a reduction in negative biopsy results to 45%. Regarding biopsy outcomes, PCa was found in 81.3% of biopsied cases, csPCa in 53.1%, and non-csPCa in 28.2%, with negative results occurring in 18.7% of instances. Therefore, PCPTRC2 risk estimates were too low, especially in the basic PCPTRC2 version.

Table 3.3.4. *The average probabilities of different versions of the PCPTRC2 risk calculator compared to biopsy outcomes*

Average probabilities for:	PCa	csPCa	non-csPCa	Negative biopsy
PCPTRC2 basic version	30%	11%	19%	70%
PCPTRC2 + PCA3	51%	20%	30%	49%
PCPTRC2 + PCA3 + T:E	55%	25%	30%	45%
Biopsy outcomes	81.3%	53.1%	28.2%	18.7%

PCPTRC2 – prostate cancer prevention trial risk calculator version 2.0; PCa –prostate cancer; csPCa – clinically significant prostate cancer; non-csPCa – non clinically significant prostate cancer; PCA3 – prostate cancer antigen 3; T:E – fusion of TMPRSS2 and ERG gene.

3.4. Missed clinically significant prostate cancer cases and saved biopsies

Missed csPCa cases and saved biopsy numbers for various models are summarized in Table 3.4.1 as described below. In terms of unnecessary biopsies that can be saved the best results can be achieved while using GUT, 46.7% and PCPTRC2 had the lowest unnecessary biopsy avoidance rate, 11%. However, GUT usage would miss the highest numbers of csPCa cases, 16.5%, while the combination of all three modalities – mpMRI, GUT and PCPTC2 achieved 0% missed csPCa. mpMRI combinations with GUT or PCPTCR2 alone also miss significantly low number of csPCa cases – close to 1%. In cases of negative mpMRI, GUT correctly prevented 72.4% unnecessary biopsies (21 of 29) and correctly identified 85.7% patients who required a biopsy (6 of 7). In terms of saved biopsies, GUT alone resulted in the highest biopsy avoidance rate (31.3%), followed by mpMRI (18.3%), while PCPTRC2 alone saved 8.3% of biopsies. All combined models were associated with lower biopsy savings, particularly mpMRI + PCPTRC2 and the triple combination, which saved only 1.7% and 1.1% of biopsies, respectively.

Table 3.4.1. *Missed csPCa cases and saved biopsy numbers for various models*

Model	Missed csPCa cases	Saved biopsies	Saved unnecessary biopsies
PCPTRC2	6 of 99; 6.1%	15 of 181; 8.3%	9 of 82; 11.0%
mpMRI	7 of 112; 6.2%	38 of 208; 18.3%	31 of 96; 32.3%
GUT	18 of 109; 16.5%	63 of 201; 31.3%	43 of 92; 46.7%
mpMRI & PCPTRC2	1 of 99; 1.0%	3 of 181; 1.7%	2 of 82; 2.4%
mpMRI & GUT	1 of 109; 0.9%	24 of 201; 11.9%	23 of 92; 25.0%
mpMRI & PCPTRC2 & GUT	0 of 96; 0%	2 of 175; 1.1%	2 of 79; 2.5%

GUT – genetic urinary test; mpMRI – multiparametric magnetic resonance imaging; PRCTPRC2 – prostate cancer prevention trial risk calculator version 2.0; csPCa – clinically significant prostate cancer.

4. DISCUSSION

The detection of csPCa remains a challenge in urologic oncology. The main goal is the early and accurate diagnosis with the avoidance of overtreatment of indolent disease. In our study 208 men were consistently involved using traditional clinical parameters, mpMRI, GUT and PCPTRC2 data to asses and improve the diagnostic accuracy for csPCa.

The 2023 EAU-ESTR-SIOG guidelines recommend clinicians to consider the use of biomarkers and mpMRI before performing a biopsy [76]. However, it is important to compare international recommendations between various different organizations. For instance, the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) similarly advise to use mpMRI prior to biopsy in selected patients, particularly those with elevated PSA or abnormal DRE [104, 105]. The United Kingdom's NICE guidelines also support mpMRI as a first-line diagnostic tool [106]. Contrarily, the adoption of urinary biomarkers remains variable across these organizations, with more limitations in some regions. This variation highlights the need for further validation and agreement on how biomarkers should be used in routine clinical practice. Our study adds valuable evidence that could help bring guidelines into better alignment across different regions [107].

Ahmed et al. reported that mpMRI shows excellent sensitivity for csPCa detection – the values ranging from 90% to 95% – helping to reduce the number of missed PCa [108]. In another systematic review by Zhen et al, mpMRI for csPCa detection also demonstrated high sensitivity of AUC = 0.87, although specificity values varied widely based on imaging protocols and patient selection [109]. Our study revealed mpMRI sensitivity of 93.8% for detecting csPCa which not only aligns with previous studies but also suggests that mpMRI could be used as part of a multimodal diagnostic strategy along with emerging new diagnostic techniques.

Various biomarker-based urinary tests aim to reduce the number of unnecessary prostate biopsies while ensuring that minimal amount of csPCa cases are overlooked [20–23]. According to Sanda et al., an assay combining PCA3 and T:E showed 93% sensitivity predicting aggressive PCa during biopsy in the cohort of 561 biopsy-naive patients [113]. This high sensitivity highlights the potential of urinary biomarkers to serve as reliable, non-invasive tools in the early detection of clinically significant disease. Similarly, in our study we included a group of biopsy naïve patients only and for all of them genetic urinary tests were performed after DRE. Therefore, our study findings confirmed the tendency that including GUT (sensitivity 84.4%) for

PCa diagnosis into clinical practice would reduce unnecessary prostate biopsies and overdiagnosis while preserving detection of csPCa. It is important to note, that overdiagnosis is not only subjects patients to potentially harmful procedures and associated anxiety, but also elevates the overall healthcare costs. A diagnostic strategy involving urinary biomarkers combining with traditional clinical parameters could potentially improve patient selection for invasive procedures. This could allow clinicians to correctly identify patients who are at risk of csPCa more accurately and preserve interventions for those who would benefit most from early and aggressive treatment.

To our knowledge this is the first study that examined the value of mpMRI, genetic urinary biomarkers (PCA3 and T:E), PCPTRC2 results and their combination in detecting csPCa among biopsy naïve patients. However, there are several similar studies, that analysed the associations of mpMRI and PCA3 combination with csPCa. One example is the study of Fenstermaker et al, where 187 men underwent mpMRI and PCA3 testing before prostate biopsy. Study results showed that PCA3 is associated with MRI suspicious score and the detection of cancer on MRI fusion targeted biopsy in biopsy naïve men population (AUC = 0.67, 95% CI: 0.59–0.76) [10]. Another study of Porpiglia et al retrospectively reviewed 120 biopsy naïve patients, who underwent mpMRI and PCA3 testing. It was revealed, that mpMRI resulted in higher gain inaccuracy for predicting csPCa compared with PCA3 (AUC = 0.78, $P < 0.01$) [11]. In comparison, our study is prospective, more extended and included not only mpMRI and PCA3 testing, but also testing of T:E and their combinations. One issue that needs to be addressed is that in our study neither GUT nor PCPTRC2 significantly prognosed csPCa in PIRADS 3 lesions, probably due to too small patients group. However, the prognostic tendency was preserved as in other PIRADS lesions and extended research is needed to confirm the significant results. Another matter requiring recognition is the diagnostic accuracy of csPCa using mpMRI only. Tay et al study results showed mpMRI sensitivity of 93% when detecting csPCa [114]. Our study demonstrated almost the same but slightly higher mpMRI sensitivity of 93.8%. However, in our study specificity of mpMRI was significantly lower than GUT alone, probably due to study limitations, addressed further. In relation to PIRADS 3 lesions, no significant differences were observed between the csPCa and non-csPCa groups, likely due to the limited size of the sub cohort (n = 7).

In terms of specificity, our study results showed interesting outcomes. The combination of diagnostic modalities resulted in markedly reduced specificity compared to standalone tests: mpMRI and PCPTRC2 2.4%, mpMRI and GUT 25.0%, mpMRI and GUT and PCPTRC2 2.5%, whereas when

applied alone, moMRI showed specificity 32.3% and GUT 46.7%. This sharp decline in specificity with combined diagnostic approaches highlights a common trade-off in medical diagnostics: increasing sensitivity often comes at the expense of specificity [115]. While combinations of mpMRI, GUT, and PCPTRC2 can effectively identify nearly all cases of csPCa, they do so at the cost of a high false-positive rate, potentially leading to overdiagnosis and overtreatment. The findings suggest that although multimodal diagnostic strategies optimize sensitivity, this benefit must often compromise specificity. In clinical terms, missing a case of csPCa may be unacceptable in high-risk individuals where aggressive detection strategies could be justified. However, in low- or intermediate-risk populations, the benefit of maximal sensitivity may be affected by the harms of overdiagnosis. This highlights the importance of tailoring diagnostic strategies to the each individual. Choosing which tests to use and in what combination should depend on specific patient factors like age, PSA levels, family history, genetic risk, and any previous biopsy findings.

Regarding AUC analysis, in our study ROC curves with corresponding AUC values were generated only for the individual diagnostic methods: mpMRI, GUT, and PCPTRC2. In contrast, ROC curve analysis with AUC calculations was not performed for the diagnostic combinations, as it was deemed methodologically inappropriate and uninformative in this context. There are several reasons for this decision. First, ROC curves are intended to assess the trade-off between sensitivity and specificity across a range of possible threshold values. However, in our diagnostic combinations, no such alternative thresholds exist – the outputs are binary (positive or negative) by design. Second, ROC curves and AUC values are most useful when the optimal cutoff is unknown or needs to be optimized, whereas in our case, all thresholds were predefined and fixed. The focus was instead placed on practical outcomes, such as the number of biopsies avoided and the number of clinically significant prostate cancer (csPCa) cases missed. Third, the shape of the ROC curve – and therefore the AUC – is determined by multiple threshold-based data points. With only a single operating point per combination, it is not feasible to construct a meaningful or representative ROC curve. Finally, the study sample size was relatively limited, reducing the statistical power needed to make robust comparisons between AUC values.

In our study we employed the PCPTRC2 risk calculator and the results revealed a sensitivity of 93.9% (95% CI: 87.3–97.7%), which is almost identical to the 93.8% sensitivity observed with mpMRI and higher than achieved by the GUT – 84.4%. However, these differences did not reach statistical significance ($P = 0.071$). Our study results are similar as previous findings of other researches. For example, Ankerst et al. reported similar sensitivity values of approximately 91–92% for detecting PCa when using risk model

based on clinical parameters [68]. However, the biggest disadvantage of the basic PCPTRC2 version was its very low specificity, only 11.0% (95% CI: 5.1–19.8%), which was significantly inferior to that of mpMRI at 32.3% (P = 0.028) and the GUT test at 46.7% ($P < 0.001$). This is in line with the same Ankerst et al. study findings, which reported that specificity levels for PCTRC2 tend to fall below 20% [68]. In contrast, when PCPTRC2 is combined with mpMRI, the sensitivity climbed dramatically to 99.0%, yet specificity dropped even further – to just 2.4%. Similar pattern was observed in PROMIS trial, where Ahmed et al. demonstrated that while mpMRI can markedly improve sensitivity up to 95% for detecting csPCa, specificity was only moderate, up to 41% [116]. Our study results, showing an excellent sensitivity but a very low specificity are in line with these observations, highlighting that while integrated diagnostic strategies can significantly improve the detection of csPCa, they also tend to produce a high number of false positive results, potentially leading to unnecessary biopsies.

To address the previous mentioned limitation, we explored whether enhancing existing risk calculator with additional biomarkers could improve diagnostic performance. Our study results demonstrate that incorporating additional urinary biomarkers into PCPTRC2 enhances the detection of csPCa. In a study of Ankerst et al., PCA3 and T:E was incorporated in PCPTRC2 and 854 biopsies were performed [73]. Areas under the curve (AUC) for predicting csPCa were 70.0% (66.0–74.0%), 76.4% (72.8–80.0%) and 77.1 (73.6–80.6%) for PCPTRC2 alone, with PCA3 added, and PCA3 and T:E added, respectively [73]. In another study, conducted by Tomlins et al., the association of urinary PCA3 and the T:E with PCPTRC (version 1.0) in csPCa detection was evaluated using urine samples from 1218 patients [74]. When using basic PCPTRC version, AUC value was 0.707, whereas adding PCA3 and PCA3 and T:E combination AUC values increased up to 0.752 and 0.779, respectively [74]. Although in our study, we found the AUC for csPCa in all three scenarios to be lower, the trend remains clear: the integration of urinary biomarkers improves the predictive performance of the risk calculator. This limitation is likely attributable to the small sample size and different patient's cohort, used in the study. When focusing on the partial AUC values – which highlights performance at higher sensitivity levels critical for csPCa detection – the PCPTRC2 including PCA3+T:E showed significantly higher values than PCPTRC2 only or including PCA3 (P = 0.043). This indicates that even if the overall AUC is modest, the multiparametric approach is particularly effective when high sensitivity is required in clinical practice. In predicting all PCa cases – both csPCa and non-csPCa – the study by Tomlins et al. reported that the PCPTRC2 alone achieved an area under the curve (AUC) of 63.9% [74]. Notably, the inclusion of PCA3

enhanced the AUC to 73.9%, and when both PCA3 and T:E ratio were incorporated, the AUC further increased to 76.2%. In our research, we observed that the use of PCPTRC2 alone resulted in a lower AUC of 59.6% for PCa detection. However, upon incorporating additional biomarkers, specifically PCA3, the AUC improved to 76.2%, and with the combination of PCA3 and T:E, it reached a maximum AUC of 79.5%. These findings suggest that adding urinary biomarkers values to existing risk calculator – PCTRC2 – could have significant clinical benefits in csPCa diagnostic. The partial AUC values indicate that this combined approach not only increases sensitivity, but also improves overall csPCa diagnostic accuracy. Therefore, unnecessary biopsies and overtreatment could be avoided or minimized.

The effectiveness of PCA3 testing in identifying PCa and its potential to decrease unnecessary biopsies has been demonstrated in previously conducted studies and metanalyses [117, 118]. Our study data suggests that including not only PCA3, but also T:E biomarkers significantly enhances the detection of PCa. However, the inclusion of PCA3 and T:E in the PCPTRC2 did not demonstrate significant added value in distinguishing csPCa from no PCa or non-cs PCa. This limitation is likely attributable to the small sample size and different patient's cohort, used in the study. Initially PCTRC2 incorporated urinary biomarkers by assessing their values through the quantification of copies obtained from MPS test.[97] In the current study, urinary biomarker values acquired via the different urinary test, were integrated into the PCTRC2 [119]. The EAU-EAN guidelines recommend using risk-calculators, that are correctly calibrated to the population prevalence [76]. When using PCTRC2 in the Lithuanian population, it may be necessary to recalibrate the model. This need for recalibration is supported by our findings, which showed that the average predicted risks for PCa and csPCa using PCTRC2 were significantly lower than the actual percentages observed in biopsy outcomes (Table 3.3.4). Incorporating PCA3 and T:E in PCPTRC2 adds significant predictive value to csPCa diagnostics in biopsy-naïve patients. Despite these challenges, the integration of PCA3 and T:E into PCPTRC2 still adds meaningful predictive value to csPCa diagnostics in biopsy naïve patients. This approach seems like a promising step toward more precise and personalized diagnostic strategies, especially in our country, Lithuania, where rising PCa mortality rates are experienced.

Our study was performed prospectively in a different unique patient's cohort than previous studies in the literature. It is known, that Lithuania is the sole country with an active PCa screening program [120]. Data from cancer registries indicates that, over the past two decades, age-adjusted mortality rates for PCa have significantly declined in the majority of nations across Northern Europe and North America [121]. However, Lithuania stands out as

an exception, exhibiting a rapid increase in PCa mortality over the past 20 years [122]. Lithuania's rapid increase in mortality further emphasizes the need for development of possible new diagnostic routes. Rapidly evolving technologies in imaging and biologic biomarkers could serve for minimizing PSA testing associated harms while preserving or even enhancing the sensitivity for identifying PCa and high-risk PCa [122]. Current PSA screening has been associated with overdiagnosis and overtreatment for a long time. Advanced imaging – like mpMRI – and novel urinary biomarker tests offer a promising new diagnostic route. These methods can improve both sensitivity and specificity of csPCa diagnostic and potentially reduce unnecessary invasive procedures. In line with mpMRI and urinary biomarkers testing, PCa risk calculators also plays a crucial role in novel PCa diagnostic. The initial version of PCPTRC2 integrated urinary biomarkers by quantifying their expression levels using the MPS test [97]. In the current study, urinary biomarker values acquired via the different urinary test, were integrated into the PCTRC2 [119]. The EAU-EAN guidelines recommend using risk-calculators, that are correctly calibrated to the population prevalence [76]. When using PCTRC2 in the Lithuanian population, it may be necessary to recalibrate the model. This need for recalibration is supported by our findings, which showed that the average predicted risks for PCa and csPCa using PCTRC2 were significantly lower than the actual percentages observed in biopsy outcomes. Incorporating PCA3 and T:E in PCPTRC2 adds significant predictive value to csPCa diagnostics in biopsy-naïve patients. Despite these challenges, the integration of PCA3 and T:E into PCPTRC2 still adds meaningful predictive value to csPCa diagnostics in biopsy naïve patients. This approach seems like a promising step toward more precise and personalized diagnostic strategies, especially in our country, Lithuania, where rising PCa mortality rates are experienced. By changing diagnostic pathways including these innovative tools, we can achieve balance in catching csPCa early and avoiding harmful side effects related to unnecessary invasive procedures. This could ultimately lead to improved patient care not only in Lithuania, but also in other regions facing rising PCa mortality. Future research should focus on validating these findings in larger, multicentre studies to see how well they apply across different conditions. There is also potential to develop more flexible, machine learning-based models that combine imaging, biomarkers, and clinical data to deliver real-time risk predictions. Tools like decision curve analysis (DCA) could help determine the most useful threshold for guiding biopsy interventions [123, 124].

Finally, the main goal of this research was to find which technique or combination could be the best diagnostic pathway for csPCa detection in biopsy naïve patients. While the mpMRI + GUT + PCPTRC2 model ensures

maximum csPCa detection (0% missed cases), it offers minimal benefit in reducing biopsy burden. On the other hand, GUT alone, while less sensitive, achieves significant reduced biopsy number, making it a practical option for initial screening in low to moderate risk populations. Moreover, our results showed that performing mpMRI along with GUT would allow to reduce unnecessary biopsies by a quarter while detecting almost all cases of aggressive cancer (99.1%). These findings highlight the potential of an integrated diagnostic strategy that combines advanced imaging with molecular urinary biomarkers for more precise PCa detection. What is more, this allows to minimize unnecessary interventions and ultimately lead to improved patient outcomes.

Recent advancements in PCa diagnostics have been focused on the integration of mpMRI with other modalities to enhance the detection of csPCa. One such modality is prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT), which has shown promise in improving csPCa detection rates. The combination of mpMRI and PSMA PET/CT has demonstrated superior diagnostic performance compared to either modality alone. For instance, a study indicated that integrating PSMA PET/CT with mpMRI increased sensitivity from 83% to 97% and improved the negative predictive value from 72% to 91% [125]. Furthermore, a study by Kumar et al. reported that combining mpMRI with PSMA PET/CT achieved an area under the curve (AUC) of 0.876, with a sensitivity of 82.8% and specificity of 100% for detecting prostate cancer [126]. This combined approach improves the ability to locate and assess the lesion, especially in cases where mpMRI findings are unclear or inconclusive.

Similarly, the integration of artificial intelligence (AI) and machine learning algorithms into mpMRI data has significantly advanced the diagnostic process for PCa. Recent studies have demonstrated that AI, particularly deep learning algorithms, can enhance the accuracy of lesion detection, classification, and segmentation in prostate MRI scans. For instance, Mehralivand et al. developed a cascaded deep learning model utilizing a 3D U-Net architecture for automated lesion detection and classification on bpMRI. Their system achieved a lesion detection sensitivity of 56.1% and a positive predictive value of 62.7%, indicating a promising step toward reliable AI-assisted diagnostics in prostate imaging [127]. One more study, that supported previous results, was a systematic review by Ramacciotti et al, which highlighted that AI-assisted mpMRI interpretation achieved diagnostic performance comparable to experienced radiologists, with some models demonstrating higher sensitivity and specificity in identifying csPCa [128]. The integration of AI into prostate imaging workflows not only improves diagnostic accuracy but also streamlines the evaluation process, potentially reducing the time

required for image analysis. As these technologies continue to evolve, their incorporation into routine clinical practice holds the promise of more precise and individualized prostate cancer diagnostics.

Looking ahead, our findings contribute to a growing care for more personalized PCa diagnostic research. While mpMRI and urinary biomarkers are important tools, newer options like genomic profiling tests – such as Decipher or Oncotype DX – can offer additional prognostic information regarding tumor aggressiveness [129]. There is also growing interest in non-invasive methods like liquid biopsies, which analyse markers like circulating tumour cells and DNA methylation. Liquid biopsies allows a real-time monitoring of tumour evolution and therapeutic efficacy, offering a less invasive alternative to traditional tissue biopsies. Additionally, DNA methylation patterns detected in ctDNA have shown promise as biomarkers for early cancer detection and prognosis prediction [130, 131]. A future diagnostic strategies may include a combination of all possible information – imaging, genetics and proteins – into a single, integrated approach. With the help of AI, it could be possible to develop smarter risk prediction tools and help to plan treatment strategies more precisely [132].

While our findings demonstrate improved diagnostic accuracy using multimodal strategies, the economic burden of these additional diagnostic methods should be taken into account. mpMRI and GUT are associated with considerable cost, both for the healthcare system and individual patients. In countries with limited resources, widespread implementation may be challenging [133, 134]. However, by reducing unnecessary biopsies and over-treatment of low-risk disease, these diagnostic tools could save money in the longer perspective by reducing follow-up procedures and treatment-related costs [135]. Also, decreased patient morbidity and smaller number of possible complications (e.g., infections, bleeding) associated with invasive procedures may reduce overall healthcare costs [136]. A detailed cost-benefit analysis could help put these advantages into clear numbers and support financial decisions, especially in healthcare systems like Lithuania's, where advanced diagnostics need to be balanced against limited budgets.

One more important but often overlooked aspect in PCa diagnostics is the patient's perspective. Unnecessary biopsies can cause not only physical side effects, but also lead to significant stress and anxiety. Our findings highlight the importance of strategies that reduce false positives and reduce the number of men undergoing unnecessary interventions. Non-invasive tests like urinary biomarkers may be more acceptable to patient, especially compared to repeated biopsies [137]. By using tools like risk calculators and mpMRI within shared decision-making models, it is possible to better involve patients in their own care, help them make more informed choices and feel more

confident thought the process [138]. Future research should also focus on understanding preferences and experiences to ensure that diagnostic strategies aligns with individual values and expectations.

Ultimately, the main goal of PCa diagnostic is to ensure that no case of clinically significant disease is missed. However, it is equally important to maintain sufficient specificity to avoid unnecessary biopsies and minimize potential patient anxiety. Our study findings support a multimodal diagnostic approach that combines mpMRI with urinary biomarkers, ultimately enhancing csPCa detection and allowing to personalize treatment strategy for each patient. By combining imaging data with molecular urinary biomarkers – like PCA3 and T:E – it is possible to create a structured risk model which could help physicians to better evaluate patient's condition. Detailed view helps in identifying high-risk cases while avoiding overtreatment of indolent disease. A multimodal approach highlights the strengths of different diagnostic tools. For example, imaging alone may show excellent sensitivity in detecting csPCa, at the same time it sometimes falls short on specificity. Here, urinary biomarkers and risk calculators can have an additional value in cutting down on false positive results and reducing the number of unnecessary invasive procedures. Further research should be focusing on standardizing methodologies across different modalities and highlighting diagnostic criteria to further improve patient outcomes. This includes calibrating risk calculators to specific populations, especially in regions with unique epidemiological profiles, and ensuring imaging techniques and urinary tests consistency.

CONCLUSIONS

1. mpMRI demonstrated high sensitivity but insufficient specificity in diagnosing clinically significant prostate cancer.
2. The genetic urine test was less sensitive than mpMRI and PCPTRC2, but was the most specific diagnostic method for clinically significant prostate cancer detection.
3. The sensitivity of the PCPTRC2 calculator in diagnosing clinically significant prostate cancer was high, but its specificity was the lowest among the diagnostic methods used. Incorporating PCA3 and T:E in PCPTRC2 added significant predictive value to PCa diagnostics in biopsy-naïve patients.
4. Combining all three diagnostic modalities (mpMRI, GUT and PCPTRC2) significantly improves sensitivity for csPCa (up to 100%) but dramatically reduces specificity (as low as 2.4%), limiting their ability to reduce overtreatment, whereas the combination of two non-invasive tests – GUT and mpMRI – in csPCa diagnosis of biopsy naïve patients has the potential to avoid unnecessary biopsies and prevent the detection of non-csPCa while keeping a minimal risk of missing csPCa.

LIMITATIONS OF THE STUDY

This study has several limitations. First, data were obtained from a single centre only, which could potentially lead to selection bias. However, bias was minimized as much as possible by including patients consecutively as they presented with documented PCa suspicion. Second, the evaluation of diagnostic performance in this study relied on the results of cognitive fusion prostate biopsies, which could introduce potential biases regarding falsely negative biopsy results. Third, the most sensitive method – MRI combined fusion with transrectal ultrasonography prostate biopsy – was not performed in this study. As a result, this omission could influence the false-negative biopsy rates and potentially impact the conclusions drawn from the study. Fourth, the patient cohort did not cover the entire pathological spectrum (i.e., Gleason score and stage). The fifth limitation was that the population was homogenous, consisting only men of the same racial and ethnic background. Also, even though our results with the implementation of a combination of GUT, mpMRI and PCPTRC2 were defined as significant regarding csPCa detection, further investigation in a larger prospective cohort is required.

PRACTICAL RECOMMENDATIONS

1. According to the updated 2023 guidelines of the European Association of Urology (EAU), the European Society for Radiotherapy and Oncology (ESTRO), and the International Society of Geriatric Oncology (SIOG), it is strongly recommended to incorporate mpMRI before performing a prostate biopsy in biopsy naive patients. Our study results support this recommendation – due to its high sensitivity (93.8%) and overall strong diagnostic accuracy (AUC = 0.72), mpMRI should be the primary imaging modality for assessing biopsy-naïve patients with suspected csPCa.
2. The sensitivity of GUT alone was 84.4%, and also it was the most specific (46.7%) method for diagnosing clinically significant prostate cancer. This suggests that GUT can accurately differentiate csPCa even in PIRADS ≤ 2 cases, where mpMRI alone may miss disease. It also achieved the highest biopsy avoidance rate (31.3%), making it especially useful for guiding decisions before biopsy or in cases where mpMRI results are unclear.
3. Although the updated PCPTRC2 version including urinary biomarkers (PCA3 and T:E) improves AUC (up to 79.5% for any PCa), it lacks sufficient specificity (11%) for csPCa detection. Therefore, PCPTRC2 should not be used as a solely diagnostic method for biopsy decisions, but rather to supplement clinical judgment and determine whether further tests like mpMRI or GUT are necessary.
4. While combining mpMRI, GUT, and PCPTRC2 achieves 100% sensitivity, the associated specificity is extremely low (2.5%), and biopsy avoidance rate is minimal (1.1%). Therefore, triple-test strategies should be reserved for high-risk or complex cases, rather than being applied routinely in everyday clinical practice. On the other hand, our study results showed that the combination of mpMRI and GUT is highly effective for the early detection of csPCa. This combination demonstrated a sensitivity of 99.1%, indicating an excellent high ability to identify clinically relevant PCa cases. Moreover, it helped reduce unnecessary biopsies by 25%, which is important not only from a clinical perspective but also in terms of reducing stress for patients and cutting healthcare costs.

SANTRAUKA

SUTRUMPINIMAI

ADC	–	menamas difuzijos koeficientas
AUC	–	kreivės plotas po ROC kreive (angl. *area under the curve*)
bpMRT	–	biparametrinis magnetinio rezonanso tyrimas
DCE	–	dinaminis kontrastinis sustiprinimas
DRT	–	digitalinis rektalinis tyrimas
DWI	–	difuzijos seka
EAU	–	Europos urologų asociacija (angl. *European Association of Urology*)
ERG	–	ETS šeimos (angl. *ETS-related gene*) transkripcijos faktoriaus genas
ERSPCRC	–	Europos randomizuotos skriningo studijos prostatos vėžio rizikos skaičiuoklė (angl. *European Randomized Study of Screening for Prostate Cancer Risk Calculator*)
ESTRO	–	Europos spindulinės terapijos ir onkologijos draugija (anlg. *European Society for Radiotherapy and Oncology*)
GS	–	Gleason balas
GŠT	–	genetinis šlapimo tyrimas
knPV	–	kliniškai nereikšmingas prostatos vėžys, apibrėžiamas kaip Gleason balas =6
krPV	–	kliniškai reikšmingas prostatos vėžys, apibrėžiamas kaip Gleason balas ≥ 7
mpMRT	–	multiparametrinis magnetinio rezonanso tyrimas
MPS2	–	prostatos vėžio rizikos įvertinimo testas (angl. *MyProstateScore 2*)
ne-krPV	–	nekliniškai reikšmingas prostatos vėžys, apimantis neigiamas biopsijas ir GS = 6 prostatos vėžio atvejus
PB	–	prostatos biopsija
PBCG-RC	–	prostatos biopsijos grupės bendradarbiavimo rizikos skaičiuoklė (angl. *Prostate Biopsy Collaborative Group Risk Calculator*)
PCA3	–	prostatos vėžio antigenas 3
PCPTRC2	–	prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė 2.0 versija (angl. *Prostate Cancer Prevention Trial Risk Calculator v.2.0*)
PHI	–	prostatos sveikatos indeksas (angl. *prostate health index*)
PI	–	pasikliautinasis intervalas
PIRADS	–	prostatos vaizdinės diagnostikos ir aprašymų sistema, 2.1 versija (angl. *prostate imaging reporting and data system v.2.1*)
PSA	–	prostatos specifinis antigenas
PV	–	prostatos vėžys
RPCRC-MRI	–	Roterdamo prostatos vėžio rizikos skaičiuoklė (angl. *Rotterdam Prostate Cancer Risk Calculator*)
SIOG	–	Tarptautinė geriatrijos onkologijos draugija (angl. *International Society of Geriatric Oncology*)
T:E	–	TMPRSS2 ir ERG genų susiliejimas
TMPRSS2	–	androgenų reguliuojama transmembraninė serino proteazė 2
vs.	–	palyginti su (lot. *versus*)

ĮVADAS

Prostatos vėžys (PV) išlieka viena dažniausiai diagnozuojamų piktybinių ligų visame pasaulyje. Tai pagrindinė su vėžiu susijusio sergamumo ir mirtingumo priežastis vyrų tarpe [1]. Klinikinė PV išraiška yra labai plati – nuo besimptominės ligos iki agresyvaus, kliniškai reikšmingo vėžio. Ypač svarbu yra atpažinti ir tiksliai diagnozuoti kliniškai reikšmingą prostatos vėžį (krPV), kuris apibrėžiamas kaip vėžys, kurio biopsijos metu nustatytas Gleason balas yra $\geq 3 + 4$. Tuo pačiu būtina mažinti perteklinės diagnostikos ir mažos rizikos PV gydymo riziką [2].

Priimant sprendimą dėl tolimesnio paciento gydymo ypatingai svarbu atskirti kliniškai reikšmingą prostatos vėžį (krPV) nuo kliniškai nereikšmingo (knPV) prostatos vėžio. KrPV apibūdinamas kaip Gleason ≥ 7 histologiniai pakitimai prostatoje, didesnis naviko tūris ar stebimas ekstrakapsulinis išplitimas – pakitimai, lemiantys prastesnes paciento išeitis, o knPV paprastai neturi reikšmingos įtakos paciento gyvenimo trukmei [40]. Tradiciškai PV diagnostika rėmėsi prostatos specifinio antigeno (PSA) tyrimu, digitaliniu rektaliniu tyrimu (DRT) ir sistemine transrektaline ultragarsu kontroliuojama biopsija. Tačiau nustatyta, kad šie metodai turi ribotą jautrumą ir specifiškumą, gali lemti tiek praleistus kliniškai reikšmingo PV atvejus, tiek nereikalingas biopsijas kliniškai nereikšmingo PV atvejais. Pastaraisiais metais vis daugiau dėmesio skiriama alternatyviems diagnostiniams metodams, tokiems kaip multiparametrinis magnetinio rezonanso tyrimas (mpMRT), genetiniai šlapimo biožymenys bei prostatos vėžio rizikos skaičiuoklės, kurie vertinami kaip perspektyvūs, neinvaziniai PV diagnostikos būdai [3].

mpMRT pripažintas efektyviu metodu vizualizuojant ir lokalizuojant kliniškai reikšmingus pakitimus bei padedančiu sumažinti nereikalingų biopsijų skaičių. Šis metodas tapo vienu iš pagrindinių PV diagnostikos įrankių, ypač pacientams, kuriems atliekama pirmoji biopsija gyvenime [4].

Genetiniai šlapimo biožymenys taip pat plačiai tiriami PV diagnostikos srityje. Šie biožymenys dažniausiai surenkami po DRT ir gali parodyti tiek PV, tiek krPV tikimyb. Jie pagrįsti specifinių genų raiškos, susijusios su aukšto laipsnio PV, nustatymu. Pagrindiniai prakitkoje naudojami biožymenys – prostatos vėžio antigenas 3 (PCA3) ir TMPRSS2:ERG genų suliejimas (T:E), kiekvienas turintis unikalią diagnostinę vertę. Naudojami kartu su žinomais rizikos veiksniais ir mpMRT rezultatais, genetiniai šlapimo biožymenys gali dar labiau padidinti diagnostinį tikslumą ir potencialiai sumažinti invazinių procedūrų poreikį [5].

Rizikos skaičiuoklės leidžia pateikti individualizuotas rizikos prognozes ir yra vis plačiau taikomos PV diagnostikos protokoluose. Prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (PCPTRC2, angl. *Prostate*

Cancer Prevention Trial Risk Calculator v.2.0) vertinimui naudoja tokius klinikinius veiksnius kaip PSA, paciento amžius, šeimos anamnezė ir DRT rezultatai, bei pateikia bendrą bei aukšto laipsnio PV rizikos prognozę [6]. Kitas plačiai Europoje taikomas įrankis – Europos atsitiktinės prostatos vėžio patikros studijos rizikos skaičiuoklė (ERSPCRC*,* angl. *European Randomized Study of Screening for Prostate Cancer Risk Calculator*) – remiasi PSA, prostatos tūriu ir ankstesnės biopsijos rezultatais, padėdama priimti sprendimus dėl tolimesnio gydymo [7]. Be šių klinikinių skaičiuoklių, biožymenų pagrindu veikiantys įrankiai, tokie kaip 4Kscore ir prostatos sveikatos indeksas (PHI, angl. *Prostate Health Index*), taip pat teikia didelę pridėtinę vertę nustatant kliniškai reikšmingą PV. 4Kscore apjungia keturis kalikreinų žymenis su klinikiniais duomenimis, kad įvertintų aukšto laipsnio PV riziką, o PHI sujungia bendrąjį, laisvąjį ir PSA prekursorių (proPSA), taip padidindamas PSA specifiškumą [8].

Naujausi tyrimai rodo, kad šių skaičiuoklių derinimas su mpMRT ar šlapimo biožymenimis, tokiais kaip PCA3 ar T:E, dar labiau pagerina PV diagnostiką ir sumažina nereikalingų biopsijų skaičių [9]. Nepaisant šių pažangių diagnostikos metodų, šiuo metu vis dar nėra visuotinai patvirtinto diagnostikos protokolo pacientams, kuriems biopsija atliekama pirmą kartą gyvenime. Todėl būtini palyginamieji tyrimai, siekiant įvertinti mpMRT, genetinių šlapimo biožymenų ir rizikos skaičiuoklių veiksmingumą ankstyvoje kliniškai reikšmingo prostatos vėžio diagnostikoje.

1. TIKSLAS IR UŽDAVINIAI

1.1. Tikslas

Nustatyti ir palyginti multiparametrinio magnetinio rezonanso tomografijos, genetinių šlapimo biožymenų tyrimo ir prostatos vėžio rizikos skaičiuoklės diagnostinę vertę nustatant kliniškai reikšmingą prostatos vėžį (Gleason $\geq 3 + 4$).

1.2. Uždaviniai

1. Įvertinti multiparametrinio magnetinio rezonanso tomografijos (mpMRT) diagnostinę vertę nustatant kliniškai reikšmingą prostatos vėžį pacientams prieš pirmą prostatos biopsiją gyvenime
2. Nustatyti genetinių šlapimo biožymenų tyrimo jautrumą ir specifiškumą kliniškai reikšmingo prostatos vėžio nustatyme pacientams prieš pirmą prostatos biopsiją gyvenime.
3. Įvertinti prostatos vėžio rizikos skaičiuoklės v.2.0 (PCPTRC2, angl. *Prostate Cancer Prevention Risk Calculator v.2.0*) tikslumą nusta-

tant kliniškai reikšmingo prostatos vėžio riziką pacientams, niekada neturėjusiems prostatos biopsijos.

4. Išanalizuoti skirtingų diagnostinių metodų derinių vertę diagnozuojant kliniškai reikšmingą prostatos vėžį pacientams, kurie niekada nėra turėję prostatos biopsijos, ir pateikti diagnostines rekomendacijas ankstyvai kliniškai reikšmingo prostatos vėžio diagnostikai.

1.3. Darbo naujumas

Mūsų žiniomis, tai yra pirmasis tyrimas, kuriame vertinama mpMRT ir genetinių šlapimo biožymenų (PCA3 ir T:E) kombinacijos reikšmė diagnozuojant kliniškai reikšmingą prostatos vėžį (krPV) pacientams, prieš pirmą prostatos biopsiją gyvenime. Klinikinėje praktikoje šiuo metu nėra patvirtintų diagnostikos protokolų, skirtų įtariamo prostatos vėžio nustatymui iki pirmosios prostatos biopsijos. Ankstesnių tyrimų metu buvo ieškoma ryšio tarp mpMRT ir PCA3 krPV nustatyme. Pavyzdžiui, Fenstermaker ir kt. išanalizavo 187 pacientus, kuriems anksčiau nebuvo atlikta biopsija ir kuriems buvo atliktas ir mpMRT, ir PCA3 testas. Atlikus prostatos biopsiją buvo nustatytas ryšys tarp PCA3 reikšmės, mpMRT išvados ir histopatologinio tyrimo atsakymo (AUC = 0,67; 95 % PI: 0,59–0,76) [10]. Porpiglia ir kt. retrospektyviai išnagrinėjo 120 pacientų, kuriems anksčiau nebuvo atlikta prostatos biopsija, duomenis ir nustatė, kad mpMRT turėjo reikšmingai didesnį prognozinį tikslumą krPV atžvilgiu nei PCA3 (AUC = 0,78; $p < 0,01$) [11]. Jau 2019 m. San Francisko konsensuso išvadose buvo pabrėžta genetinių biožymenų klinikinė vertė prostatos vėžio diagnostikoje [12]. Išvadose aiškiai apibrėžta papildoma diagnostinių testų ir biožymenų vertė, kurią mūsų tyrimas siekia įvertinti ir pagrįsti taikant mpMRT, genetinių biožymenų bei jų derinių vertinimą. Vis dėlto mūsų tyrimo naujumas labiausiai susijęs su prospektyviu tyrimo dizainu, didesne pacientų imtimi ir platesniu diagnostinių metodų taikymo vertinimu. Skirtingai nei ankstesniuose tyrimuose, mūsų darbe buvo ne tik vertinami mpMRT ir PCA3 rezultatai, bet ir įtrauktas T:E biožymuo, prostatos vėžio rizikos skaičiuoklės (PCPTRC2) nustatyta rizika bei atlikta įvairių diagnostinių metodų kombinacijų vertės analizė. Integruodami kelis diagnostikos metodus, siekėme pateikti išsamesnę ir kliniškai pritaikomą strategiją ankstyvam krPV nustatymui pacientams, prieš pirmą prostatos biopsiją gyvenime.

Šiuo metu Lietuvoje yra įgyvendinta keletas vėžio prevencinių patikros programų, tačiau prostatos vėžio ankstyvosios diagnostikos programa išlieka viena labiausiai kritikuojamų. Ji dažnai vertinama kaip nepakankamai pagrįsta, dažniausiai argumentuojant per dideliu ankstyvos stadijos kliniškai nereikšmingo PV (knPV) atvejų, kurie nereikalauja gydymo, skaičiaus nusta-

tymu. PV mirtingumas yra tiesiogiai susijęs su nustatyta rizikos grupe. 2013 m. atliktas tyrimas parodė, kad mažos rizikos pacientų mirtingumo rodikliai yra tokie patys, kaip sveikų asmenų kontrolinėje grupėje. Tuo tarpu didelės rizikos pacientai, ypač sergantys išplitusiu PV, pasižymi reikšmingai didesniu mirtingumu nei bendroji populiacija [13]. Šie duomenys rodo, kad mažos rizikos pacientams neturėtų būti taikomas gydymas ar papildomos invazinės diagnostinės procedūros – jie turėtų būti stebimi taikant aktyvų stebėjimą. Pagrindinis dėmesys gydyme turėtų būti skiriamas didelės rizikos pacientų valdymui.

2. METODIKA

2.1. Tyrimo eiga

Prospektyvusis vieno centro tyrimas buvo atliktas Lietuvos sveikatos mokslų universiteto ligoninėje Kauno klinikų (Kauno klinikų) Radiologijos ir Urologijos klinikose. Pagrindinis tyrimo tikslas buvo įvertinti mpMRT ir genetinių šlapimo biožymenų – PCA3 ir T:E – diagnostinę vertę nustatant krPV vyrams, prieš pirmą prostatos biopsiją gyvenime. Tyrimo protokolą patvirtino Regioninis biomedicininių tyrimų etikos komitetas (sprendimo Nr. BE-2-116, 2020-09-28) (1 priedas). Visi dalyviai prieš įtraukimą į tyrimą pasirašė informuoto sutikimo formą, laikantis Helsinkio deklaracijos principų.

2022 m. sausio – 2024 m. rugpjūčio laikotarpiu buvo atrinkti 246 vyrai, turintys padidėjusį PSA kiekį (nuo >2 iki <20 ng/ml) ir (arba) nenormalius digitalinio rektalinio tyrimo (DRE) rezultatus. Atmetus atitinkamų kriterijų neatitinkančius asmenis – turėjusius ankstesnę prostatos biopsiją, diagnozuotą ar gydomą onkologinę ligą, netinkamą amžių pagal PCPTRC2 skaičiuoklės taikymo ribas (55–90 m.), nesėkmingą šlapimo mėginių analizę arba kontraindikacijas MRT tyrimui – į galutinę imtį buvo įtraukti 208 pacientai.

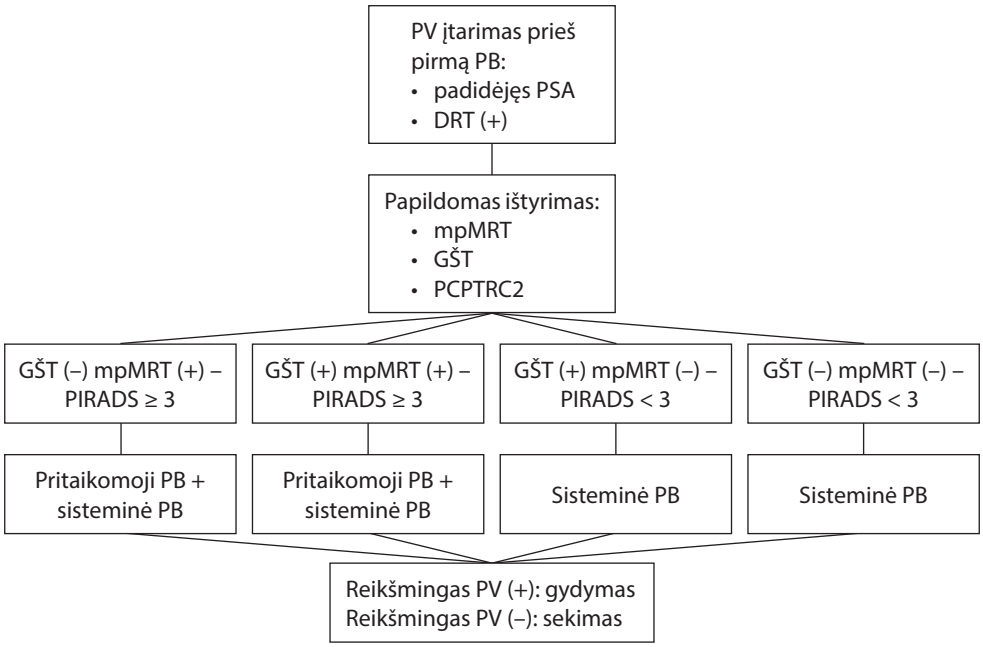
Visiems dalyviams buvo atliktas mpMRT tyrimas su intraveniniu kontrastiniu preparatu, naudojant 1,5 T arba 3 T magnetinio rezonanso aparatus („Siemens“ arba „Philips“). Buvo taikytas standartizuotas tyrimo protokolas, apimantis pasiruošimą (mikroklizma, 4–6 val. badavimas) ir kontrastinės medžiagos (gadolinio) suleidimą. Atvykęs į tyrimą pacientas užpildė standartinę MRT sutikimo formą (2 priedas). Visiems pacientams buvo atliktos sekančios mpMRT sekos: T1, T2, DWI ir dinaminio kontrastavimo (DCE). Vaizdus vertino du patyrę radiologai, naudodami PIRADS v2.1 klasifikaciją. Nustatyti PIRADS 3–5 pažeidimai buvo pažymėti prostatos žemėlapyje ir tapo pagrindu kognityvinės taikinių biopsijos atlikimui kartu su sistemine 12 mėginių transrektaline biopsija. Esant nustatytiems PIRADS 1–2 pažeidimams buvo atlikta tik sisteminė prostatos biopsija.

Be mpMRT, visiems pacientams buvo atliktas neinvazinis genetinių biožymenų tyrimas – surinkus pirmąją šlapimo porciją po digitalinio rektalinio tyrimo, mėginiai stabilizuoti naudojant specialius „Colli-Pee“ mėginių surinkimo indus ir analizuoti UAB „Diagnolita“ laboratorijoje, akredituotoje pagal ISO 15189:2023 standartą. RT-qPCR metodu buvo kiekybiškai įvertinta PCA3 ir T:E genų raiška, normalizuota pagal PSA mRNR. Šie biožymenys pasirinkti dėl jų žinomo ryšio su krPV ir buvo integruoti į PV rizikos vertinimo skaičiuoklę.

Tyrimo metu taip pat buvo naudojama prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (PCPTRC2). Buvo vertinamos trys šios skaičiuoklės versijos: bazinė (įtraukianti demografinius ir klinikinius duomenis), versija su papildomai įtraukta PCA3 biožymens verte bei išplėsta versija su PCA3 ir T:E biožymenų vertėmis. Kiekvienos versijos rezultatai buvo palyginti su histologiniais biopsijos rezultatais, įvertinant jų gebėjimą prognozuoti bendrą prostatos vėžį, krPV ir knPV bei neigiamus atvejus, kai vėžiniams būdingi pakitimai nebuvo nustatyti.

Po histologinio audinių ištyrimo tolimesnė pacientų priežiūra priklausė nuo krPV buvimo arba nebuvimo. Nustačius krPV, pacientams buvo paskirtas atitinkamas gydymas, o nenustačius krPV pacientai buvo nukreipti aktyviai stebėsenai. Pacientų diagnostinis algoritmas pateiktas 2.2.1 pav.

Visi statistiniai skaičiavimai buvo atlikti naudojant R programos 4.3.2 versiją. Duomenų normalumas vertintas Shapiro-Wilk testu, grupių palyginimai atlikti naudojant Student t-testą, Wilcoxon rangų sumos testą ir Fisher tiksliąjį testą. Jautrumas, specifiškumas ir 95 proc. pasikliautiniai intervalai buvo skaičiuoti taikant tikslius binominius metodus. ROC kreivių analizė buvo atlikta visiems PCPTRC2 modeliams, ypatingą dėmesį skiriant 75–100 proc. jautrumo intervalui, kuris svarbus kliniškai reikšmingo vėžio nustatymui [102]. Modelių palyginimui naudotas vienpusis DeLong testas, o daliniai AUC palyginimai atlikti naudojant bootstrap metodą. Skirtumai buvo statistiškai reikšmingi kai $p \leq 0,05$.



2.2.1 pav. *Pacientų diagnostinio algoritmo schema*

PV – prostatos vėžys; mpMRT – multiparametrnis magnetinio rezonanso tomografijos tyrimas; GŠT – genetinis šlapimo testast; PIRADS –Prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (PCPTRC2, angl. *Prostate Cancer Prevention Trial Risk Calculator 2*); PB – prostatos biopsija; krPV – kliniškai reikšmingos prostatos vėžys.

3. REZULTATAI

3.1. Tyrimo populiacijos charakteristika

Į tyrimą buvo įtraukti 208 pacientai vyrai, jų charakteristikos, mpMRT, GŠT, PCPTRC2 rezultatai ir prostatos biopsijos duomenys pateikti 3.1.1 lentelėje. Tiriamųjų vidutinis amžius buvo 63 metai, svyravęs nuo 43 iki 87 metų, vidutinė PSA koncentracija siekė 6,3 ng/ml, o PSA tankio vidurkis buvo 0,15 ng/ml/ml. Vidutinis prostatos tūris buvo 51,2 ml, o digitalinio rektalinio tyrimo (DRT) metu įtartini pakitimai nustatyti 51,4 proc. atvejų. Teigiama prostatos vėžio šeiminė anamnezė buvo nustatyta 13,5 proc. pacientų. Remiantis GŠT vertinimu, 67,8 proc. pacientų (141 atvejis) buvo priskirti prie GŠT teigiamų, 28,8 proc. (60 atvejų) – prie GŠT neigiamų, o 3,4 proc. (7 atvejais) GŠT vertinimas nebuvo atliktas. Vidutinė prognozuota kliniškai reikšmingo prostatos vėžio (krPV) rizika pagal GŠT modelį sudarė 26,1 proc. Multiparametrinės magnetinio rezonanso tomografijos (mpMRT) duomenimis, 81,7 proc. pacientų (170 atvejų) PIRADS balas buvo ≥ 3, o 18,3 proc.

(38 atvejai) – mažesnis nei 3. Vidutinė prognozuota krPV rizika pagal PRCTPRC2 skaičiuoklę sudarė 11,6 proc. Biopsijos rezultatai parodė, kad 53,8 proc. pacientų (112 atvejų) buvo nustatytas krPV (Gleasono balas ≥ 7), o 46,2 proc. (96 atvejai) buvo neigiami arba nustatytas Gleasono balas < 7. Kombinuota GŠT ir mpMRT analizė parodė, kad 63,2 proc. pacientų (127 atvejai) buvo GŠT teigiami ir mpMRT teigiami, 10,9 proc. (22 atvejai) buvo GŠT neigiami ir mpMRT neigiami, 7 proc. (14 atvejų) buvo GŠT teigiami, bet mpMRT neigiami, o 18,9 proc. (38 atvejai) buvo GŠT neigiami, bet mpMRT teigiami.

3.1.1 lentelė. *Pacientų charakteristikos*

Parameteras		**Reikšmė**
Atvejų skaičius, n		208
Amžius (metais)	Vidurkis ± SD	62,9 ± 7,2
	Mediana	63
	Intervalas	43–87
Bendras PSA (ng/ml)	Vidurkis ± SD	6,3 ± 2,9
	Mediana	5.5
	Intervalas	2,7–19,1
PSA tankumas (ng/ml/ml)	Vidurkis ± SD	0,15 ± 0,11
	Mediana	0,12
	Intervalas	0,04–0,79
Prostatos tūris	Vidurkis ± SD	51,2 ± 22,1
	Mediana	44,8
	Intervalas	13,5–129,1
DRT įtartini pakitimai, n (proc.)	Nustatyti	107 (51,4)
	Nenustatyti	101 (48,6)
Šeiminė anamnezė, n (proc.)	Teigiama	28 (13,5)
	Neigiama	180 (86,5)
GŠT vertinimas, n (proc.)	Neigiamas	60 (28,8)
	Teigiamas	141 (67,8)
	Nevertintas	7 (3,4)
GŠT prognozuojama krPV rizika (proc.)	Vidurkis ± SD	26,1 ± 18,7
	Mediana	23
	Intervalas	1,0–86,9
mpMRT, n (proc.)	PIRADS < 3	38 (18,3)
	PIRADS ≥ 3	170 (81,7)

3.1.1 lentelės tęsinys

Parameteras		Reikšmė
PRCTPRC2 krPV rizika (proc.)	Vidurkis ± SD	11,6 ± 5,9
	Mediana	10
	Intervalas	4–41
Biopsijos rezultatas, n (proc.)	Neigiamas GS < 7	96 (46,2)
	GS ≥ 7	112 (53,8)
GŠT vertinimas ir mpMRI PIRADS vertė, n (proc.)	GŠT teigiamas, mpMRI teigiamas	127 (63,2)
	GUT neigiamas, mpMRI neigiamas	22 (10,9)
	GUT teigiamas, mpMRI neigiamas	14 (7)
	GUT neigiamas, mpMRI teigiamas	38 (18,9)
	Nevertinta	7 (3,4)

n – skaičius; SN – standartinis nuokrypis; PSA – prostatos specifinis antigenas; PSAD – PSA tankis; DRT – digitalinis rektalinis tyrimas; GŠT – genetinis šlapimo tyrimas; mpMRT – multiparametrinis magnetinio rezonanso tyrimas; PIRADS – prostatos vaizdinės diagnostikos ir aprašymo sistema 2.1 versija (angl. *prostate imaging reporting and data system v.2.1*); PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator* version 2.0).

Iš į tyrimą įtrauktų pacientų, 165 pacientams (79,3 proc.) buvo diagnozuotas prostatos vėžys (PV), įskaitant 112 atvejų (53,8 proc.) kliniškai reikšmingo prostatos vėžio (krPV) ir 53 atvejus (25,5 proc.) kliniškai nereikšmingo prostatos vėžio (knPV), o 43 pacientams (20,7 proc.) piktybinio naviko požymių nenustatyta. Bendra pacientų amžiaus mediana buvo 63 metai, amžiaus ribos – nuo 43 iki 87 metų, o vidutinis PSA lygis sudarė 6,3 ng/ml. PSA koncentracija statistiškai reikšmingai skyrėsi tarp grupių – krPV pacientams vidutinė reikšmė siekė 6,7 ng/ml, tuo tarpu neigiamo PV grupėje – 5,3 ng/ml ($p = 0,015$). PSA tankis taip pat stipriai koreliavo su kliniškai reikšmingu vėžiu – krPV grupėje jo vidurkis sudarė 0,16 ng/ml/ml, palyginti su 0,11 ng/ml/ml neigiamo PV grupėje ($p < 0,001$). Teigiamas GŠT rezultatas buvo nustatytas 82,1 proc. krPV atvejų (92 iš 112), reikšmingai dažniau nei neigiamo PV ir knPV grupėje, kuriose teigiamą GŠT turėjo tik 55,8 proc. ir 45,2 proc. pacientų, atitinkamai kiekvienoje grupėje ($p < 0,001$). GŠT modelio prognozuota rizika susirgti krPV taip pat buvo reikšmingai didesnė krPV grupėje – šios grupės pacientų rizika mediana siekė 28,7 proc., tuo tarpu knPV grupėje – 23,4 proc., o neigiamo PV grupėje – 5,7 proc. ($p < 0,001$). mpMRT tyrimo rezultatai atitiko šias tendencijas – 93,8 proc. krPV pacientų PIRADS įvertinimas buvo ≥ 3, nustatytas reikšmingai didesniam skaičiui pacientų palyginti su 73,6 proc. knPV grupėje ir 60,5 proc. pacientų neigiamo PV grupėje ($p < 0,001$). GŠT ir mpMRT derinys dar labiau sustiprino diag-

nostinę vertę – 76,8 proc. krPV pacientų buvo teigiami abiejuose vertinimuose ir tik 0,9 proc. buvo neigiami pagal abu metodus ($p < 0,001$). Priešingai, tik 1,9 proc. pacientų knPV grupėje buvo neigiami pagal abu vertinimus ir 11,5 proc. neigiamo PV atvejų buvo teigiami pagal abu testų rezultatus. Pacientų pasiskirstymas pagal histopatologinius biopsijos rezultatus pateikiamas 3.1.2 lentelėje.

Tolimesniems statistiniams skaičiavimams pacientai buvo suskirstyti į dvi grupes, remiantis histopatologinio tyrimo duomenimis: kliniškai reikšmingo prostatos vėžio (krPV) ir kliniškai nereikšmingo prostatos vėžio (ne-krPV). KrPV buvo apibrėžtas kaip pakitimai, kurių Gleasono balas yra 7 arba didesnis, atitinkantis ISUP 2 arba aukštesnę laipsnių grupę. ne-krPV grupei priskirti navikai su Gleasono balu 6 (ISUP 1 laipsnio grupė), taip pat atvejai, kai biopsijoje piktybinių pokyčių nebuvo nustatyta. Bendras PSA kiekis ir PSA tankis reikšmingai skyrėsi tarp šių grupių ($p \leq 0,05$). PSA tankis taip pat buvo reikšmingai didesnis krPV pacientams (0,16 ng/ml/ml), palyginti su ne-krPV pacientais ($0,13 \pm 0,11$ ng/ml/ml, $p < 0,001$). Teigiamas GŠT rezultatas buvo nustatytas reikšmingai didesnei daliai krPV atvejų – 92 iš 112 (82,1 proc.) – palyginti su 49 iš 96 (51 proc.) ne-krPV grupėje ($p < 0,001$). Be to, GŠT modelio prognozuojama krPV rizika buvo reikšmingai didesnė krPV grupėje – vidutinė reikšmė siekė 28,7 %, palyginti su 12,8 proc. ne-krPV grupėje ($p < 0,001$). Teigiamas mpMRT rezultatas, apibrėžiamas kaip PIRADS ≥ 3 ir buvo nustatytas 93,8 proc. krPV atvejų, reikšmingai dažniau nei 67,7 proc. ne-krPV grupėje. GUT rezultatų ir mpMRT duomenų derinys parodė, kad dauguma krPV pacientų (78,9 proc.) buvo tiek GŠT teigiami, tiek mpMRT teigiami, o tai buvo reikšmingai dažniau nei ne-krPV grupėje (44,6 proc.), tuo tarpu tiek GŠT, tiek mpMRT neigiami rezultatai dažniau pasitaikė ne-krPV pacientams (22,8 proc. *vs.* 0,9 proc., $p < 0,001$). Pacientų pasiskirstymas pagal biopsijos metu patvirtintus histopatologinius rezultatus (krPV ir ne-krPV) pateiktas 3.1.3 lentelėje.

3.1.2 lentelė. *Pacientų charakteristikų stratifikacija pagal prostatos biopsijos rezultatus*

Parametras		**Neigiamas PV rezultatas**	**Visas PV**	**knPV**	**krPV**	**p reikšmė**
Atvejų skaičius, n		43 (20,7)	165 (79,3)	53 (25,5)	112 (53,8)	
Amžius (metais)	Vidurkis ± SD	61,0 ± 7,2	62,3 ± 7,2	62,3 ± 7,3	63,4 ± 7,1	0,245
	Mediana	62	63	63	63	
	Intervalas	43–73	50–87	51–82	50–87	
Bendras PSA (ng/ml)	Vidurkis ± SD	**5,3 ± 1,5**	6,2 ± 2,8	6,5 ± 2,6	**6,7 ± 3,0**	**0,015**
	Mediana	5,3	5,6	5,6	5,7	
	Intervalas	3,2–10,9	2,7–18,4	2,9–18,1	3,0–19,1	
PSA tankumas (ng/ml/ml)	Vidurkis ± SD	**0,11 ± 0,09**	0,15 ± 0.11	0.14 ± 0.11	**0,16 ± 0,11**	**< 0,001**
	Mediana	0,09	0,13	0,11	0,14	
	Intervalas	0,04–0,52	0,04–0,79	0,04–0,76	0,05–0,79	
GŠT vertinimas, n (proc.)	Neigiamas	18 (41,9)	43 (26,3)	26 (49,5)	17 (15,2)	**< 0,001**
	Teigiamas	**24 (55,8)**	116 (70,3)	**24 (45,3)**	**92 (82,1)**	
	Nevertintas	1 (2,3)	6 (3,7)	3 (5,7)	3 (2,7)	
GŠT prognozuojama krPV rizika (proc.)	Vidurkis ± SD	**9,2 ± 9,1**	24,9 ± 19,4	**27,8 ± 18,1**	**30,8 ± 17,5**	**< 0,001**
	Mediana	5,7	21,6	23,4	28,7	
	Intervalas	1.0–35,4	1.0–86.9	1.0–72.8	3.3–86.9	

3.1.2 lentelės tęsinys

Parametras		Neigiamas PV rezultatas	Visas PV	knPV	krPV	p reikšmė
mpMRT, n (proc.)	PIRADS < 3	16 (37,2)	21 (12,7)	14 (28,2)	7 (6,2)	**< 0,001**
	PIRADS ≥ 3	**26 (60,5)**	144 (87,3)	**39 (73,6)**	**105 (93,8)**	
GŠT vertinimas ir mpMRI PIRADS vertė, n (proc.)	GŠT teigiamas, mpMRI teigiamas	**5 (11,5)**	122 (73,9)	**36 (67,8)**	**86 (76,8)**	**< 0,001**
	GUT neigiamas, mpMRI neigiamas	**20 (46,5)**	2 (1,2)	1 (1,9)	**1 (0,9)**	
	GUT teigiamas, mpMRI neigiamas	**2 (4,7)**	12 (7,3)	6 (11,4)	**6 (5,4)**	
	GUT neigiamas, mpMRI teigiamas	**14 (32,6)**	24 (14,5)	**8 (15,1)**	**16 (14,3)**	
	Nevertinta	2 (4,7)	5 (3,1)	2 (3,8)	3 (2,6)	

n – skaičius; SN – standartinis nuokrypis; PSA – prostatos specifinis antigenas; PSAD – PSA tankis; DRT – digitalinis rektalinis tyrimas; GŠT – genetinis šlapimo tyrimas; mpMRT – multiparametrinis magnetinio rezonanso tyrimas; PIRADS – prostatos vaizdinės diagnostikos ir aprašymo sistema versija 2.1 (angl. *prostate imaging reporting and data system v.2.1*); PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); krPV – kliniškai reikšmingas prostatos vėžys; knPV – kliniškai nereikšmingas prostatos vėžys.

3.1.3 lentelė. *Pacientų charakteristikų stratifikacija pagal prostatos biopsijos rezultatus*

Parameteras		**ne-krPV**	**krPV**	**p reikšmė**
Atvejų skaičius, n (proc.)		96 (46,2)	112 (53,8)	
Amžius (metais)	Vidurkis ± SD	62,3 ± 7,3	63,4 ± 7,1	0,267
	Mediana	63	63	
	Intervalas	43–82	50–87	
Bendras PSA (ng/ml)	Vidurkis ± SD	5,8 ± 2,7	6,7 ± 3,0	0,013
	Mediana	5,2	5,7	
	Intervalas	2,7–18,7	3,0–19,1	
PSA tankumas (ng/ml/ml)	Vidurkis ± SD	0,13 ± 0,11	0,16 ± 0,11	< 0,001
	Mediana	0,1	0,14	
	Intervalas	0,04–0,73	0,05–0,79	
Prostatos tūris	Vidurkis ± SD	56,2 ± 26,4	46,9 ± 16,6	0,041
	Mediana	48,4	43,4	
	Intervalas	13,7–129,1	13,5–92,0	
DRE įtartini pakitimai, n (proc.)	Taip	44 (45,8)	63 (56,2)	0,164
	Ne	52 (54,2)	49 (43,8)	
Šeiminė anamnezė, n (proc.)	Teigiama	14 (14,6)	14 (12,5)	0,688
	Neigiama	82 (85,4)	98 (87,5)	
GŠT vertinimas, n (proc.)	Neigiamas	43 (44,8)	17 (15,2)	< 0,001
	Teigiamas	49 (51,0)	92 (82,1)	
	Nevertintas	4 (4,2)	3 (2,7)	
GŠT prognozuojama krPV rizika (proc.)	Vidurkis ± SD	20,7 ± 18,6	30,8 ± 17,5	< 0,001
	Mediana	12,8	28,7	
	Intervalas	1,0–72,8	3,3–86,9	
mpMRI PIRADS vertė, n (proc.)	PIRADS < 3	31 (32,3)	7 (6,2)	< 0,001
	PIRADS ≥ 3	65 (67,7)	105 (93,8)	
PRCTPRC2 krPV rizika (proc.)	Vidurkis ± SD	10,8 ± 5,7	12,3 ± 6,0	0,031
	Mediana	10	11	
	Intervalas	4–35	4–41	

3.1.3 lentelės tęsinys

Parameteras		ne-krPV	krPV	p reikšmė
GŠT vertinimas ir mpMRI PIRADS vertė, n (proc.)	GUT teigiamas, mpMRI teigiamas	41 (44,6)	86 (78,9)	< 0,001
	GUT neigiamas, mpMRI neigiamas	21 (22,8)	1 (0,9)	
	GUT teigiamas, mpMRI neigiamas	8 (8,7)	6 (5,5)	
	GUT neigiamas, mpMRI teigiamas	22 (23,9)	16 (14,7)	
	Nevertinta	4 (4,2)	3 (2,7)	

n – skaičius; SN – standartinis nuokrypis; PSA – prostatos specifinis antigenas; PSAD – PSA tankis; DRT – digitalinis rektalinis tyrimas; GŠT – genetinis šlapimo tyrimas; mpMRT – multiparametrinis magnetinio rezonanso tyrimas; PIRADS – prostatos vaizdinės diagnostikos ir aprašymo sistema versija 2.1 (angl. *prostate imaging reporting and data system v.2.1*); PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); krPV – kliniškai reikšmingas prostatos vėžys; ne-krPV – nekliniškai reikšmingas prostatos vėžys.

3.2. mpMRI, GUT ir PCPTRC2 metodų diagnostinio tikslumo palyginimas nustatant kliniškai reikšmingą prostatos vėžį

mpMRT pasižymėjo panašiu jautrumu – 93,8 proc. (95 proc. PI: 87,5–97,5) nustatant kliniškai reikšmingą prostatos vėžį (krPV), lyginant su PCPTRC2 (93,9 proc.), taip pat buvo pranašesnis už GŠT (84,4 proc., p = 0,033) (3.2.1 lentelė). Derinant mpMRT su PCPTRC2 arba GŠT, jautrumas dar labiau padidėjo – atitinkamai iki 99,0 proc. ir 99,1 proc. (p reikšmės nuo 0,025 iki < 0,001). Galiausiai, visų trijų metodų – mpMRT, GŠT ir PCPTRC2 – derinys pasiekė 100 proc. jautrumą (96,2–100) ir buvo jautriausias csPCa nustatymo variantas.

Vertinant specifiškumą (3.2.2 lentelė), mpMRT rodė geresnius rezultatus nei PCPTRC2 (32,3 proc. *vs.* 11,0 proc., p = 0,028), tačiau nusileido GŠT (46,7 proc., p = 0,011). Kombinuojant mpMRT su GŠT, specifiškumas siekė 25,0 proc.. Įdomu tai, kad visų diagnostinių metodų kombinacijos reikšmingai sumažino specifiškumą: mpMRT ir PCPTRC2 – 2,4 proc. (0,3–8,5), mpMRT ir GŠT – 25,0 proc. (16,6–35,1), o visų trijų derinys – 2,5 proc. (0,3–8,8).

3.2.1 lentelė. *Jautrumo palyginimas prognozuojant kliniškai reikšmingą prostatos vėžį (krPV), 95 proc. pasikliautiniai intervalai pateikti skliaustuose.*

Modelis	**krPV, n**	**Jautrumas, proc.**	**p reikšmė *vs.* PCPTRC2**	**p reikšmė *vs.* mpMRI**	**p reikšmė *vs.* GŠT**
PCPTRC2	99	93,9 (87,3–97,7)	NA	1	0,071
mpMRT	112	93,8 (87,5–97,5)	1	NA	0,033
GŠT	109	84,4 (76,2–90,6)	0,071	0,033	NA
mpMRT ir PCPTRC2	99	99,0 (94,5–100)	0,025	0,025	0,001
mpMRT ir GŠT	109	99,1 (95,0–100)	0,059	0,014	< 0,001
mpMRT ir PCPTRC2 ir GŠT	96	100 (96,2–100)	0,014	0,014	< 0,001

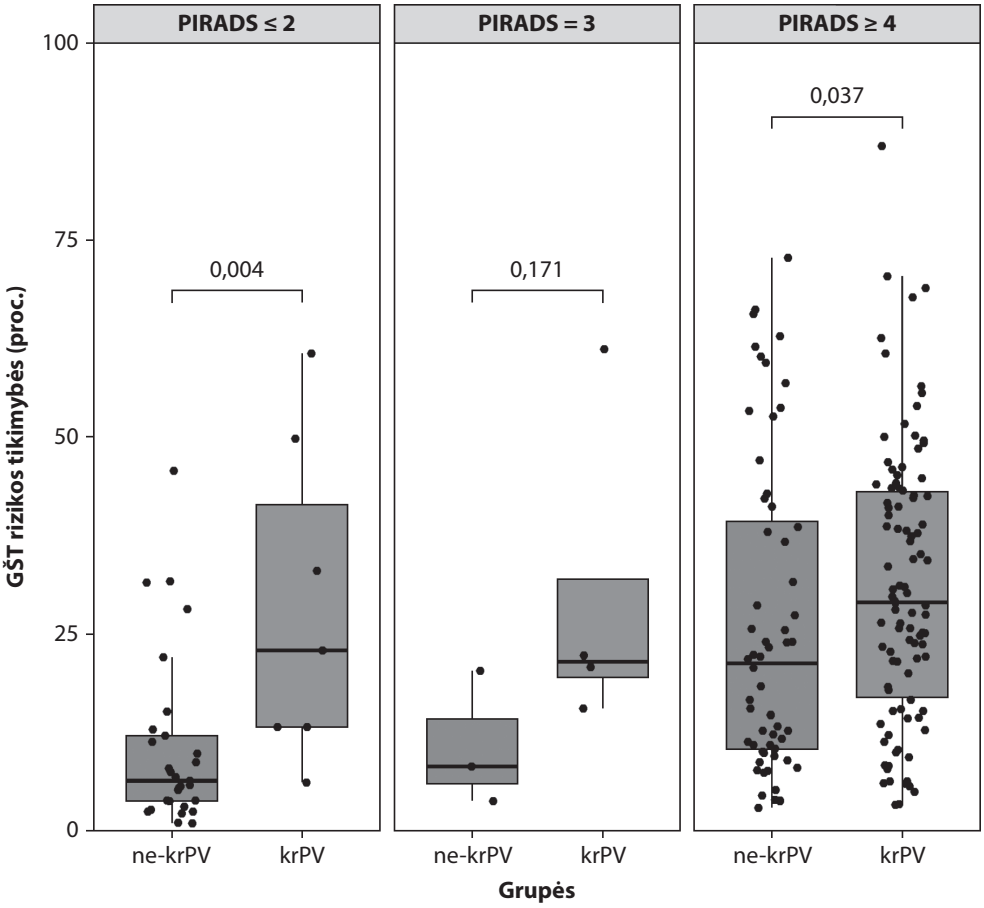
GŠT – genetinis šlapimo tyrimas; mpMRT – multiparametrinis magnetinio rezonanso tyrimas; PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); krPV – kliniškai reikšmingas prostatos vėžys; ne-krPV – nekliniškai reikšmingas prostatos vėžys.

3.2.2 lentelė. *Specifiškumo palyginimas prognozuojant kliniškai reikšmingą prostatos vėžį (krPV), 95 proc. pasikliautiniai intervalai pateikti skliaustuose*

Modelis	ne-krPV, n	Specifiškumas, proc.	p reikšmė *vs.* PCPTRC2	p reikšmė *vs.* mpMRI	p reikšmė *vs.* GŠT
PCPTRC2	82	11,0 (5,1–19,8)	NA	0,028	< 0,001
mpMRT	96	32,3 (23,1–42,6)	0,028	NA	0,011
GŠT	92	46,7 (36,3–57,4)	< 0,001	0,011	NA
mpMRT ir PCPTRC2	82	2,4 (0,3–8,5)	0,008	< 0,001	< 0,001
mpMRT ir GŠT	93	25,0 (16,6–35,1)	0,251	0,058	< 0,001
mpMRT ir PCPTRC2 ir GŠT	79	2,5 (0,3–8,8)	0,008	< 0,001	< 0,001

GŠT – genetinis šlapimo tyrimas; mpMRT – multiparametrinis magnetinio rezonanso tyrimas; PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); krPV – kliniškai reikšmingas prostatos vėžys; ne-krPV – nekliniškai reikšmingas prostatos vėžys.

Tarp pacientų, kurių PIRADS ≤ 2, GŠT prognozuotos krPV rizikos vertė buvo reikšmingai didesnė krPV grupėje nei ne-krPV (p = 0,004), o tai rodo, kad GŠT testas gali pagerinti diagnostinį jautrumą net ir esant mpMRT neigiamiems pakitimams (PIRADS ≤ 2). PIRADS 3 atvejais reikšmingo skirtumo tarp krPV ir ne-krPV grupių nepastebėta (p = 0,171). Tuo tarpu pacientams, kurių PIRADS ≥ 4, GŠT rizikos tikimybė vėl buvo statistiškai reikšmingai didesnė krPV grupėje, palyginti su ne-krPV (p = 0,037) (3.2.1 pav.).



3.2.1 pav. *GŠT rizikos tikimybės, suskirstytos pagal mpMRT PIRADS įvertinimus ir biopsijos rezultatus*

GŠT – genetinis šlapimo tyrimas, mpMRT – multiparametrinis magnetinio rezonanso tyrimas, PIRADS – prostatos vaizdinės diagnostikos ir aprašymų Sistema versija 2.1 (angl. *prostate imaging reporting and data system v.2.1*), krPV – kliniškai reikšmingas prostatos vėžys, ne-krPV – nekliniškai reikšmingas prostatos vėžys, apimantis neigiamas biopsijas ir GS = 6 prostatos vėžio atveju

3.3. Prostatos vėžio prevencijos tyrimo rizikos skaičiuoklės 2 versijos (PCPTRC2) veiksmingumas nustatant prostatos vėžį pacientams prieš pirmą prostatos biopsiją gyvenime

PCPTRC2 pasiekė 93,9 proc. jautrumą (95 proc. PI: 87,3–97,7), kuris buvo panašus į mpMRT (93,8 proc.) ir pranašesnis už GŠT testą (84,4 proc.), nors šis skirtumas nebuvo statistiškai reikšmingas (p = 0,071) (3.2.1 lentelė). Tačiau, kaip parodyta 3.2.2 lentelėje, skaičiuoklės specifiškumas buvo labai žemas – 11,0 proc. (95 proc. PI: 5,1–19,8), reikšmingai mažesnis nei mpMRT (32,3 proc., p = 0,028) ir GŠT (46,7 proc., p < 0,001). Visgi derinant PCPTRC2 su mpMRT, jautrumas padidėjo iki 99,0 proc., bet specifiškumas dar labiau sumažėjo – iki 2,4 proc., kas rodo, kad derinimas su vaizdinimu pagerina krPV nustatymą, bet tuo pačiu padidina klaidingai teigiamų rezultatų skaičių.

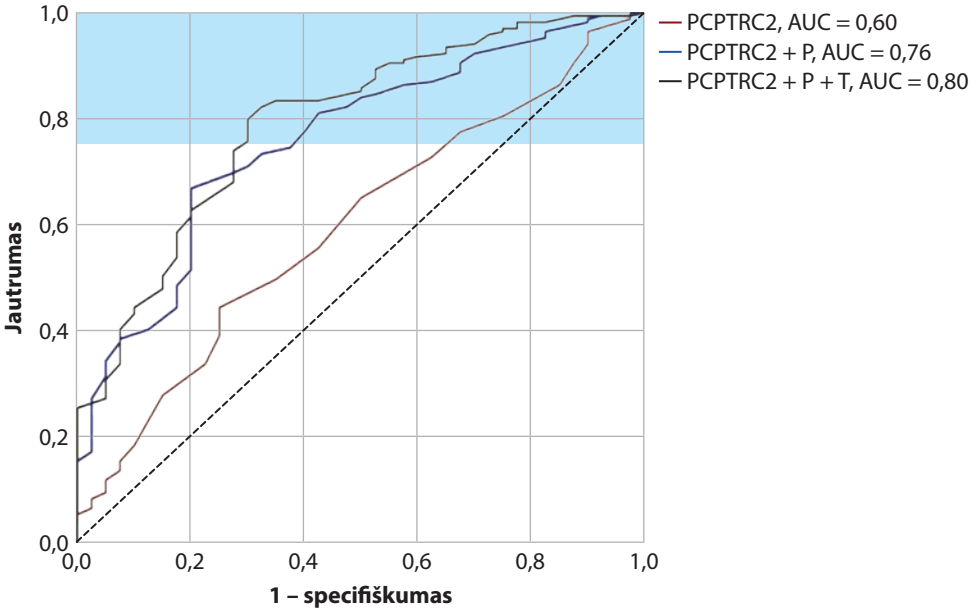
Vertinant PV rizikos prognozavimą, analizavome tris PCPTRC2 skaičiuoklės versijas. Bazinės versijos AUC siekė 59,6 proc., o atnaujinta versija su įtraukta PCA3 rodiklio verte padidino šį rodiklį iki 76,2 proc., o versija su integruotais PCA3 ir T:E rodikliais – iki 79,5 proc.. Atnaujintos versijos pasižymėjo statistiškai reikšmingai didesniu jautrumu nei originali (atitinkamai p = 0,001 ir p < 0,001) (3.3.1 lentelė, 3.3.1 pav.).

3.3.1 lentelė. *AUC palyginimai prognozuojant prostatos vėžį (PV), 95 proc. pasikliautiniai intervalai (PI) pateikti skliaustuose*

Modelis	AUC su PI, proc.	p reikšmės *vs.* PCPTRC2
PCPTRC2	59,6 (50,2–69,1)	NA
PCPTRC2 įtraukiant PCA3	76,2 (68,3–84,1)	0,001
PCPTRC2 įtraukiant PCA3 + T:E	79,5 (71,9–87,1)	< 0,001

Sisteminių ir taikinių biopsijų rezultatai buvo lyginami su DRT atliktų šlapimo mėginių duomenų duomenimis. Maksimalios leistinos PCA3 ir (arba) T:E reikšmės buvo priskirtos tais atvejais, kai apskaičiuoti biožymenų rodikliai viršijo skaičiuoklės nustatytas ribas. AUC palyginimai atlikti tiems atvejams, kuriuose skaičiuoklės rezultatai išliko galiojantys po reikšmių priskyrimo (n = 209).

PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. prostate cancer prevention trial risk calculator version 2.0); PCA3 – prostatos vėžio antigenas 3; T:E – TMPRSS2 ir ERG genų susiliejimas.



3.3.1 pav. *Įvairių prostatos vėžio rizikos skaičiuoklių versijų ROC kreivės ir AUC palyginimai, prognozuojant prostatos vėžį (PV)*

PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*), PCPTRC2+P – PCPTRC2 versija su PCA3 rodikliu, PCPTRC2 + P + T – PCPTRC2 versija su PCA3 ir TMPRSS2:ERG rodikliais.
Mėlyna spalva pažymėta sritis rodo 75–100 proc. jautrumo intervalą, kuris buvo naudojamas dalinės AUC skaičiavimui.

Vertinant krPV prieš PV nebuvimą arba ne-krPV, reikšmingų skirtumų tarp bazinės ir atnaujintų versijų nebuvo nustatyta ($p > 0,05$) (3.3.2 lentelė). Kadangi aukštas jautrumas yra itin svarbus diagnozuojant krPV [80], mūsų analizėje buvo sutelktas dėmesys į ROC kreivės dalį tarp 75 proc. ir 100 proc. jautrumo [14], sekant ankstesnių PV prognozavimo tyrimų metodika [82].

Prognozuojant krPV, atnaujinta PCPTRC2 versija su PCA3 pasiekė 7,8 proc. dalinę AUC, o versija su PCA3 ir T:E – 8,6 proc. Pastaroji rodė statistiškai reikšmingai geresnį veiksmingumą ($p = 0,043$) (3.3.3 lentelė, 3.3.2 pav.).

3.3.2 lentelė. *AUC palyginimai prognozuojant kliniškai reikšmingą prostatos vėžį (krPV), 95 proc. pasikliautiniai intervalai (PI) pateikti skliaustuose*

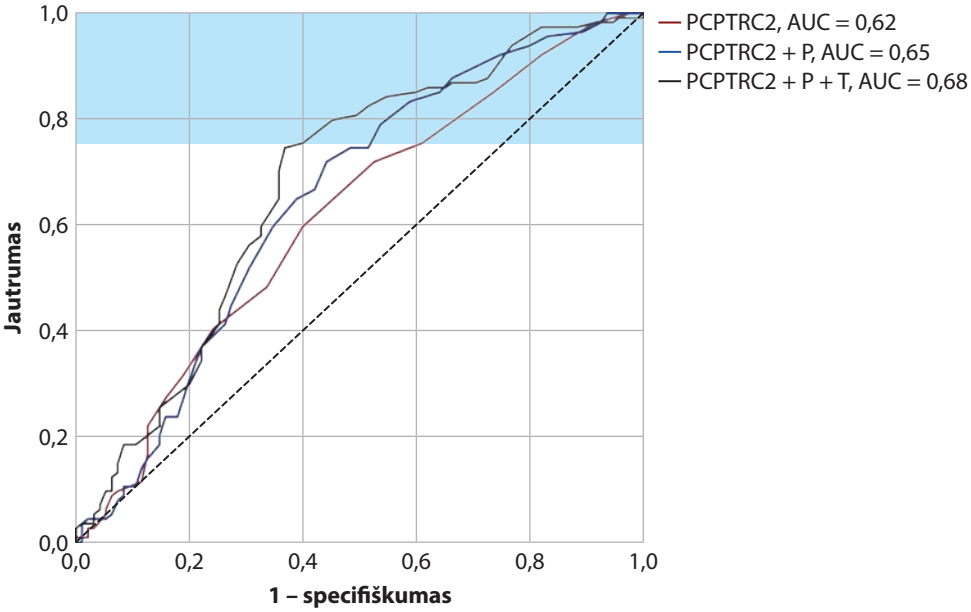
Modelis	AUC su PI, proc.	p reikšmė *vs.* PCPTRC2
PCPTRC2	61,6 (53,9–69,3)	NA
PCPTRC2 įtraukiant PCA3	64,9 (57,3–72,6)	0,150
PCPTRC2 įtraukiant PCA3 + T:E	67,8 (60,3–75,3)	0,058

Sisteminių ir taikinių biopsijų rezultatai buvo lyginami su DRT atliktų šlapimo mėginių duomenų duomenimis. Maksimalios leistinos PCA3 ir (arba) T:E reikšmės buvo priskirtos tais atvejais, kai apskaičiuoti biožymenų rodikliai viršijo skaičiuoklės nustatytas ribas. AUC palyginimai atlikti tiems atvejams, kuriuose skaičiuoklės rezultatai išliko galiojantys po reikšmių priskyrimo (n = 209).
PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); PCA3 – prostatos vėžio antigenas 3; T:E – TMPRSS2 ir ERG genų susiliejimas.

3.3.3 lentelė. *Dalinės AUC (1–0,75 jautrumo intervalas) palyginimai prognozuojant kliniškai reikšmingą prostatos vėžį (krPV), 95 proc. pasikliautiniai intervalai (PI) pateikti skliaustuose*

Modelis	Dalinės AUC su PI, proc.	p reikšmė *vs.* PCPTRC2
PCPTRC2	5,8 (3,7–8,5)	NA
PCPTRC2 įtraukiant PCA3	7,8 (5,4–10,7)	0,063
PCPTRC2 įtraukiant PCA3 + T:E	8,6 (5,7–11,8)	0,043

PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); PCA3 – prostatos vėžio antigenas 3; T:E – TMPRSS2 ir ERG genų susiliejimas.



3.3.2 pav. *Įvairių prostatos vėžio rizikos skaičiuoklių versijų ROC kreivės ir AUC palyginimai, prognozuojant kliniškai reikšmingą prostatos vėžį (krPV)*

PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); PCPTRC2 + P – PCPTRC2 versija su PCA3 rodikliu; PCPTRC2 + P + T – PCPTRC2 versija su PCA3 ir TMPRSS2:ERG rodikliais.
Mėlyna spalva pažymėta sritis rodo 75–100 proc. jautrumo intervalą, kuris buvo naudojamas dalinės AUC skaičiavimui.

3.3.3 lentelėje pateikiamos vidutinės skirtingų PCPTRC2 skaičiuoklės versijų – tiek bazinės, tiek papildytų šlapimo biožymenimis – prognozės, palyginant su faktiniais biopsijos rezultatais. Bazinėje PCPTRC2 versijoje vidutinė bet kokio prostatos vėžio (PV) nustatymo tikimybė siekė 30 proc., krPV – 11 proc., o ne-krPV – 19 proc. Neigiamų biopsijos rezultatų tikimybė vidutiniškai buvo prognozuojama 70 proc.

Į PCPTRC2 modelį įtraukus PCA3 biožymenį, vidutinė PV nustatymo tikimybė padidėjo iki 51 proc., krPV – iki 20 proc., ne-krPV – iki 30 proc., o neigiamų biopsijos rezultatų tikimybė sumažėjo iki 49 proc. Pridėjus tiek PCA3, tiek T:E biožymenis, prognozuojami nustatymo rodikliai dar labiau padidėjo: PV – iki 55 proc., krPV – iki 25 proc., ne-krPV liko 30 proc., o neigiamų biopsijų tikimybė sumažėjo iki 45 proc.

Remiantis biopsijos rezultatais, PV buvo nustatytas 81,3 proc. tirtų atvejų, iš jų krPV – 53,1 proc., ne-krPV – 28,2 proc., o neigiami rezultatai pasitaikė 18,7 proc. atvejų. Taigi galima daryti išvadą, kad PCPTRC2 rizikos

įvertinimai, ypač bazinėje versijoje, buvo per maži ir nepakankamai atspindėjo faktinę riziką.

3.3.4 lentelė. *Skirtingų PCPTRC2 rizikos skaičiuoklės versijų vidutinės prognozuojamos tikimybės, palygintos su biopsijos rezultatais (proc.)*

Vidutinės tikimybės	PV	krPV	ne-krPV	Neigiama biopsija
PCPTRC2 bazinė versija	30	11	19	70
PCPTRC2 + PCA3	51	20	30	49
PCPTRC2 + PCA3 + T:E	55	25	30	45
Biopsijos rezultatai	81,3	53,1	28,2	18,7

PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); PV – prostatos vėžys; krPV – kliniškai reikšmingas prostatos vėžys; ne-krPV – nekliniškai reikšmingas prostatos vėžys; PCA3 – prostatos vėžio antigenas 3; T:E – TMPRSS2 ir ERG genų susiliejimas.

3.4. Praleisti kliniškai reikšmingo prostatos vėžio atvejai ir išvengtos biopsijos

Įvairių modelių praleistų krPV atvejų bei išvengtų biopsijų skaičius pateikiamas 3.3.1 lentelėje. Nereikalingų biopsijų prevencijos požiūriu, efektyviausias buvo GŠT modelis – jis leido išvengti net 46,7 proc. biopsijų. Vis dėlto, naudojant tik GŠT būtų praleistas didžiausias krPV atvejų skaičius – 16,5 proc. Tuo tarpu visų trijų metodų derinys – mpMRT, GŠT ir PCPTRC2 – nepraleido nė vieno krPV atvejo (0 proc.). MpMRT deriniai su GŠT arba PCPTRC2 taip pat pasižymėjo itin mažu praleistų krPV atvejų skaičiumi – apie 1 proc. Esant neigiamam mpMRT, GŠT teisingai leido išvengti 72,4 proc. nereikalingų biopsijų (21 iš 29 atvejų) ir teisingai identifikavo 85,7 proc. pacientų, kuriems biopsija buvo būtina (6 iš 7). Visi kombinuoti modeliai buvo susiję su mažesniu išvengtų biopsijų skaičiumi – ypač mpMRT ir PCPTRC2 derinys (1,7 proc.) bei visų trijų metodų derinys, kuris sutaupė tik 1,1 proc. biopsijų (3.4.1 lentelė).

3.4.1 lentelė. *Praleisti kliniškai reikšmingo prostatos vėžio atvejai ir išvengtos biopsijos, taikant skirtingus modelius*

Modelis	Praleisti krPV atvejai	Sutaupytos biopsijos	Sutaupytos nereikalingos biopsijos
PCPTRC2	6 iš 99; 6,1 proc.	15 iš 181; 8,3 proc.	9 iš 82; 11,0 proc.
mpMRT	7 iš 112; 6,2 proc.	38 iš 208; 18,3 proc.	31 iš 96; 32,3 proc.
GŠT	18 iš 109; 16,5 proc.	63 iš 201; 31,3 proc.	43 iš 92; 46,7 proc.
mpMRT ir PCPTRC2	1 iš 99; 1,0 proc.	3 iš 181; 1,7 proc.	2 iš 82; 2,4 proc.
mpMRT ir GŠT	1 iš 109; 0,9 proc.	24 iš 201; 11,9 proc.	23 iš 92; 25,0 proc.
mpMRT ir PCPTRC2 ir GŠT	0 of 96; 0 proc.	2 of 175; 1,1 proc.	2 of 79; 2,5 proc.

GŠT – genetinis šlapimo tyrimas; mpMRT – daugiaparametrinis magnetinio rezonanso tyrimas; PCPTRC2 – prostatos vėžio prevencijos tyrimo rizikos skaičiuoklė versija 2.0 (angl. *prostate cancer prevention trial risk calculator version 2.0*); krPV – kliniškai reikšmingas prostatos vėžys.

IŠVADOS

1. MpMRT pasižymėjo aukštu jautrumu, tačiau nepakankamu specifiškumu diagnozuojant krPV.
2. GŠT yra mažiau jautrus, nei mpMRT ir PCPTRC2, tačiau pats specifiškiausias tyrimo metodas krPV diagnostikoje.
3. PCPTRC2 jautrumas diagnozuojant krPV buvo aukštas, tačiau specifiškumas žemiausias iš naudotų tyrimo metodų. Įtraukus PCA3 ir T:E, PCPTRC2 reikšmingai pagerino PV diagnostiką biopsijos anksčiau neturėjusiems pacientams.
4. Visų trijų diagnostikos metodų (mpMRT, GŠT ir PCPTRC2) derinys reikšmingai padidina krPV nustatymo jautrumą (iki 100 proc.), tačiau kartu labai sumažina specifiškumą (iki 2,4 proc.), todėl apriboja galimybę sumažinti perteklinių biopsijų skaičių. Tuo tarpu dviejų neinvazinių metodų – GŠT ir mpMRT – derinys gali reikšmingai sumažinti nereikalingų biopsijų skaičių, tuo pačiu minimaliai didinant krPV atvejų praleidimo riziką.

PRAKTINĖS REKOMENDACIJOS

1. Pagal 2023 metų Europos urologų asociacijos (EAU), Europos spindulinės terapijos ir onkologijos draugijos (ESTRO) bei Tarptautinės geriatrijos onkologijos draugijos (SIOG) atnaujintas klinikines gaires, prieš atliekant pirmąją prostatos biopsiją paciento gyvenime, rekomenduojama atlikti mpMRT tyrimą. Mūsų tyrimo rezultatai patvirtina šią rekomendaciją – dėl aukšto jautrumo (93,8 proc.) ir gero bendro diagnostinio tikslumo (AUC = 0,72) mpMRT turėtų būti pirmo pasirinkimo diagnostikos metodas įtariant krPV prostatos biopsijos anksčiau neturėjusiems pacientams.
2. Vien GŠT jautrumas siekė 84,4 proc., be to, šis metodas buvo specifiškiausias krPV diagnostikoje. Tai rodo, kad GŠT gali tiksliai atskirti krPV net PIRADS ≤ 2 atvejais, kai vien mpMRT ligą gali praleisti. Be to, šis testas pasiekė didžiausią biopsijų išvengimo rodiklį (31,3 proc.), taip prisidedant prie perteklinio gydymo ir nereikalingų prostatos biopsijų skaičiaus mažinimo.
3. Nors atnaujinta PCPTRC2 versija su įtrauktais šlapimo biomžymenimis (PCA3 ir T:E) pagerino bendrą skaičiuoklės diagnostinį tikslumą (AUC iki 79,5 proc. bet kokiam PV), ji vis dar nėra pakankamai specifiška (11 proc.) krPV nustatymui. Todėl PCPTRC2 neturėtų būti naudojama kaip vienintelis diagnostinis metodas sprendžiant dėl prostatos biopsijos, tačiau gali būti naudinga kaip papildomas įrankis klinikiniam sprendimui pagrįsti ir tolimesniems tyrimams, tokiems kaip mpMRT ar GŠT, rekomenduoti.
4. Nors trijų metodų derinys – mpMRT, GŠT ir PCPTRC2 – pasiekė 100 proc. jautrumą, šiam deriniui taip pat būdingas itin žemas specifiškumas (2,5 proc.) ir minimalus biopsijų išvengimo rodiklis (1,1 proc.). Todėl šie trigubi diagnostikos metodai turėtų būti taikomi tik didelės rizikos arba sudėtingais atvejais, o ne rutiniškai kasdienėje klinikinėje praktikoje. Kita vertus, mūsų tyrimo rezultatai parodė, kad mpMRT ir GŠT derinys yra reikšmingai efektyvus ankstyvai krPV diagnostikai. Šis derinys pasiekė 99,1 proc. jautrumą, rodantį puikią krPV diagnostiką. Be to, minėtas derinys leido sumažinti nereikalingų biopsijų skaičių 25 proc., kas svarbu ne tik klinikiniu požiūriu, bet ir siekiant sumažinti pacientų patiriamą stresą bei sveikatos apsaugos sistemos kaštus.

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Publications related to the results of the dissertation:

1. **Kemesiene J**, Nicolau C, Cholstauskas G, Zviniene K, Lopeta M, Veneviciute S, Asmenaviciute I, Tamosauskaite K, Pikuniene I, Jievaltas M. Performance of PCA3 and TMPRSS2:ERG Within the Prostate Cancer Prevention Trial Risk Calculator Version 2 in a Lithuanian Cohort. Res Rep Urol. 2025 Mar 29;17:95-103. doi: 10.2147/RRU.S511523. PMID: 40176971; PMCID: PMC11963794.
2. **Kemesiene J**, Nicolau C, Cholstauskas G, Zviniene K, Lopeta M, Veneviciute S, Asmenaviciute I, Tamosauskaite K, Pikuniene I, Jievaltas M. Usefulness of urinary biomarker-based risk score and multiparametric MRI for clinically significant prostate cancer detection in biopsy-naïve patients. Abdom Radiol (NY). 2025 Jan 25. doi: 10.1007/s00261-024-04727-5. Epub ahead of print. PMID: 39862284.

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A1

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RESEARCH

Usefulness of urinary biomarker-based risk score and multiparametric MRI for clinically significant prostate cancer detection in biopsy-naïve patients

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Abstract

Objectives This study aimed to investigate the accuracy of multiparametric magnetic resonance imaging (mpMRI), genetic urinary test (GUT), and prostate cancer prevention trial risk calculator version 2.0 (PCPTRC2) for the clinically significant prostate cancer (csPCa) diagnostic in biopsy-naïve patients.

Materials and methods In a single center study between 2021 and 2024 participants underwent prostate mpMRI, GUT, and ultrasound (US) guided biopsy. The csPCa risk was calculated using PCPTRC2. After conducting a digital rectal examination (DRE), a GUT was performed. It incorporated the RNA levels of prostate cancer antigen 3 (PCA3) and transmembrane serine protease 2 (TMPRSS2) gene and ETS-related gene (ERG) fusion genes (T: E), along with the patient's age and PSA density. The McNemar test compared detection rates between modalities.

Results 208 (mean age 62.9 years +/- 8.2) men were included prospectively. A positive GUT score was found in 67.8% and PIRADS ≥3 in 81.7% of all cases. The combination of GUT with mpMRI showed significantly higher sensitivity (99.1%) than GUT and mpMRI alone, 84.4% and 93.8%, respectively ($p \leq 0.05$). Similarly, very high sensitivity (99.0%) was achieved by combining mpMRI with PCPTCR2. Nevertheless, mpMRI plus GUT combination exceeded mpMRI plus PCPTCR2 by allowing to save a higher fraction of unnecessary biopsies, 25% and 2.4%, respectively.

Conclusion GUT and mpMRI combination would allow saving a substantial fraction of unnecessary biopsies with minimal risk of missing csPCa cases.

Keywords Prostate · Cancer · MRI · Biomarker · Biopsy-naïve · Risk calculator

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Abbreviations

PCa	Prostate cancer
PSA	Prostate specific antigen
CsPCa	Clinically significant prostate cancer defined as having a Gleason Score ≥ 7
Non	csPCa–non–clinically significant prostate cancer that comprises negative biopsy and GS = 6 PCa
mpMRI	Multiparametric magnetic resonance imaging
GUT	Genetic urinary test
PCPTRC2	Prostate cancer prevention trial risk calculator version 2.0
US	Ultrasound
DRE	Digital rectal examination
PCA3	Prostate cancer antigen 3
TMPRSS2	Androgen–regulated transmembrane serine protease 2
ERG	ETS–related gene
T:E	Fusion of TMPRSS2 and ERG genes
PIRADS	Prostate imaging reporting and data system version 2.1
T1W	T1–weighted imaging
T2W	T2–weighted imaging
DWI	Diffusion weighted imaging
DCE	Dynamic contrast–enhanced imaging
GS	Gleason score

Introduction

Prostate cancer is the second most diagnosed oncological disease in men [1] The main purpose of screening is to detect prostate cancer (PCa) at early stages when it is potentially curable [2]. However, it is agreed that prostate specific antigen (PSA) screening is associated with over-diagnosis of a large number of low-risk PCa and increased number of unnecessary prostate biopsies [2]. Moreover, men undergoing US-guided biopsy are at risk of several common complications, including lower urinary tract symptoms, hematuria, hematospermia, rectal bleeding (in case of transrectal procedure), pain, and infection that could even lead to sepsis and death. Therefore, antibiotic prophylaxis is recommended for US-guided biopsy [3].

Multiparametric MRI (mpMRI) in PCa patients has demonstrated better diagnosis while performing targeted biopsy and decreased diagnosis of non-clinically significant prostate cancer (non-csPCa) [4]. Currently, there is a strong recommendation to use mpMRI not only for second and all other biopsies but also in biopsy-naïve men [5] Urine, on the other hand, is a versatile body fluid for non-invasive urological malignancies detection [6] Prostate cancer antigen 3 (PCA3), also known as DD3, is markedly higher expressed in 95% of cancerous compared to adjacent non-cancerous prostate tissue [7]. Another genetic biomarker is a fusion of androgen-regulated transmembrane serine protease 2 (TMPRSS2) gene and ETS-related gene (ERG) (T: E) which is believed to play a major role in PCa tumorigenesis. Several studies have demonstrated that both PCA3 and T: E fusion gave significant predictive value in identifying prostate cancer. [8–10]. For individualized risk of PCa and clinically significant PCa (csPCa) evaluation in recent years there has been a proliferation of risk calculators that use various factors such as PSA, age, family history, and ethnicity to determine individualized risk of PCa and clinically significant PCa (csPCa) [11]. The prostate cancer prevention trial risk calculator version 2.0 (PCPTRC2) is a widely recognized tool that has been developed for assessing the risk of PCa. Its original version has been extensively tested and validated in various independent cohorts. In recent times, updated versions of the calculator have been introduced, which have shown promising results in populations that differ from those for which it was initially designed [12–14]. This suggests that the calculator may have potential application in a broader range of settings beyond its original purpose.

The aim of this study was to investigate the accuracy of different techniques (MRI, GUT, PCPTRC2) and their combinations for clinically significant prostate cancer (csPCa) diagnostic.

Materials and methods

Study population

The investigation was approved by the regional Bioethical Commission, Decision no. BE-2-116. In a single-center prospective study, 208 Caucasian patients were consecutively included over a period between 2021 January and 2024 January. Informed consent was obtained from all individual participants. Men who were scheduled for initial prostate biopsy, based on elevated total PSA level (selected elevated value in this study was >2 ng/ml and <20ng/ml confirmed) or abnormal digital rectal examination (DRE) were included in the study. Exclusion criteria were a history of PCa or other neoplasms under active treatments, prior prostate biopsy, and contraindications for MRI examination. All subjects underwent diagnostic tests– prostate GUT and mpMRI. After the examination, targeted cognitive fusion US-guided prostate biopsy, as well as systematic prostate biopsy, was performed in 170 cases of mpMRI visible PIRADS 3, 4, and 5 lesions. Only systematic US-guided biopsy was performed in 38 cases without visible lesions (mpMRI PIRADS 1 and 2), as specified in the study protocol. The risk of csPCa was

Table 1 Patients' characteristics (number, %, median +-SD, median, range)

Parameter	Value
Number of cases, n	208
Age (years)	
Mean +/-SD	62.9 +/-7.2
Median	63
Range	43–87
Total PSA (ng/ml)	
Mean +/-SD	6.3 +/- 2.9
Median	5.5
Range	2.7–19.1
PSA density (ng/ml/ml)	
Mean +/- SD	0.15 +/- 0.11
Median	0.12
Range	0.04–0.79
Prostate volume	
Mean +/- SD	51.2 +/-22.1
Median	44.8
Range	13.5–129.1
DRE suspicious, n (%)	
Yes	107 (51.4)
No	101 (48.6)
Family history, n (%)	
Yes	28 (13.5)
No	180 (86.5)
GUT score, n (%)	
Negative	60 (28.8)
Positive	141 (67.8)
NA	7 (3.4)
GUT predicted risk for csPCa (%)	
Mean +/-SD	26.1+/- 18.7
Median	23
Range	1–86.9
mpMRI, n (%)	
PIRADS < 3	38 (18.3)
PIRADS > = 3	170 (81.7)
PRCTPRC2 csPCa risk (%)	
Mean +/- SD	11.6 +/- 5.9
Median	10
Range	4–41
Biopsy outcomes, n (%)	
Negative and GS < 7	96 (46.2)
GS > = 7	112 (53.8)
GUT score and mpMRI PIRADS score, n (%)	
GUT positive, mpMRI positive	127 (63.2)
GUT negative, mpMRI negative	22 (10.9)
GUT positive, mpMRI negative	14 (7)
GUT negative, mpMRI positive	38 (18.9)

n number, SD standard deviation, PSA prostate-specific antigen, PSAD PSA density, DRE digital rectal examination, GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PIRADS prostate imaging reporting and data system, PCPTRC2 prostate cancer prevention trial risk calculator 2

calculated by using PCPTRC2 only in patients aged 55–90 years ($n = 182$, 87,5%) as required by the calculator [13]. All subjects had the right to terminate further involvement in the study at any time.

Prostate mpMRI

All subjects included in the study group were submitted to a mpMRI using either a 1.5T or 3T MR scanner. A standard

Table 2 Stratification of patients' characteristics on the basis of prostatic biopsy results (number, %, mean +-SD, median, range)

Parameter	Non-cs PCa	Cs PCa	*P* value
Number of cases, n (%)	96 (46.2)	112 (53.8)	
Age (years)			0.267
Mean +/-SD	62.3 +/-7.3	63.4 +/- 7.1	
Median	63	63	
Range	43–82	50–87	
Total PSA (ng/ml)			0.013
Mean +/-SD	5.8 +/- 2.7	6.7 +/- 3	
Median	5.2	5.7	
Range	2.7–18.7	3-19.1	
PSA density (ng/ml/ml)			< 0.001
Mean +/- SD	0.13 +/- 0.11	0.16 +/- 0.11	
Median	0.1	0.14	
Range	0.04–0.73	0.05–0.79	
Prostate volume			0,041
Mean +/- SD	56,2 +/-26,4	46,9 +/- 16,6	
Median	48,4	43,4	
Range	13,7–129,1	13,5–92	
DRE suspicious, n (%)			0.164
Yes	44 (45.8)	63 (56.2)	
No	52 (54.2)	49 (43.8)	
Family history, n (%)			0.688
Yes	14 (14.6)	14 (12.5)	
No	82 (85.4)	98 (87.5)	
GUT score, n (%)			< 0.001
Negative	43 (44.8)	17 (15.2)	
Positive	49 (51)	92 (82.1)	
Not evaluated	4 (4.2)	3 (2.7)	
GUT predicted risk for csPCa (%)			< 0.001
Mean +/-SD	20.7 +/- 18.6	30.8 +/- 17.5	
Median	12.8	28.7	
Range	1-72.8	3.3–86.9	
mpMRI PI-RADS score, n (%)			< 0.001
PIRADS < 3	31 (32.3)	7 (6.2)	
PIRADS > = 3	65 (67.7)	105 (93.8)	
PRCTPRC2 csPCa risk (%)			0.031
Mean +/- SD	10.8 +/- 5.7	12.3 +/- 6	
Median	10	11	
Range	4–35	4–41	
GUT score and mpMRI PIRADS score, n (%)			< 0.001
GUT positive, mpMRI positive	41 (44.6)	86 (78.9)	
GUT negative, mpMRI negative	21 (22.8)	1 (0.9)	
GUT positive, mpMRI negative	8 (8.7)	6 (5.5)	
GUT negative, mpMRI positive	22 (23.9)	16 (14.7)	

n number, SD standard deviation, PSA prostate-specific antigen, PSAD PSA density, DRE digital rectal examination, GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PIRADS prostate imaging reporting and data system, PCPTRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

combination of T1-weighted (T1W) images, T2-weighted (T2W) images, diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) studies were used and the PIRADS version 2.1 (v2.1) was used for grading the lesions from 1 to 5 [15]. PSA density (PSAD) was calculated in all cases. All mpMRI examinations were performed before prostate biopsy and analyzed by two expert radiologists (10 and 5 years of experience) independently without previous knowledge of the urine test scores and biopsy outcomes. Both readers were aware of the clinical information and consensus was obtained in cases of discrepancy.

Table 3 Patient characteristics of a subgroup with PIRADS = 3 stratified on the basis of prostatic biopsy results (number, %, mean +-SD, median, range)

Parameter	Non-cs PCa	Cs PCa	*P* value
Number of cases, n (%)	3 (42.9)	4 (57.1)	
Age (years)			0.727
Mean +/-SD	61.7 +/- 4.9	63.5 +/- 8.1	
Median	64	61.5	
Range	56–65	56–75	
Total PSA (ng/ml)			0.629
Mean +/-SD	7.4 +/- 2.9	10 +/- 4.4	
Median	6	10	
Range	5.481–10.66	5.4-14.52	
PSA density (ng/ml/ml)			1
Mean +/- SD	0.16 +/- 0.07	0.23 +/- 0.18	
Median	0.17	0.16	
Range	0.08–0.23	0.11–0.5	
Prostate volume			1
Mean +/- SD	50.5 +/- 19.4	51.8 +/- 23.7	
Median	47.1	49.5	
Range	33.1–71.4	29–79	
DRE suspicious, n (%)			1
Yes	1 (33.3)	2 (50)	
No	2 (66.7)	2 (50)	
Family history, n (%)			1
Yes	1 (33.3)	1 (25)	
No	2 (66.7)	3 (75)	
GUT score, n (%)			0.143
Negative	2 (66.7)	0 (0)	
Positive	1 (33.3)	4 (100)	
Not evaluated	0 (0)	0 (0)	
GUT predicted risk for csPCa (%)			0.229
Mean +/-SD	11.6 +/- 8.5	29.8 +/- 20.9	
Median	11	20.4	
Range	3.4–20.3	17.4–61.2	
PRCTPRC2 csPCa risk (%)			1
Mean +/- SD	13 +/- 1	15 +/- 7	
Median	13	14.5	
Range	12–14	9–22	
GUT negative, mpMRI positive	22 (23.9)	16 (14.7)	

n number, SD standard deviation, PSA prostate-specific antigen, PSAD PSA density, DRE digital rectal examination, GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PIRADS prostate imaging reporting and data system, PCPTRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

Genetic urinary test (GUT)

All subjects included in the study group underwent urine sample examination. First-voided urine samples were collected after a prostate massage and before a prostate biopsy. Colli-Pee 20 mL devices (Novosanis) prefilled with 10 mL of stabilization media (Diagnolita) were used for urine collection and instant stabilization. Samples were transferred to the Diagnolita laboratory for analysis. A proprietary laboratory-developed Diagnolita genetic urinary test (GUT) was employed to measure PCA3 and T: E biomarker levels in urine and combine them with age and PSA density clinical data [16, 17]. The results of GUT contained the patient's individualized risk for clinically significant PCa (Gleason score (GS) ≥ 7). The GUT score was positive or negative depending on whether the threshold of the test was exceeded. Originally, the threshold of the GUT was set to achieve a sensitivity of nearly 90% based solely on the results of systematic biopsy [16, 17].

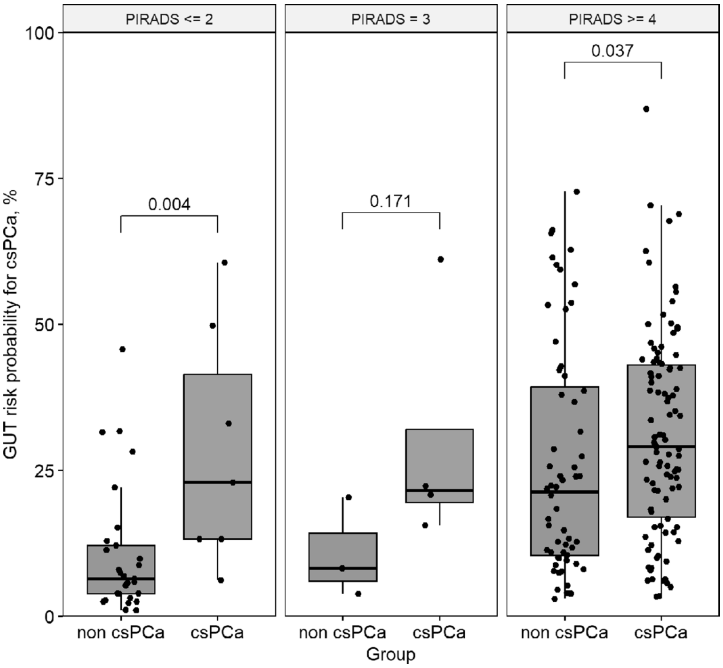

Fig. 1 GUT risk probabilities stratified by mpMRIPIRADS scores and biospy results. GUT genetic urinary test, mpMRI multiparameteric magnetic resonance imaging, csPCa clinically significant prostate cancer that comprises negative biospy and GS = 6 PCa cases

Prostate cancer prevention trial risk calculator version 2.0 (PCPTRC2)

A basic version of PCPTRC2 was used that involved these variables: race, age, PSA level (ng/ml), family history of prostate cancer, DRE result, and prior biopsy. The calculated probability of high-grade PCa was used in all calculations. As there was no predefined cutoff for PCPTRC2 we chose the cutoff of 6% to match the sensitivity of mpMRI. This allowed us to compare saved biopsy numbers at a similar sensitivity level.

Prostate biopsy

All subjects included in the study were submitted to a US-guided prostate biopsy performed in the university hospital, by the same urologist. In all cases, 12 random systematic cores were obtained. In cases when a PI-RADS score of 3–5 at mpMRI was obtained, additional targeted samples (2 cores per lesion) were obtained using a cognitive targeted prostate technique. All samples were evaluated in our clinic by an experienced genitourinary pathologist. Histological grading was assessed according to the Gleason grading system as well as the Gleason Grade Groups [18].

Table 4 Sensitivity comparisons for prediction of csPCa with 95% CI given in brackets

Model	*n*, csPCa	Sensitivity, %	*P* value vs. PCPTRC2	*P* value vs. mpMRI	*P* value vs. GUT
PCPTRC2	99	93.9 (87.3–97.7)	NA	1	0.071
mpMRI	112	93.8 (87.5–97.5)	1	NA	0.033
GUT	109	84.4 (76.2–90.6)	0.071	0.033	NA
mpMRI & PCPTRC2	99	99.0 (94.5–100)	0.025	0.025	0.001
mpMRI & GUT	109	99.1 (95.0-100)	0.059	0.014	<0.001

GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PRCTPRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

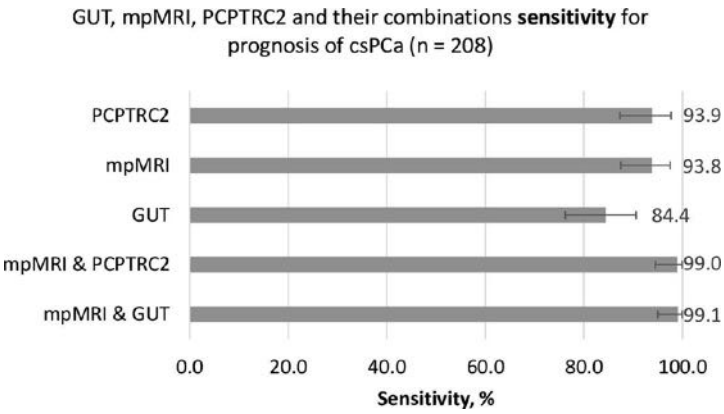

Fig. 2 Sensitivity comparisons for prediction of csPCa. GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PRCTPRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

Statistical analysis

All calculations were performed using R version 4.3.2. A p-value ≤ 0.05 was deemed to show a statistical significance. The normality of the data was estimated with Shapiro-Wilk test. The comparisons of continuous parameter values between groups were performed using a two-sided Student's t-test for normally distributed data and a two-sided Wilcoxon rank sum test otherwise. Analogously, categorical parameter counts were compared with two-sided Fisher's exact test.

Descriptive statistics were used to describe patients' characteristics. The GUT findings were categorized as positive or negative depending on whether the predicted csPCa risk exceeded the predefined threshold. The mpMRI results were considered positive if reported as PIRADS 3–5 and negative if PIRADS 1–2. To evaluate the performance of using both tests together, positive cases required at least one positive result from either GUT or mpMRI.

Combined systematic and targeted biopsy results were used to allocate a patient to clinically significant ($GS \geq 7$) prostate cancer (csPCa) or non-clinically significant prostate cancer (non-cs PCa) groups. The highest Gleason score identified by either the systematic or targeted biopsy was used for the assignment. All calculated sensitivity, specificity and, missed csPCa, saved biopsies, and saved unnecessary biopsies numbers were based on the aforementioned grouping of patients. 95% confidence intervals for sensitivity and specificity were calculated with an exact binomial test using binom.test function from R stats package. The sensitivity and specificity values were contrasted with the McNemar test using sesp.mcnemar function from R package DTComPair version 1.2.2. The comparisons were made only among complete cases for both compared models.

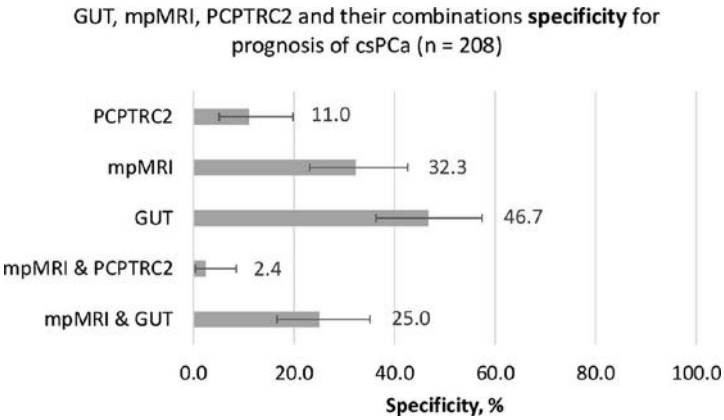

Fig. 3 Specificity comparisons for prediction of csPCa. GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PRCTPRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

Table 5 Specificity comparisons for prediction of csPCa with 95% CI given in brackets

Model	*N*, non-cs PCa	Specificity, %	*P* value vs. PCPTRC2	*P* value vs. mpMRI	*P* value vs. GUT
PCPTRC2	82	11.0 (5.1–19.8)	NA	0.028	<0.001
mpMRI	96	32.3 (23.1–42.6)	0.028	NA	0.011
GUT	92	46.7 (36.3–57.4)	<0.001	0.011	NA
mpMRI & PCPTRC2	82	2.4 (0.3–8.5)	0.008	<0.001	<0.001
mpMRI & GUT	93	25.0 (16.6–35.1)	0.251	0.058	<0.001

GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PRCTPRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer, non-cs PCa non-clinically significant prostate cancer

Results

Study population

In total, data from 208 men were included in the analysis. Patient characteristics, mpMRI, GUT, PCPTRC2, and biopsy outcomes are summarized in Table 1. The median age of all patients was 63 years (range 43–87) and the mean PSA level was 6.3 ng/ml. Upon a biopsy 112 (53.8%) of patients were diagnosed with csPCa (GS≥7). A positive GUT score was found in 141 cases (67.8%) and PIRADS score ≥3 in 170 cases (81.7%). GUT and mpMRI scores matched in 149 cases (74.1%) and positive scores matched in 127 cases (63.2%). Based on histopathology results patients were divided into two groups– csPCa and non-clinically significant PCa (non-cs PCa). Total PSA levels and PSA density levels significantly differed among groups ($p \leq 0.05$). The GUT score was positive in statistically significantly ($p < 0.001$) larger number of csPCa cases– 92 of 112 (82.1%) than in non-cs PCa cases– 49 of 96 (51%). The GUT predicted risk for csPCa was significantly higher ($p < 0.001$) in csPCa (median value 28.7%) than in non-cs PCa cases (median value 12.8%). Positive mpMRI score (PIRADS ≥3) was reported in a statistically significantly larger number of csPCa group (93.8%), than in non-cs PCa group (67.7%). Stratification of subjects based on histopathology results at biopsy (csPCa and non-cs PCa) is reported in Table 2. Seven cases were referred as PIRADS 3 lesions and the same stratification of subjects is reported in Table 3.

Comparison of diagnostic parameters between urinary biomarkers, mpMRI, PCPTRC2 and their combinations

The GUT predicted risks for csPCa were significantly higher in csPCa versus non csPCa for both negative mpMRI (PIRADS≤2) and positive mpMRI (PIRADS≥4) subgroups (Fig. 1). The sensitivity and specificity of different methods to predict csPCa at biopsy are presented in Tables 4 and 5 and are also illustrated visually in Figs. 2 and 3, as detailed below. GUT showed significantly lower sensitivity (84.4% vs. 93.8%, $p = 0.033$) and significantly higher specificity (46.7% vs. 32.3%, $p = 0.011$) than mpMRI in predicting csPCa at the biopsy. The specificity of GUT or mpMRI was higher than PCPTRC2, 46,7% and 32,3% vs. 11,0%, respectively and the difference was statistically significant ($p \leq 0,05$). The combination of GUT with mpMRI demonstrated a significantly higher sensitivity (99.1%) compared to GUT and mpMRI alone, which had sensitivities of 84.4% and 93.8%, respectively ($p < 0.05$). A similar level of sensitivity was attained with the combination of mpMRI plus PCPTRC2 (99.0%). Nonetheless, regarding specificity, mpMRI plus GUT combination significantly surpassed mpMRI plus PCPTRC2, 25,0% and 2,4%, respectively ($p = 0,001$). Specificity of mpMRI and GUT combination (25.0%) was not significantly different from mpMRI alone (32.3%), however GUT alone demonstrated significantly higher specificity than mpMRI and GUT combination, 46.7% and 25.0%, respectively ($p < 0.001$). Missed csPCa cases and saved biopsy numbers for various models are summarized in Table 6 as described below. In terms of unnecessary biopsies that can be saved the best results can be achieved while using GUT, 46.7%, respectively. However, GUT usage would miss the highest numbers of csPCa

Table 6 Missed csPCa cases and saved biopsy numbers for various models

Model	Missed csPCa cases	Saved biopsies	Saved unnecessary biopsies
PCPTRC2	6 of 99; 6.1%	15 of 181; 8.3%	9 of 82; 11.0%
mpMRI	7 of 112; 6.2%	38 of 208; 18.3%	31 of 96; 32.3%
GUT	18 of 109; 16.5%	63 of 201; 31.3%	43 of 92; 46.7%
mpMRI & PCPTRC2	1 of 99; 1.0%	3 of 181; 1.7%	2 of 82; 2.4%
mpMRI & GUT	1 of 109; 0.9%	24 of 201; 11.9%	23 of 92; 25.0%

GUT genetic urinary test, mpMRI multiparametric magnetic resonance imaging, PRCTPRC2 prostate cancer prevention trial risk calculator 2, csPCa clinically significant prostate cancer

cases, 16.5%, while mpMRI combinations with GUT or PCPTCR2 miss the lowest number of csPCa cases– close to 1%. In cases of negative mpMRI, GUT correctly prevented 72,4% unnecessary biopsies (21 of 29) and correctly identified 85,7% patients who required a biopsy (6 of 7) (Table 2).

Discussion

The 2023 EAU-ESTR-SIOG Guidelines recommend clinicians to consider the use of biomarkers and mpMRI before performing a biopsy [19]. Our study results showed a high mpMRI and GUT combination sensitivity in detecting csPCa.

Various biomarker-based urinary tests have been suggested to reduce unnecessary prostate biopsies while missing a low fraction of csPCA [20–23]. According to Sanda et al., an assay combining PCA3 and T: E showed 93% sensitivity predicting aggressive PCa during biopsy in the cohort of 561 biopsy-naive patients [23]. Similarly, in our study we included a group of biopsy naïve patients only and for all of them genetic urinary tests were performed after DRE. Therefore, our study findings confirmed the tendency that including GUT (sensitivity 84.4%) for PCa diagnosis into clinical practice would reduce unnecessary prostate biopsy and overdiagnosis while preserving detection of aggressive cancer. To our knowledge this is the first study that examined the value of mpMRI and genetic urinary biomarkers (PCA3 and T: E) combination in detecting csPCa among biopsy naïve patients. However, there are several studies, that analyzed the associations of mpMRI and PCA3 combination with csPCa. One example is the study of Fenstermaker et al., where 187 men underwent mpMRI and PCA3 testing before prostate biopsy. Study results showed that PCA3 is associated with MRI suspicious score and the detection of cancer on MRI fusion targeted biopsy in biopsy naïve men population (AUC = 0,67, 95% CI 0,59 − 0,76) [24]. Another study of Porpiglia et al. reterospectively reviewed 120 biopsy naïve patients, who underwent mpMRI and PCA3 testing. It was revealed, that mpMRI resulted in higher gain inaccuracy for predicting csPCa compared with PCA3 (AUC = 0.78, $p < 0{,}01$) [25]. In comparison, our study is prospective, more extended and included not only mpMRI and PCA3 testing, but also testing of T: E and their combinations. One issue that needs to be addressed is that in our study GUT did not significantly prognosed csPCa in PIRADS 3 lesions, probably due to too small patients group. However, the prognostic tendency was preserved as in other PIRADS lesions, extended research is needed to confirm the significant results. Another matter requiring recognition is the diagnostic accuracy of csPCa using mpMRI only. Tay et al. study results showed mpMRI sensitivity of 93% when detecting csPCa [26]. Our study demonstrated almost the same but slightly higher mpMRI sensitivity of 93.8%. However, in our study specificity of mpMRI was significantly lower than GUT alone, probably due to study limitations, addressed further. In relation to PIRADS 3 lesions, no significant differences were observed between the csPCa and non-csPCa groups, likely due to the limited size of the subcohort ($n = 7$). Finally, the main goal of this research was to find which technique or combination could be the best diagnostic pathway for csPCa detection in biopsy naïve patients. Our results showed that performing mpMRI along with GUT would allow to reduce unnecessary biopsies by a quarter while detecting almost all cases of aggressive cancer (99.1%).

Our study has a few limitations. First, data were obtained from a single center only, which could potentially lead to selection bias. However, bias was minimized as much as possible by including patients consecutively as they presented with documented PCa suspicion. Second, the evaluation of diagnostic performance in this study relied on the results of prostate biopsies, which could introduce potential biases regarding falsely negative biopsy results. Third, the most sensitive method– MRI combined fusion with transrectal ultrasonography prostate biopsy– was not performed in this study. As a result, this omission could influence the false-negative biopsy rates and potentially impact the conclusions drawn from the study. Fourth, the patient cohort did not cover the entire pathological spectrum (i.e., Gleason score and stage). The fifth limitation was that the population was homogenous, consisting only men of the same racial and ethnic background. Also, even though our results with the implementation of a combination of GUT and mpMRI were defined as significant regarding csPCa detection, further investigation in a larger prospective cohort is required.

The combination of two non-invasive tests– GUT and mpMRI– in csPCa diagnosis of biopsy naïve patients has the potential to avoid unnecessary biopsies and prevent the detection of non-cs PCa while keeping a minimal risk of missing csPCa. Further prospective mulicentric studies with a larger and more diverse patient group should be conducted to confirm the true impact on clinical practice.

Author contributions JK was involved in conceptualization, data curation, investigation, methodology and supervision of the study, also wrote the original draft and was involved in reviewing and editing process.CN was involved in data curation, methodology and supervision of the study, also wrote the original draft and was involved in reviewing and editing process.GCh was involved in conceptualization, data curation, investigation and supervision of the study, also wrote the original draft and was involved in reviewing and editing process. KZ was involved in conceptualization, data curation, investigation and methodology of the study, also was involved in reviewing and editing process.ML was involved in conceptualization, data curation and methodology of the study, also wrote the original draft and was involved in reviewing and editing process.SV was involved in data cura-

tion, investigation, methodology and supervistion of the study.IA was involved in data curation, investigation, methodology and supervistion of the study.KT was involved in data curation, investigation, methodology and supervistion of the study.IP was involved in data curation, investigation, methodology and supervistion of the study.MJ was involved in conceptualization, data curation, investigation, methodology and supervision of the study, also wrote the original draft and was involved in reviewing and editing process.All authors read and approved the final manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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A2

Title: Performance of PCA3 and TMPRSS2:ERG Within the Prostate Cancer Prevention Trial Risk Calculator Version 2 in a Lithuanian Cohort

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ORIGINAL RESEARCH

Performance of PCA3 and TMPRSS2:ERG Within the Prostate Cancer Prevention Trial Risk Calculator Version 2 in a Lithuanian Cohort

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Background: Prostate cancer (PCa) remains a significant health concern due to its high incidence and associated mortality. Conventional screening approaches, like PSA testing, often lack specificity, resulting in unnecessary biopsies and overtreatment. This study seeks to overcome these limitations by assessing the integration of novel urinary biomarkers into established risk prediction models.

Objective: This study aimed to evaluate the performance of incorporating urinary biomarkers – prostate cancer antigen 3 (PCA3) and transmembrane serine protease 2 (TMPRSS2) gene and ETS-related gene (ERG) fusion genes (T:E) – into the Prostate Cancer Prevention Trial Risk Calculator version 2 (PCPTRC2) in a Lithuanian cohort to enhance the detection of clinically significant prostate cancer (csPCa).

Materials and methods: A single-centre prospective study included 246 men scheduled for initial prostate biopsy between January 2021 and August 2024 due to elevated total PSA levels or abnormal digital rectal examination (DRE). Following ethical approval and informed consent, urinary samples were collected post-DRE and analysed for PCA3 and T:E. Each patient's risk was calculated using the basic PCPTRC2 and updated versions incorporating biomarkers. Biopsies were performed based on multiparametric magnetic resonance imaging (mpMRI) findings.

Results: Of 209 biopsy samples analysed, 111 (53.1%) were diagnosed with csPCa. The AUC for PCa detection was 59.6% for the original PCPTRC2, improving to 76.2% with PCA3 and further to 79.5% when both PCA3 and T:E were included. Both updated versions demonstrated significantly higher sensitivity compared to the original ($p<0.001$). However, no significant differences were noted in distinguishing csPCa from non-csPCa.

Conclusion: Incorporating PCA3 and T:E into PCPTRC2 substantially enhances diagnostic accuracy for detecting PCa in biopsy-naïve patients. Despite limitations, these findings underscore the potential for optimizing risk calculators in clinical practice, advocating for larger cohorts to validate these results.

Keywords: prostate cancer, biomarker-based risk assessment, PCA3, TMPRSS2:ERG, multiparametric MRI, risk calculator

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer after lung cancer and the sixth leading cause of cancer-related deaths among men worldwide.[1] Early detection is crucial, yet PSA-based screening has low specificity (20–30%), often leading to unnecessary treatments for clinically insignificant tumours.[2] Efforts are being made to optimize screening practices by using prediction models and risk calculators to improve accuracy and reduce unnecessary medical procedures.

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There are several well-known externally validated calculator models for PCa risk assessment, including the Prostate Cancer Prevention Trial Risk Calculator version 2 (PCPTRC2)[3] These models integrate various factors—such as age, PSA levels, digital rectal examination results, and family history—to estimate the probability of PCa detection through histological examination. Studies have shown that incorporating urinary biomarkers, such as Prostate Cancer Antigen 3 (PCA3) noncoding RNA and the TMPRSS2:ERG (T:E) gene fusion, into PCPTRC2 enhances diagnostic accuracy and may improve the detection of clinically significant prostate cancer (csPCa).[4] The selection of PCA3 and TMPRSS2:ERG for this study is based on their proven potential to improve the specificity and sensitivity of PCa detection, ultimately reducing the rate of unnecessary biopsies and enhancing patient management.[5,6]

The study aimed to assess the performance of incorporating PCA3 and T:E into PCPTRC2 within a Lithuanian cohort, using an alternative urinary biomarkers testing method.

Methods

Study Population

The investigation was approved by the regional Bioethical Commission, Decision no. BE-2-116. In a single-centre prospective study, 246 patients were consecutively enrolled between January 2021 and August 2024. The study was conducted at the Lithuanian University of Health Sciences Kaunas Clinics in Kaunas, Lithuania. Informed consent was obtained from all individual participants. Men who were scheduled for initial prostate biopsy, based on elevated total PSA level (defined in this study as >2 ng/mL and <20 ng/mL) or abnormal digital rectal examination (DRE) were included in the study. Exclusion criteria were a history of PCa or other neoplasms under active treatments and prior prostate biopsy. A total of two patients did not undergo prostate biopsy for personal reasons, while seven patients were excluded due to unsuccessful purifying of urinary test samples. Additionally, 28 patients were excluded due to age restrictions, as PCPTRC2 calculates csPCa risk only for individuals aged 55–90 years, in accordance with the calculator's guidelines.[7] The remaining 209 subjects underwent genetic urinary testing after DRE as well as multiparametric Magnetic Resonance Imaging (mpMRI). (). In this study, genetic urine testing involved analysing the urinary biomarkers PCA3 and TMPRSS2:ERG using a validated assay. This process included collecting first-void urine samples after a DRE, stabilizing them, and quantifying biomarker levels through precise molecular techniques.[8] Following these examinations, targeted cognitive fusion US-guided prostate biopsy and systematic prostate biopsy were performed in

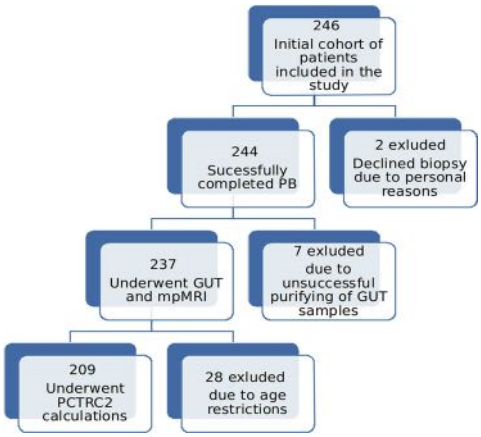

Figure 1 Study Cohort Flowchart: Patient Selection and Data Processing.Abbreviations: mpMRI, multiparametric magnetic resonance imaging; GUT, genetic urinary test; PCPTRC2, prostate cancer prevention trial risk calculator 2.

cases where mpMRI detected PIRADS 3, 4, and 5 lesions. In cases where mpMRI revealed PIRADS 1 or 2 lesions, only systematic US-guided biopsy was conducted, as per the study protocol.

PCTRC2 with and without Biomarkers

A basic version of PCPTRC2 was used in all patients aged 55 to 90 years old (n=209), as required by the calculator.[9] The calculator incorporated the following variables: race, age, PSA level (ng/mL), family history of PCa, DRE result, and prior biopsy. The probability of high-grade PCa was first estimated using basic PCPTRC2 model. Originally, PCPTRC2 integrated biomarkers by calculating their values based on copy numbers determined through the MPS test. The MPS test combines serum PSA, urine T:E, and PCA3 to predict a patient's risk for having PCa detected by standard biopsy after digital rectal examination.[10] In this study, urinary biomarker values of PCA3 and the PCA3/T:E combination, obtained through the Diagnolita urinary test, were incorporated in PCTRC2. First-voided urine samples were collected after a prostate massage and prior to biopsy. Colli-Pee 20 mL devices (Novosanis), prefilled with 10 mL of stabilization media (Diagnolita), were used for immediate sample stabilization. The samples were then transferred to the Diagnolita laboratory for analysis.[8,11]

Additional Tests

All subjects included in the study group underwent mpMRI using either a 1.5T or 3T MR scanner. A standard imaging protocol was applied, incorporating T1-weighted (T1W) images, T2-weighted (T2W) images, diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences. Lesions were graded using PIRADS version 2.1 (v2.1) on a scale from 1 to 5.[12] Finally, all participants underwent US-guided prostate biopsy. In each case, 12 systematic cores were collected. For lesions with a PI-RADS score of 3–5 on mpMRI, additional targeted samples (two cores per lesion) were obtained using a cognitive targeted prostate biopsy technique. Histological grading was performed according to both the Gleason grading system and the Gleason Grade Groups.[13]

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, including age, family history, serum PSA levels, prostate volume, urinary biomarkers results, and biopsy outcomes. Continuous variables were reported as mean and median [interquartile range (IQR)], while categorical variables were expressed as numbers and percentages. Biopsy outcomes were compared with PCPTRC2 results alone, as well as with models incorporating PCA3 and the PCA3/T:E combination, using mean and median values as numbers and percentages. Patients were categorized into clinically significant prostate cancer (csPCa; GS $\geq$7) or non-clinically significant prostate cancer (non-csPCa) groups based on combined systematic and targeted biopsy results.

To assess the predictive capability of different PCPTRC2 models, we calculated the area under the receiver operating characteristic curve (AUC) for three versions: the original PCPTRC2, the updated version incorporating PCA3, and the model including both PCA3 and T:E. Further analysis focused on csPCa versus no PCa or non-csPCa. Given the importance of high sensitivity in diagnosing csPCa, we examined the portion of the ROC curve ranging from 75% to 100% sensitivity, aligning with methodologies from previous studies.[14]

We evaluated how accurately the predicted probabilities from the PCPTRC2 model correspond to actual biopsy results. The calculated probabilities for PCa, csPCa, non-csPCa, and negative biopsy outcomes were averaged across the three PCPTRC2 models: the basic version, the version including PCA3, and the model incorporating both PCA3 and T:E. These predictions were then with actual biopsy outcomes, providing insights into the detection rates of overall PCa, csPCa, non-csPCa, and negative biopsy results. The findings were organized into a table for a clear comparative overview of each PCPTRC2 model's performance in PCa diagnosis.

All statistical analyses were performed using R version 4.3.2 with a p-value ≤ 0.05 considered statistical significance. Data normality was assessed using the Shapiro–Wilk test. Continuous variables were compared using a two-sided Student's *t*-test for normally distributed data and a two-sided Wilcoxon rank sum test for non-normally distributed data. Categorical variables were analysed using a two-sided Fisher's exact test.

To compare AUC values, a one-sided DeLong test was performed, with the alternative hypothesis stating that the AUC values of PCPTRC2 models incorporating one or both biomarkers would be higher than the PCPTRC2 version without biomarkers. The approach was supported by existing literature demonstrating biomarker-enhanced AUC performance.[3,4,8] Similarly, partial AUC values were calculated and compared using the bootstrap method, limited to a high sensitivity range (75% and 100%). The AUC values, partial AUC values, their 95% confidence intervals, and comparison test results were computed using functions from the R package pROC version 1.18.5.

Results

In total, data from 209 men were analysed. Patient characteristics, PCPTRC2 results before and after incorporating urinary biomarkers, and biopsy outcomes are summarized in Table 1. The median age of participants was 65 years (range 55–87) and the mean PSA level was 6.4 ng/mL. Upon biopsy 111 (53.1%) of patients were diagnosed with csPCa (GS>7).

To evaluate PCa prediction we assessed three versions of the PCPTRC2 risk calculator. The original PCPTRC2 had an AUC of 59.6%, while incorporating PCA3 increased it to 76.2%. Adding both PCA3 and T:E further improved the AUC to 79.5%. The updated calculators demonstrated significantly higher sensitivity compared to the original ($p=0.001$ and $p<0.001$, respectively). (Table 2 and Figure 2). However, when distinguishing csPCa form no PCa or non-csPCa, no statistically significant differences were found between the original and updated versions ($p > 0.05$) (Table 3). Since high sensitivity is crucial for diagnosing csPCa,[14] we focused on the ROC curve portion between 75% and 100% sensitivity, mirroring a methodology similar to a previous PCa prediction study.[14] For csPCa prognosis, the updated PCPTRC2 model with PCA3 had a partial AUC of 7.8%, while the version including both PCA3 and T:E achieved 8.6%. The latter demonstrated significantly higher performance ($p=0.043$). (Table 4 and Figure 3).[14] Table 5 presents a comparison of the average predictions from different PCPTRC2 versions – including the basic version and those incorporating urinary biomarkers – against actual biopsy results. In the basic PCPTRC2 version, the average predicted probability of detecting

Table 1 Patients' Characteristics (Number, %, Mean +-SD, Median, Range)

Parameter	Value
Number of cases, n	209
Age (years)	
Mean ±SD	64.6 ±5.7
Median	64
Range	55–87
Total PSA (ng/mL)	
Mean ±SD	6.4 ± 2.9
Median	5.6
Range	2.1–19.1
PSA density (ng/mL/mL)	
Mean ± SD	0.15 ± 0.12
Median	0.12
Range	0.04–1.2

(*Continued*)

Table 1 (Continued).

Parameter	Value
Prostate volume	
Mean ± SD	52.1 ±23.4
Median	46.8
Range	13.5–148.7
DRE suspicious, n (%)	
Yes	99 (47.4)
No	110 (52.6)
Family history, n (%)	
Yes	21 (10)
No	188 (90)
PCA3	
Mean ± SD	136.5 ± 118.2
Median	99.3
Range	7.58–664.7
T:E	
Mean	37.5 ± 70.9
Median	11.7
Range	0–487.13
Biopsy outcomes, n (%)	
GS <7	98 (46.9)
GS≥7	111 (53.1)

Abbreviations: n, number; SD, standard deviation; PSA, prostate-specific antigen; PSAD, PSA density; DRE, digital rectal examination; PIRADS, prostate imaging reporting and data system version 2.1; PCPTPRC2, prostate cancer prevention trial risk calculator 2; csPCa, clinically significant prostate cancer.

Table 2 AUC Comparisons for Predicting PCa with 95% CI, Given in Brackets.

Model	AUC with CI, %	P value vs PCPTRC2
PCPTRC2	59.6 (50.2–69.1)	NA
PCPTRC2 including PCA3	76.2 (68.3–84.1)	**0.001**
PCPTRC2 including PCA3+T:E	79.5 (71.9–87.1)	**<0.001**

Notes: T:E fusion of TMPRSS2 and ERG gene. Significant Differences (p<0.05) are Highlighted in Bold.
Abbreviations: PCPTRC2, prostate cancer prevention trial risk calculator 2; PCA3, prostate cancer antigen 3.

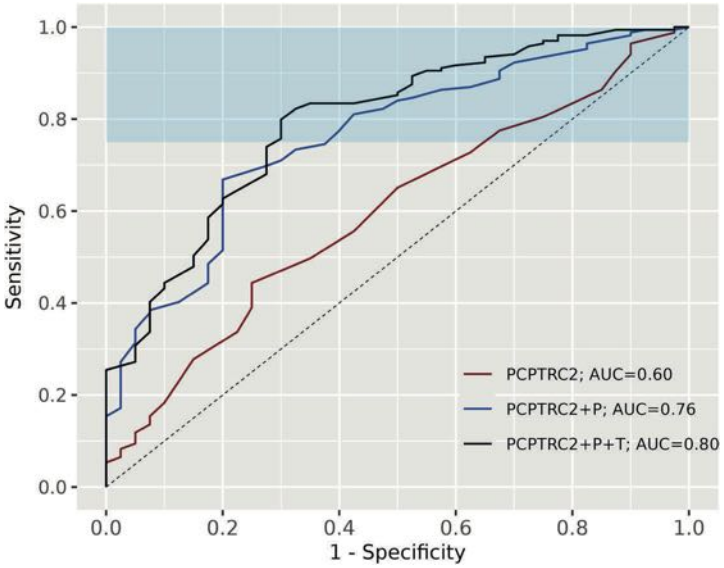

Figure 2 ROC curves and AUC of various PCa risk calculators for predicting PCa. *PCPTRC2* - prostate cancer prevention trial risk calculator version 2.0, *PCPTRC2+P* – PCPTRC2 version including PCA3 scores, *PCPTRC2+P+T* – PCPTRC2 version including PCA3 and TMPRSS2: ERG scores. The blue shaded area indicates a sensitivity range of 75% to 100% that was used for partial AUC calculations.

any PCa was 30%, with csPCa at 11% and non-csPCa at 19%. Negative biopsy results were predicted at 70% on average. Adding PCA3 to the PCPTRC2 increased the predicted probability of detecting PCa to 51%, csPCa to 20%, and non-csPCa to 30%, while negative biopsy results decreased to 49%. Incorporating both PCA3 and T:E further improved average predicted detection rates, with PCa reaching 55%, csPCa at 25%, and non-csPCa remaining at 30%, alongside

Table 3 AUC Comparisons for Predicting csPCa with 95% CI, Given in Brackets

Model	AUC with CI, %	P value vs PCPTRC2
PCPTRC2	61.6 (53.9–69.3)	NA
PCPTRC2 including PCA3	64.9 (57.3–72.6)	0.150
PCPTRC2 including PCA3+T:E	67.8 (60.3–75.3)	0.058

Note: T:E fusion of TMPRSS2 and ERG gene.
Abbreviations: PCPTRC2, prostate cancer prevention trial risk calculator 2; PCA3, prostate cancer antigen 3.

Table 4 Partial AUC (1–0.75 Sensitivity) Comparisons for Predicting csPCa with 95% CI, Given in Brackets.

Model	Partial AUC with CI, %	P value vs PCPTRC2
PCPTRC2	5.8 (3.7–8.5)	NA
PCPTRC2 including PCA3	7.8 (5.4–10.7)	0.063
PCPTRC2 including PCA3+T:E	8.6 (5.7–11.8)	**0.043**

Note: T:E fusion of TMPRSS2 and ERG gene. Significant Differences ($p<0.05$) are Highlighted in Bold.
Abbreviations: PCPTRC2, prostate cancer prevention trial risk calculator 2; PCA3, prostate cancer antigen 3.

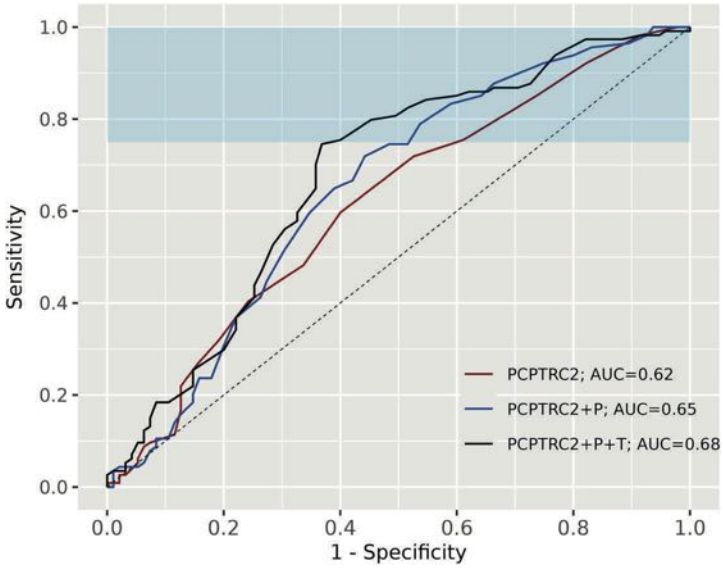

Figure 3 ROC curves and AUC of various PCa risk calculators for predicting csPCa. *PCPTRC2* - prostate cancer prevention trial risk calculator version 2.0, *PCPTRC2+P* – PCPTRC2 version including PCA3 scores, *PCPTRC2+P+T* – PCPTRC2 version including PCA3 and TMPRSS2: ERG scores. The blue shaded area indicates a sensitivity range of 75% to 100% that was used for partial AUC calculations.

a reduction in negative biopsy results to 45%. Regarding biopsy outcomes, PCa was detected in 81.3% of cases, csPCa in 53.1%, and non-csPCa in 28.2%. Negative biopsy results were observed in 18.7% of cases.

Discussion

The currently used biomarker, PSA, exhibits low specificity in detecting csPCa, leading to a high number of unnecessary prostate biopsies.[15] Our study results demonstrate that incorporating additional urinary biomarkers into PCPTRC2 improves csPCa detection.

In a study of Ankerst et al, PCA3 and T:E was incorporated in PCPTRC2, leading to 854 biopsies being performed.[4] The areas under the curve (AUC) for predicting csPCa were 70.0% (66.0–74.0%) for PCPTRC2 alone, 76.4% (72.8–80.0%) with PCA3 added and 77.1 (73.6–80.6%) with both PCA3 and T:E incorporated.[4] Similarly, Tomlins et al evaluated the association of urinary

Table 5 The Average Probabilities of Different Versions of the PCPTRC2 Risk Calculator Compared to Biopsy Outcomes.

Average Probabilities For:	PCa	CsPCa	Non-csPCa	Negative Biopsy
PCPTRC2 basic version	30%	11%	19%	70%
PCPTRC2+PCA3	51%	20%	30%	49%
PCPTRC2+PCA3+T:E	55%	25%	30%	45%
Biopsy outcomes	81.3%	53.1%	28.2%	18.7%

Note: T:E fusion of TMPRSS2 and ERG gene.
Abbreviations: PCPTRC2, prostate cancer prevention trial risk calculator 2; PCa, prostate cancer; csPCa, clinically significant prostate cancer; non-csPCa, non clinically significant prostate cancer; PCA3, prostate cancer antigen 3.

PCA3 and the T:E with PCPTRC (version 1) in detecting csPCa, using urine samples from 1218 patients.[16] Their findings showed that the AUC for the basic PCPTRC version was 0.707, which increased to 0.752 with PCA3 and further rose to 0.779 when both PCA3 and T:E were included.[16] Our study found Lower AUC values for csPCa across all three scenarios. However, when analysing partial AUC values, PCPTRC2 including both PCA3 and T:E demonstrated significantly higher performance compared to PCPTRC2 alone (p=0.043). For predicting all PCa cases – both csPCa and non-csPCa –Tomlins et al reported that PCPTRC2 alone achieved AUC of 63.9%.[16] Notably, adding PCA3 improved the AUC to 73.9%, and incorporating both PCA3 and T:E further increased it to 76.2%. Our study revealed a lower AUC of 59.6% for PCa detection with PCPTRC2 alone. However, when incorporating additional biomarkers, specifically PCA3, the AUC improved to 76.2%, and with the addition of both PCA3 and T:E, it reached a maximum AUC of 79.5%. Moreover, our study was performed prospectively in a distinct and unique patient cohort. Notably, Lithuania remains the country with an active PCa screening program.[17] Data from cancer registries indicates that, over the past two decades, age-adjusted mortality rates for PCa have significantly declined across most Northern Europe and North America nations.[15] However, Lithuania stands out as an exception, exhibiting a rapid increase in PCa mortality over the same period.[18] This concerning trend underscores the urgent need for developing new diagnostic strategies. Advancements in imaging technologies and biomarker-based diagnostics have the potential to reduce the harms associated with PSA testing while maintaining—or even improving—the sensitivity of PCa and high-risk PCa detection.[18]

The effectiveness of PCA3 testing in detecting PCa and reducing unnecessary biopsies has been demonstrated in previously conducted studies and metanalyses[19,20] Our findings a suggests that incorporating both PCA3 and T:E biomarkers significantly enhances the detection of PCa. However, their addition in PCPTRC2 did not provide significant advantage in distinguishing csPCa from no PCa or non-cs PCa. This limitation is likely due to study's relatively small sample size and the different patient's cohort. Originally, PCTRC2 incorporated urinary biomarkers by quantifying their values based on copy numbers obtained through the MPS test.[10] In this study, we integrated urinary biomarker values obtained through a different urinary test into PCPTRC2.[8] The EAU-EAN guidelines emphasize the importance of using risk calculators that are properly calibrated to reflect the prevalence of PCa in the target population.[2] When applying PCPTRC2 to the Lithuanian population, recalibration may be necessary. This need for recalibration is further supported by our findings, which revealed that the average predicted risks for PCa and csPCa using PCPTRC2 were significantly lower than the actual biopsy-confirmed rates (Table 5).

Our study had several limitations. Firstly, data collection was restricted to a single centre, which could introduce selection bias. To minimize this, patients were included consecutively as they presented with documented suspicion of PCa. Second, the patients sample size was relatively small, highlighting the need for further research with larger cohorts to validate these findings. Third, the assessment of diagnostic performance relied on prostate biopsy results, which may introduce bias due to potential false-negative outcomes. Fourth, MRI combined fusion with transrectal ultrasonography prostate biopsy was not performed in this study, instead, histological results were obtained solely from TRUS guided prostate biopsies. Fifth, the patient cohort did not cover the entire pathological spectrum (ie, Gleason score and stage) and consisted exclusively of men from a single country. Therefore, further investigation in a larger, more diverse prospective cohort is required.

The incorporation of PCA3 and T:E in PCPTRC2 provides significant predictive value to csPCa diagnostics in biopsy-naïve patients. To validate these findings in clinical practice, larger prospective studies involving diverse patient populations are needed.

Data Sharing Statement

Data are available from the authors upon reasonable request.

Ethics Approval and Informed Consent

This study complies with the principles outlined in the Declaration of Helsinki. The investigation was approved by the Lithuanian regional Bioethical Commission, Decision no. BE-2-116. Informed consent was obtained from all individual participants.

Disclosure

The authors declare no conflicts of interest in this work.

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APPENDICES

Appendix 1

KAUNO REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

Lietuvos sveikatos mokslų universitetas, A. Mickevičiaus g. 9, LT 44307 Kaunas, tel. (+370) 37 32 68 89;el.paštas: kaunorbtek@lsmuni.lt

LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2020-12-15 Nr. BE-2-116

Biomedicininio tyrimo pavadinimas: „Magnetinio rezonanso tomografijos (MRT) tyrimo ir genetinių šlapimo biožymenų vertė diagnozuojant kliniškai reikšmingą prostatos vėžį“	
Protokolo Nr.:	**001**
Data:	**2020-09-28**
Versija:	**1**
Asmens informavimo forma	**Versija 001 , data 2020-09-28**
Pagrindinis tyrėjas:	Prof. dr. Mindaugas Jievaltas
Biomedicininio tyrimo vieta: Įstaigos pavadinimas:	Lietuvos sveikatos mokslų universiteto ligoninė Kauno klinikos
Adresas:	Eivenių g. 2, LT-50161 Kaunas, Lietuva

Išvada:

Kauno regioninio biomedicininių tyrimų etikos komiteto posėdžio, įvykusio **2020 m. gruodžio mėn. 1 d.** (protokolo Nr. BE-10-12) sprendimu pritarta biomedicininio tyrimo vykdymui.

Mokslinio eksperimento vykdytojai įsipareigoja: (1) nedelsiant informuoti Kauno Regioninį biomedicininių Tyrimų Etikos komitetą apie visus nenumatytus atvejus, susijusius su studijos vykdymu, (2) iki sausio 15 dienos – pateikti metinį studijos vykdymo apibendrinimą bei, (3) per mėnesį po studijos užbaigimo, pateikti galutinį pranešimą apie eksperimentą.

Kauno regioninio biomedicininių tyrimų etikos komiteto nariai			
Nr.	Vardas, Pavardė	Veiklos sritis	Dalyvavo posėdyje
1.	Doc. dr. Gintautas Gumbrevičius	Klinikinė farmakologija	Taip
2.	Prof. dr. Kęstutis Petrikonis	Neurologija	Taip
3.	Dr. Saulius Raugelė	Chirurgija	Taip
4.	Dr. Lina Jankauskaitė	Pediatrija	Taip
5.	Prof. dr. Džilda Veličkienė	Endokrinologija	Taip
6.	Doc. dr. Eimantas Peičius	Visuomenės sveikata	Taip
7.	Aušra Degutytė	Visuomenės sveikata	Taip
8.	Dr. Žydrūnė Luneckaitė	Visuomenės sveikata	Taip
9.	Viktorija Bučinskaitė	Teisė	Taip

Kauno regioninis biomedicininių tyrimų etikos komitetas dirba vadovaudamasis etikos principais nustatytais biomedicininių tyrimų Etikos įstatyme, Helsinkio deklaracijoje, vaistų tyrinėjimo Geros klinikinės praktikos taisyklėmis.

Kauno RBTEK pirmininkas Doc. dr. Gintautas Gumbrevičius

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS * KAUNO REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

Appendix 2

Paciento apklausos forma magnetinio rezonanso tomografijai atlikti

PATVIRTINTA
Kauno klinikų generalinio direktoriaus
2014 m. vasario 25 d. įsakymų Nr. V-192
Priedas Nr. 7

PACIENTO APKLAUSOS FORMA MAGNETINIO REZONANSO TOMOGRAFIJAU ATLIKTI

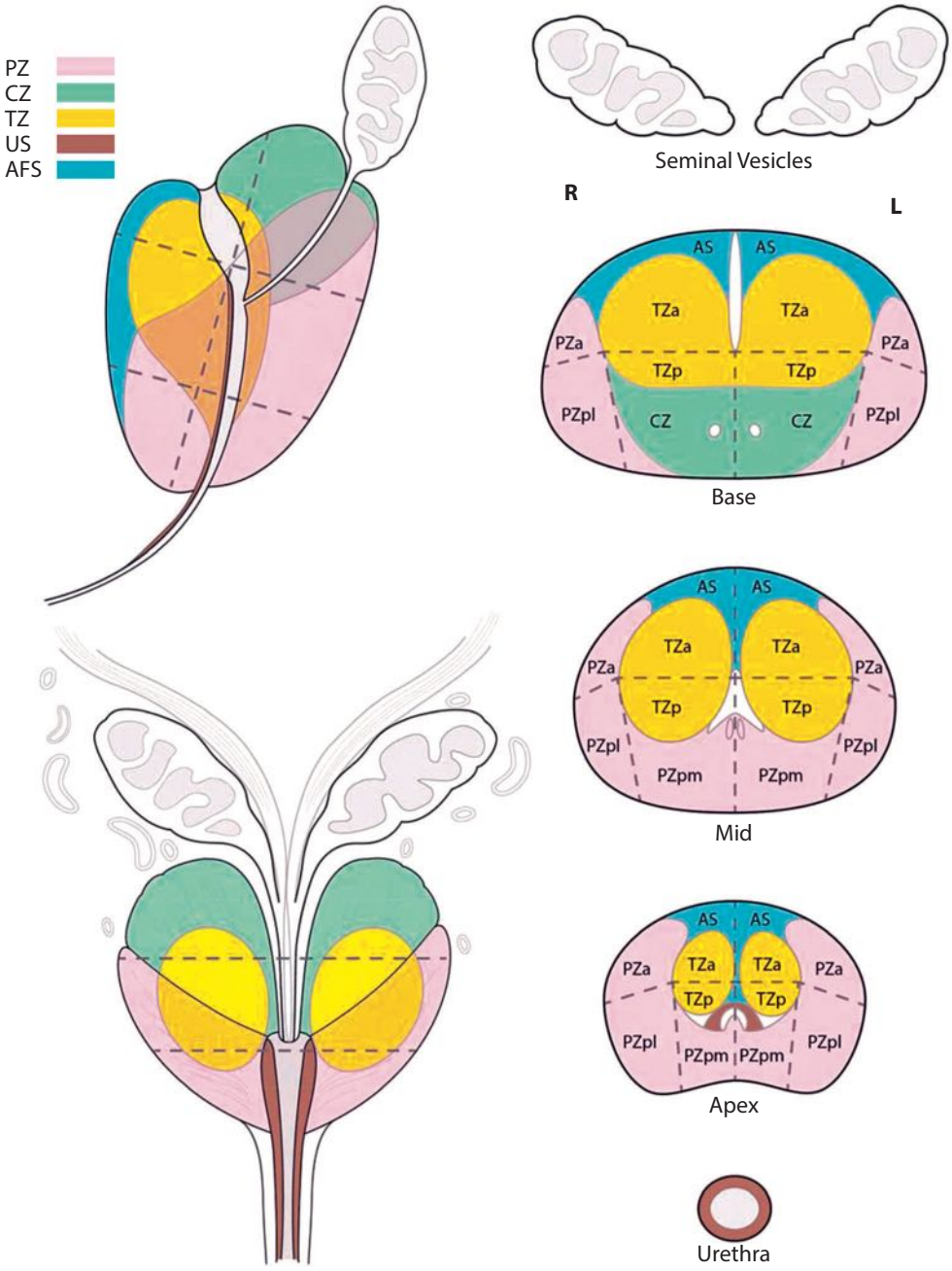
Pacientas _____ Gimimo data _____ Svoris _____ Ūgis _____
(Vardas, Pavardė)

Ar Jūsų kūne yra kuris nors iš žemiau išvardytų prietaisų, protezų ar svetimkūnių?	**TAIP**	**NE**
Širdies stimuliatorius ar poodinis širdies defibriliatorius		
Smegenų kraujagyslių kabutės ar metalinės plokštelės po neurochirurginės operacijos, smegenų skysčio drenas		
Dirbtiniai širdies vožtuvai		
Kraujagyslių implantai (stentai, filtrai, kateteriai)		
Elektroniniai ar mechaniniai implantai (neurostimuliatorius, vaistų pompą – ne intraveninis kateteris)		
Metalinės kabutės kitose kūno vietose		
Kitoks stimuliatorius		
Akių, ausų implantai		
Sąnarių, galūnių protezai, kaulų fiksatoriai		
Dantų protezai ar „sidabro“ plombos, metalo keramikos karūnėlės, breketai, kabės		
Kitokie, aukščiau nepaminėti protezai		
Metaliniai implantai naudojami kaulų lūžiams gydyti		
Metaliniai implantai po stuburo operacijos		
Buitiniai metalo svetimkūniai (kulkos, metalinės atplaišos ir skeveldros)		
Bet koks kitas aukščiau nepaminėtas elektroninis, mechaninis ar magnetinis implantas, protezas		
Medicininiai pleistrai		
Tatuiruotės, permanentinis (ilgalaikis makiažas)		
Ar jūs naudojate:	**TAIP**	**NE**
Klausos aparatą		
Akių kontaktinius lęšius		
Insulino, morfijaus ar kitų vaistų pompą (ne intraveninis kateteris)		

Bendri klausimai:	**TAIP**	**NE**
Ar jums kada buvo atlikta neurochirurginė operacija?		
Ar jums kada nors buvo atlikta laparoskopinė (neatveriant pilvo ertmės) operacija?		
Ar jums kada nors buvo metalinėmis skeveldromis sužeistos akys?		
Ar bijote uždarų patalpų?		
Ar esate jautrus (i) vaistams ar kontrastinėms medžiagoms?		
Ar sergate bronchine astma, alerginėmis ligomis, epilepsija, inkstų ligomis ar cukriniu diabetu?		
(*Tik moterims*) Spiralė		
(*Tik moterims*) Ar jūs esate nėščia arba manote esanti nėščia?		
(*Tik moterims*) Ar jūs maitinate kūdikį?		

Aš perskaičiau ir suprantu visą anketos tekstą. Tvirtinu, kad visus aukščiau pateiktus klausimus atsakiau teisingai ir kiek galima tiksliau.

Paciento (jo atstovo) parašas _____ Data _____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Apex
Urethra

Appendix 4

PATVIRTINTA
Lietuvos sveikatos mokslų universiteto ligoninės
Kauno klinikų generalinio direktoriaus
2024 m. gruodžio 10 d. įsakymu
Nr. V-(1.4E)-1017

PATVIRTINTA
Lietuvos sveikatos mokslų universiteto ligoninės Kauno klinikų direktoriaus medicinai ir slaugai (įgalioto Kauno klinikų generalinio direktoriaus 2024 m. gruodžio 10 d. įsakymu Nr. V-(1.4E)-1017)

_____
(data)
Registracijos Nr. _____

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETO LIGONINĖ KAUNO KLINIKOS
Viešoji įstaiga, Eivenių g. 2, 50161 Kaunas, te (+370 37) 32 63 60, (+370 37) 32 69 75,
faks. (+370 37) 32 64 27, el.p. rastine@kaunoklinikos.lt.
Duomenys kaupiami ir saugomi Juridinių asmenų registre, kodas 135163499

PACIENTO SUTIKIMAS DEL CHIRURGINES OPERACIJOS, INVAZINĖS IR (AR) INTERVENCINĖS PROCEDŪROS ATLIKIMO, FORMA E3

Kauno klinikų paciento identifikavimo žymuo:
KK kodas/ KK ID kodas _____
atvejo/ apsilankymo Nr. _____

PACIENTAS	**PACIENTO ATSTOVAS**
vardas.....	vardas.....
pavardė.....	pavardė.....
gimimo data.....	atstovavimo pagrindas,.....

1. _____ **UROLOGIJOS KLINIKA, TEL (0-37) 326090** _____
(profilinės klinikos, skyriaus, kuriame atliekama chirurginė operacija, invazinė ir (ar) intervencinė procedūra, pavadinimas, telefonas)

2. _____
(gydytojo, atliksiančio chirurginę operaciją, invazinę ir (ar) intervencinę procedūrą, vardas, pavardė, profesinė kvalifikacija)

3. _____ **PROSTATOS TRANSREKTINĖ BIOPSIJA** _____
(chirurginės operacijos, invazinės ir (ar) intervencinės procedūros pavadinimas)

4. ***Chirurginės operacijos, invazinės ir (ar) intervencinės procedūros esmė (trumpas ir aiškus aprašymas), pobūdis, tikslai***
...Prostatos transrektinė biopsija. **Operacijos tikslas** – Paimti bioptatus iš prostatos histologiniam ištyrimui. **Operacijos aprašymas:** operacija atliekamas pacientui gulint ant šono. Per išeinamąją angą į tiesiąją žarną įstumiamas pailgos formos rektalinis ultragarso daviklis. Iš prostatos paimami bioptatai. Paimti audiniai siunčiami histologiniam ištyrimui.....

5. ***Operacijos, invazinės ir (ar) intervencinės procedūros apimties keitimo leistinumo aptarimas, jei jos metu su pacientu papildomai to aptarti nebus galimybės, o sutikimo metu to nuspėti negalima***

... Pacientas sutinka, kad esant reikalui operacijos metu chirurgas spręstų dėl procedūros eigos pakeitimo.....

6. ***Planuojamos atlikti chirurginės operacijos, invazinės ir (ar) intervencinės procedūros alternatyvių diagnostikos ir gydymo metodų esmė, jų tikslai, ypatumai, rizikos ir kitos paciento apsisprendimui svarbios aplinkybės***

...Nepaisant didelio rūpestingumo, atskirais atvejais operacijos metu arba po jos, gali kilti komplikacijos, kurios, esant tam tikroms sąlygoms, reikalauja skubaus gydymo ir net gali būti gyvybiškai pavojingos.....

7. ***Galimos ir svarbios paciento apsisprendimui dėl sutikimo davimo planuojamai chirurginei operacijai, invazinei ir (ar) intervencinei procedūrai komplikacijos:***

7.1. *žinomos ir dažnai pasitaikančios komplikacijos*... Skausmas procedūros metu, pooperacinis skausmingumas tarpvietėje. Kraujas tuštinantis, šlapinantis, spermoje. Pasunkėjęs šlapinimasis.

7.2. *retai pasitaikančios komplikacijos*... infekcinės komplikacijos (prostatos uždegimas, abscesas, sepsis). Šlapimo susilaikymas. Nesustabdomas kraujavimas. Nepaisant didelio rūpestingumo, atskirais atvejais operacijos metu arba po jos, gali kilti komplikacijos, kurios, esant tam tikroms sąlygoms, reikalauja skubaus gydymo ir net gali būti gyvybiškai pavojingos.

7.3. *galimos šiam konkrečiam pacientui, įvertinus jo būklę*

.....

8. ***Kitos aplinkybės, svarbios paciento apsisprendimui***

.....

.....

9. ***Anestezijos taikymas/ netaikymas****.....

---

* Jei anestezija bus taikoma, nurodyti anestezijos atlikimo būdą, riziką bei galimas komplikacijas arba pildyti specialią sutikimo anestezijai formą.

10. PACIENTO PATVIRTINIMAS:

- Aš, pasirašydamas (-a) šį dokumentą, patvirtinu, kad gydytojas man suprantamai paaiškino apie mano ligą, šios ligos gydymo metodus, numatomos atlikti chirurginės operacijos, invazinės ir (ar) intervencinės procedūros esmę, pobūdį, tikslus, žinomas ir galimas komplikacijas, ketinamos atlikti chirurginės operacijos, invazinės ir (ar) intervencinės procedūros alternatyvių diagnostikos ir gydymo metodų esmę, jų tikslus, ypatumus, riziką ir kitas svarbias aplinkybes, kurios galėjo turėti įtakos mano apsisprendimui sutikti ar atsisakyti chirurginės operacijos, invazinės ir (ar) intervencinės procedūros, o taip pat galimas pasekmes, jei chirurginė operacija, invazinė ir (ar) intervencinė procedūra nebūtų atlikta.
- Aš, pasirašydamas (-a) šį dokumentą, sutinku ir prašau, kad aukščiau nurodytą operaciją (procedūrą) atliktų šios klinikos gydytojai. Aš žinau, kad gydytojas gali pasikviesti kitus gydytojus asistuoti jam, dalyvauti operacijoje (procedūroje) ar atlikti dalį jos.
- Man suprantamai paaiškinta, kad chirurginės operacijos, invazinės ir (ar) intervencinės procedūros metu gali paaiškėti, jog reikia keisti numatytą operacijos (procedūros) apimtį. Jei taip atsitiktų, aš sutinku, kad gydytojai patys nuspręstų dėl operacijos apimties.
- Aš suprantu, kad operacijos (procedūros) metu gali būti naudojami skausmą malšinantys medikamentai, kurie gali sukelti mieguistumą ar laikiną kūno dalies aptirpimą.
- Man suprantamai paaiškinta, kad dėl chirurginės operacijos, invazinės ir (ar) intervencinės procedūros galiu nukraujuoti, ir gali prireikti perpilti kraują, ar kraujo pakaitalus. Esu supažindintas (-a) su rizika. Sutinku, kad kraujas ar jo produktai būtų man perpilti, jei gydytojai nuspręstų, kad tai reikalinga. Aš žinau, jei įvyktų komplikacija – man bus suteikta kvalifikuota pagalba.
- Aš žinau, kad medicinos mokslas nėra tobulas (tikslus) ir daugelį dalykų sunku numatyti.
- Aš žinau, kad gydytis ligoninėje gali tekti ilgiau, negu buvo numatyta, o gijimas ir nedarbingumas gali tęstis ilgiau, negu tikėtasi.

▪ Aš žinau, kad turiu pasakyti gydytojams apie visus praeityje buvusius sveikatos sutrikimus, persirgtas ligas, atliktas operacijas, vartotus ir vartojamus vaistus, narkotines medžiagas, alergines reakcijas, genetinį paveldimumą ir kitus man žinomus duomenis, reikalingus tinkamai suteikti sveikatos priežiūros paslaugas. Esu informuotas (-a) apie pareigą bendradarbiauti su gydytoju, vykdyti jo paskyrimus ir nurodymus, pranešti apie bet kokius nukrypimus nuo paskyrimų.
▪ Aš perskaičiau (ar man buvo perskaitytas) šį sutikimo chirurginei operacijai, invazinei ir (ar) intervencinei procedūrai tekstą. Aš supratau gydytojo paaiškinimus žodžiu bei šį tekstą ir

sutinku, kad man būtų atlikta chirurginė operacija, invazinė ir (ar) intervencinė procedūra

PACIENTO (jo atstovo) parašas _____ **Data** _____ **Laikas** _____

11. GYDYTOJO PATVIRTINIMAS:

▪ Aš patvirtinu, kad išsamiai aptariau ir įvertinau su pacientu (jo atstovu) chirurginės operacijos, invazinės ir (ar) intervencinės procedūros naudą ir riziką, pacientui (jo atstovui) suteikiau pakankamai informacijos, tam, kad apsispręstų dėl siūlomos chirurginės operacijos, invazinės ir (ar) intervencinės procedūros.

GYDYTOJO vardas, pavardė, pareigos _____

Supažindinimo data_____**Laikas** _____

12. PATVIRTINIMAS, KAD PACIENTAS NEGALI IŠREIKŠTI SAVO VALIOS:

Patvirtinu, kad pacientas negali išreikšti savo valios dėl šių priežasčių (*įrašyti*):.....

.....

Gydytojo vardas, pavardė, profesinė kvalifikacija, parašas

_____

Patvirtinimo data _____ Laikas _____

CURRICULUM VITAE

Name, Surname:	**Jūratė Kemėšienė**
Address:	Department of Radiology, Hospital of Lithuanian University of Health Sciences Kauno klinikos. Eivenių 2, LT-50009 Kaunas, Lithuania
E-mail:	jurate.kemesiene@lsmu.lt

Workplace:

August 2015–present	Radiologist, Department of Radiology, Hospital of Lithuanian University of Health Sciences Kauno klinikos
September 2024–present	Junior assistant, Lithuanian University of Health Sciences

Education:

August 2019–August 2025	PhD Student, Lithuanian University of Health Sciences
September 2015–June 2019	Medical Resident, Hospital of Lithuanian University of Health Sciences Kauno klinikos
September 2009–June 2015	Master Degree in Medicine, Lithuanian University of Health Sciences

Membership at professional societies:

Lithuanian Radiologists' Association
Radiology Society of North America
European Society of Radiology
European Society of Gastrointestinal and Abdominal Radiology
Europeans Society of Urogenital Radiology

2024 m. gautas apdovanojimas už stendinį pranešimą didžiausioje tarptautinėje radiologijos srities konferencijoje „Radiological Society of North America annual meeting“ Čikagoje, Jungtinėse Amerikos Valstijose.

RSNA
Radiological Society
of North America

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Citation to

Jurate Kemesiene

In recognition of the excellence of your

Scientific Poster Exhibit

R5B-SPGU-6: USEFULNESS OF URINARY BIOMARKER-BASED RISK SCORE AND MULTIPARAMETRIC MRI FOR CLINICALLY SIGNIFICANT PROSTATE CANCER DETECTION IN BIOPSY-NAIVE PATIENTS

Presented during the

RSNA 110TH SCIENTIFIC ASSEMBLY AND ANNUAL MEETING OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

DECEMBER 1–5, 2024

Curtis P. Langlotz, MD, PhD
RSNA President

PADĖKA

Pirmiausiai norėčiau padėkoti buvusiam Lietuvos sveikatos mokslų universiteto ligoninės Kauno klinikų Radiologijos klinikos vadovui, prof. dr. Algidui Basevičiui, už paskatinimą ir pagalbą ruošiantis stoti į doktorantūros studijas bei už nuolatinį palaikymą visų studijų metu.

Savo darbo vadovui, prof. dr. Mindaugui Jievaltui, dėkoju už pagalbą ruošiant tyrimo metodiką, rašant mokslinius straipsnius ir ruošiant pranešimus konferencijoms, už vertingus patarimus, suteiktus kontaktus ir buvimą šalia viso disertacijos rengimo proceso metu.

Savo darbo konsultantams, prof. dr. Carlos Nicolau ir prof. dr. Kristinai Žvinienei, dėkoju už palaikymą visais klausimais, tiek tyrimo metodologijoje, tiek mokslinių straipsnių rašyme. Prof. dr. Carlos Nicolau esu dėkinga už pirmą supažindinimą su prostatos magnetinio rezonanso tyrimu ir mokslinių straipsnių rašymu.

Gydytojui urologui Gyčiui Cholstauskui ir med. m. dr. Ingridai Pikūnienei dėkoju už atliktą „juodą darbą“ – Gyčiui dėkoju už pacientų kuravimą ir atliktas visas prostatos biopsijas, Ingridai – už profesionalų prostatos magnetinio rezonanso tyrimų vertinimą, vertingas pastabas ir palaikymą rašant disertaciją.

UAB „Diagnolita“ komandai esu dėkinga už tai, kad patikėjo mūsų idėja ir suteikė vertingą paramą visų pacientų šlapimo mėginių ištyrimui. Atskirai noriu padėkoti Mantvydui Lopetai iš „Diagnolitos“ už neskaičiuotas darbo valandas formuojant straipsnių idėjas ir rengiant statistinę disertacijos dalį.

Galiausiai, visada būsiu dėkinga savo artimiausiems – vyrui Donatui ir sūnui Jonui, savo tėvams, už galimybę studijuoti ir besąlygišką visų mano idėjų palaikymą, jūs esate mano įkvėpimas.