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# The Value of Adding Exosome-Based Prostate Intelliscore to Multiparametric Magnetic Resonance Imaging in Prostate Biopsy: A Retrospective Analysis

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**Abstract:** Introduction: Currently, there is limited evidence for the relationship of Exosome-based Prostate Intelliscore (EPI) and multiparametric magnetic resonance imaging (mpMRI) in stratifying risk for clinically significant prostate cancer. Using a retrospective cohort study design, we sought to characterize the relationship between these two noninvasive metrics and prostate biopsy outcome. Methods: Data were collected via electronic medical record for all patients who underwent EPI testing from 1 January 2019 to 3 February 2022 and had available medical records at a single mid-western university medical center. Positive test result was defined as >15.6 for EPI, ≥3 PI-RADS score and ≥3 + 4 Gleason Score for biopsy findings. Utility of EPI, mpMRI and combined use was characterized through calculation of sensitivity, specificity, positive predictive value, negative predictive value, and ROC analysis. Results: A total of 226 patients were identified as receiving EPI testing for risk stratification of clinically significant prostate cancer. Sensitivity for EPI was 91%, mpMRI was 90%, and the highest was combined use at 96%. With ROC analysis, AUC for EPI alone was 0.57 (95% CI, 0.47–0.67) and 0.78 (95% CI, 0.70–0.87) for mpMRI alone. With prior positive EPI result, AUC for combined use with mpMRI was 0.80 (95% CI, 0.71–0.89). Further subgroup analysis resulted in increased AUC values of EPI 0.67 (95% CI, 0.48–0.87), mpMRI 0.90 (95% CI, 0.76–1.0), and combined 0.90 (95% CI, 0.75–1.0) in the African American population. Discussion: We observed that the combined use of EPI and mpMRI led to an avoided biopsy in 43% of patients. Using both parameters increased the overall sensitivity and diagnostic accuracy in detecting clinically significant prostate cancer. The best test performance was observed in the African American cohort. Identifying optimal noninvasive tools to assess risk for prostate cancer is crucial to providing accurate and cost-effective care. Future study should utilize a prospective study design to further support the combined use of these metrics.

**Keywords:** magnetic resonance imaging; MRI; prostate cancer; ExoDx; exosome-based prostate intelliscore



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## 1. Introduction

Prostate cancer is the most commonly diagnosed and second leading cause of cancer death in men in the United States. Current estimates indicate 268,490 new cases of prostate cancer per year, with older and African American patients being affected disproportionally [1–3]. Furthermore, current diagnostic methodology makes the accurate and cost-effective identification of prostate cancer challenging [3,4].

Prostate cancer has traditionally been diagnosed via digital rectal examination (DRE) and prostate specific antigen (PSA) biomarker testing, with subsequent transrectal ultrasonography (TRUS)-guided biopsy as the gold standard for confirming diagnosis [5,6].

However, while DRE has been shown to improve outcomes in the detection of high-grade prostate cancer (HGPC), PSA has been demonstrated as unreliable, leaving a gap in screening coverage and increasing the number of unnecessary biopsies [7–11]. This burdens patients with the additional cost of a biopsy and the associated complications [10,12].

Two prominent tools, the Exosome-based Prostate Intelliscore (EPI) and multiparametric magnetic resonance imaging (mpMRI) have demonstrated the potential to increase sensitivity of detecting clinically significant cancer and reduce unnecessary biopsies. EPI, a noninvasive urine exosome gene assay, is a validated tool for risk stratification of benign and low-grade cancer versus Gleason score 7 or greater [13–15]. Additionally, its noninvasive nature and utility in patients with a "gray zone" PSA (2–10 ng/mL) has resulted in influence over the decision to proceed with biopsy [14–16]. The addition of EPI to standard of care has been shown to outperform standard of care or EPI alone [13–15]. Furthermore, the addition of a liquid biomarker such as 4Kscore prior to evaluation with mpMRI has demonstrated improvement in diagnostic accuracy [17].

The use of mpMRI with standardized scoring systems, such as the Prostate Imaging–Reporting and Data System (PI-RADS) v2 has additionally shown promise in stratifying risk. Abnormal mpMRI has been demonstrated to be positively associated with high tumor grade and increased tumor volume, while normal mpMRI can help rule out significant disease [18–20]. The biopsy decision, when guided by mpMRI findings, can help avoid unnecessary biopsies and correctly identify more clinically significant prostate cancer [21].

To date, the relationship between noninvasive modalities such as EPI, 4kscore, and mpMRI and their compound effects on the decision to proceed with a biopsy have limited studies, but with promising results [12,17,22]. This study retrospectively investigated the combined use of EPI and mpMRI in clinical decision-making and its accuracy in identifying clinically significant prostate cancer at a single institution. Analysis of their combined use will help clinicians provide optimal care in men at risk for prostate cancer.

## 2. Methods

### *2.1. Participant Identification and Data Collection*

A retrospective chart review of patients at a single mid-western university medical center gathered data regarding EPI, mpMRI testing, and biopsy findings in men with suspicion for clinically significant prostate cancer. Data were collected via electronic medical record for all patients who underwent EPI testing from 1 January 2019 to 3 February 2022 and had available medical records in either Clinical Portal® or Athena®. No other exclusion criteria were utilized to avoid selection bias. Chart review of identified patients was performed by multiple people. Collected data included demographic variables, past medical history, family history (prostate cancer and BRCA, ovarian, breast cancer), PSA levels, EPI, DRE findings, mpMRI findings, and biopsy pathology findings for patients. If multiple test results were available for a given variable, the closest in date to the EPI was used. Duplicates were removed from the final data set.

### *2.2. Statistical Analysis*

All statistical analysis was completed with IBM SPSS Statistics 29 package with consult from a statistician. For all patients a positive test result was defined as >15.6 for EPI, $\geq$3 PI-RADS score and $\geq$3 + 4 Gleason Score for biopsy findings.

The final dataset was utilized to derive frequency characteristics of the cohort. Median with interquartile range (IQR) and mean with standard deviation (SD) were used to define continuous variables. All statistical analysis used a 95% confidence interval with respective $p$-value of 0.05. Independent-Samples Mann–Whitney U Test was used to determine statistical significance of distributions represented by median values. Independent-Samples t-Test was used to determine statistical significance of distributions represented by mean values. Analysis of clinical test utility was characterized by sensitivity, specificity, positive predictive value, and negative predictive value calculations for EPI, mpMRI and combined use. Patients not receiving conclusive EPI and/or mpMRI testing were not used in calcula-

tions. A positive test result for the combined use analysis was defined as a positive EPI, PI-RADS score, or both.

Receiver Operator Characteristics (ROC) curve analysis was used to characterize the value of increasing scores for EPI, mpMRI PI-RADS and combined use in predicting clinically significant prostate cancer. Patients without conclusive scores for the respective test were excluded from ROC analysis. Criterion for the combined group in ROC analysis was defined as an EPI of >15.6 with an available mpMRI PI-RADS score. Area Under Curve (AUC) describes the accuracy of the test, with a value of 1.0 indicating a perfect predictor of the outcome and 0.5 equating to chance [23].

## 3. Results

A total of 226 patients were identified as receiving EPI testing for risk stratification of clinically significant prostate cancer. Demographic data are listed in Table 1, including age, race, PSA, and family history. Use of one or both metrics in addition to standard of care resulted in a shared decision to avoid a biopsy in 98/226 (43%) of the total cohort. A biopsy was avoided in 36/226 (16%) patients with EPI testing alone and 62/226 (27%) patients with both EPI and mpMRI testing. Of the 226 patients screened with EPI, 216 had conclusive scores, with 176 being >15.6 or at-risk for clinically significant prostate cancer (Table 2).

**Table 1.** Patient demographics and clinical characteristics of identified cohort.

| | |
|---|---|
| Age, y | |
| Median (IQR) | 69 (62,74) |
| Range | 40–92 |
| Race | |
| White (%) | 165 (73) |
| African American (%) | 44 (19) |
| Spanish American Indian (%) | 6 (2.7) |
| Asian (%) | 4 (1.8) |
| Middle Eastern or North African (%) | 2 (0.9) |
| Other (%) | 5 (2.2) |
| PSA (ng/mL) | |
| Median (IQR) | 5.6 (4.1, 8.0) |
| Family History | |
| Prostate Cancer (%) | 72 (32) |
| BRCA, Breast or Ovarian Cancer (%) | 32 (14) |

Abbreviations: y, years; IQR, Interquartile range; FHx, Family History; PSA, Prostate-specific antigen; BRCA, Breast Cancer gene.

**Table 2.** EPI, mpMRI, and biopsy metrics of the identified cohort.

| | |
|---|---|
| EPI | |
| Total | 226 |
| Inconclusive (%) | 10 (4.4) |
| Negative [a] (%) | 42 (19) |
| Positive [b] (%) | 174 (77) |
| Median (IQR) | 31 (18, 46) |
| mpMRI | |
| Total | 175 |
| Undetermined (%) | 7 (4.0) |
| PI-RADS 1 (%) | 3 (1.7) |
| PI-RADS 2 (%) | 69 (39) |
| PI-RADS 3 (%) | 26 (15) |
| PI-RADS 4 (%) | 58 (33) |
| PI-RADS 5 (%) | 12 (6.9) |

**Table 2.** *Cont.*

| | |
|---|---|
| Biopsy | |
| Total | 128 |
| N/A [c] (%) | 50 (39) |
| 3 + 3 (%) | 18 (14) |
| 3 + 4 (%) | 33 (26) |
| 4 + 3 (%) | 12 (9.4) |
| 3 + 5 (%) | 1 (0.8) |
| 4 + 4 (%) | 11 (8.6) |
| 4 + 5 (%) | 3 (2.3) |

Abbreviations: EPI, Exosome-based Prostate Intelliscore; IQR, Interquartile range; PI-RADS, Prostate Imaging–Reporting and Data System. [a] Negative result defined as a score of <15.6. [b] Positive result defined as a score of >15.6. [c] N/A defined as no positive cores reported on pathology results.

Table 3 displays cohort characteristics and test distributions by African American race versus non-African American race. The PSA distribution in the African American cohort was of higher value than the non-African American cohort (7.0, 5.5–9.4 vs. 5.3, 4.0–7.8; $p = 0.001$). Additionally, the age of the African American cohort was lesser (67, 61–70 vs. 70, 63–74; $p = 0.005$). Positivity rates of EPI and biopsies were highest in the African American cohort (88% and 57% versus 79% and 44%), while the mpMRI positivity rate was highest in the non-African American cohort (55% versus 49%).

**Table 3.** Cohort specific characteristics by African American versus other race.

| | **African American** | **Other** | **Significance** |
|---|---|---|---|
| Age, y | | | |
| Median (IQR) | 67 (61, 70) | 70 (63, 74) | 0.005 * |
| PSA | | | |
| Median (IQR) | 7.0 (5.5, 9.4) | 5.3 (4.0, 7.8) | 0.001 * |
| EPI | | | |
| Median (IQR) | 31 (24, 47) | 31 (17, 47) | 0.387 |
| Positive test, n (%) | 37 (88) | 137 (79) | |
| mpMRI | | | |
| Mean (SD) | 3.0 (1.1) | 3.1 (1.1) | 0.706 |
| Positive test, n (%) | 18 (49) | 55 (78) | |
| Biopsy | | | |
| Positive test, n (%) | 17 (57) | 43 (44) | |

Abbreviations: EPI, Exosome-based Prostate Intelliscore; PSA, Prostate-specific antigen; mpMRI, Multiparametric Magnetic Resonance Imaging; IQR, Interquartile Range; SD, Standard Deviation; y, years; * Indicates statistical significance ($p$-value < 0.05). A positive test result was defined as >15.6 for EPI, ≥3 PI-RADS score and ≥3 + 4 Gleason Score for biopsy findings.

Table 4 displays the cohort of 42 patients in which EPI was negative. Of this cohort, 11 patients proceeded with a biopsy, 3 of which had elevated PSA and 5 had a positive PI-RADS score. Of the patients biopsied, 4/11 (36%) had positive findings with all having either previous elevated PSA (>10 ng/mL) or positive PI-RADS score.

**Table 4.** Patients with negative EPI result and following clinical management.

| | | **Elevated PSA [a]** | **Positive mpMRI [b]** | **FH Prostate Cancer** | **Abnormal DRE [c]** |
|---|---|---|---|---|---|
| Negative EPI | 42 | | | | |
| Proceeded to Biopsy (%) | 11 (26) | 3 | 5 | 2 | 2 |
| Positive Biopsy (%) | 4 (36) | 3 | 3 | 1 | 1 |

Abbreviations: EPI, Exosome-based Prostate Intelliscore; PSA, Prostate-specific antigen; mpMRI, Multiparametric Magnetic Resonance Imaging; PI-RADS, Prostate Imaging–Reporting and Data System; DRE, Digital Rectal Examination; FH, Family History. [a] Elevated PSA defined as >10 ng/mL. [b] Positive mpMRI defined as ≥3 PI-RADS. [c] Findings of a prostate nodule or induration.

In Table 5, the utility of EPI, mpMRI, and combined metrics are assessed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Sensitivity for EPI was 91%, mpMRI was 90% and the highest was combined use with 96%. PPV and NPV were also greatest with mpMRI alone. In Table 6, test accuracy is assessed by African American versus non-African American race. Sensitivity in the African American cohort was greater for EPI, mpMRI, and combined groups (94%, 93%, and 100%) compared to the non-African American cohort (Table 6). Furthermore, the PPV of all three test groups is greatest in this cohort at 58%, 87%, and 67% (EPI, mpMRI, combined).

**Table 5.** Sensitivity, specificity, PPV and NPV metrics for EPI, mpMRI and combined cohort.

| | **EPI** | **mpMRI** | **Combined [a]** |
|---|---|---|---|
| Sensitivity | 91% | 90% | 96% |
| Specificity | 11% | 49% | 2.0% |
| PPV | 48% | 62% | 52% |
| NPV | 58% | 83% | 33% |

Abbreviations: PPV, Positive Predictive Value; NPV, Negative Predictive Value; EPI, Exosome-based Prostate Intelliscore; mpMRI, Multiparametric Magnetic Resonance Imaging. [a] Combined is defined as a positive test of EPI, mpMRI or both.

**Table 6.** Sensitivity, specificity, PPV and NPV metrics for EPI, mpMRI and combined cohort by African American versus other race.

| | **EPI** | | **mpMRI** | | **Combined [a]** | |
|---|---|---|---|---|---|---|
| Race [b] | Afr. Am. | Other | Afr. Am. | Other | Afr. Am. | Other |
| Sensitivity | 94% | 90% | 93% | 88% | 100% | 95% |
| Specificity | 15% | 10% | 78% | 43% | 0% | 2.4% |
| PPV | 58% | 44% | 87% | 56% | 67% | 47% |
| NPV | 67% | 56% | 88% | 82% | N/A [c] | 33% |

Abbreviations: PPV, Positive Predictive Value; NPV, Negative Predictive Value; EPI, Exosome-based Prostate Intelliscore; mpMRI, Multiparametric Magnetic Resonance Imaging; Afr. Am., African American. [a] Combined is defined as a positive test of EPI, mpMRI or both. [b] Other race defined as non-African American. [c] N/A due to absence of confirmed false negative in cohort.

Receiver Operating Characteristics (ROC) curve analysis (Figures 1 and 2) was used to further analyze the accuracy of EPI, mpMRI and combined use. Total cohort ROC analysis of EPI is displayed in Figure 1, including 125/226 patients that had both a conclusive EPI and a prostate biopsy. Increasing EPI value was scaled as a higher probability of a positive biopsy, with a resulting Area Under Curve (AUC) of 0.57 (95% CI, 0.47–0.67). Analysis of mpMRI includes the 106/226 patients receiving both an mpMRI PI-RADS score and a prostate biopsy with a value of 0.78 (95% CI, 0.70–0.87). With combined group analysis, 98/226 patients had an EPI >15.6, mpMRI PI-RADS score, and a prostate biopsy. The resulting AUC for the combined group was highest at 0.80 (95% CI, 0.71–0.89). Further ROC analysis by comparing African American versus non-African American race is displayed in Figure 2. All three tests have greater AUC values when delineated by African American race. This includes an EPI AUC of 0.67 (95% CI, 0.48–0.87), mpMRI of 0.90 (95% CI, 0.76–1.0), and a combined of 0.90 (95% CI, 0.75–1.0).

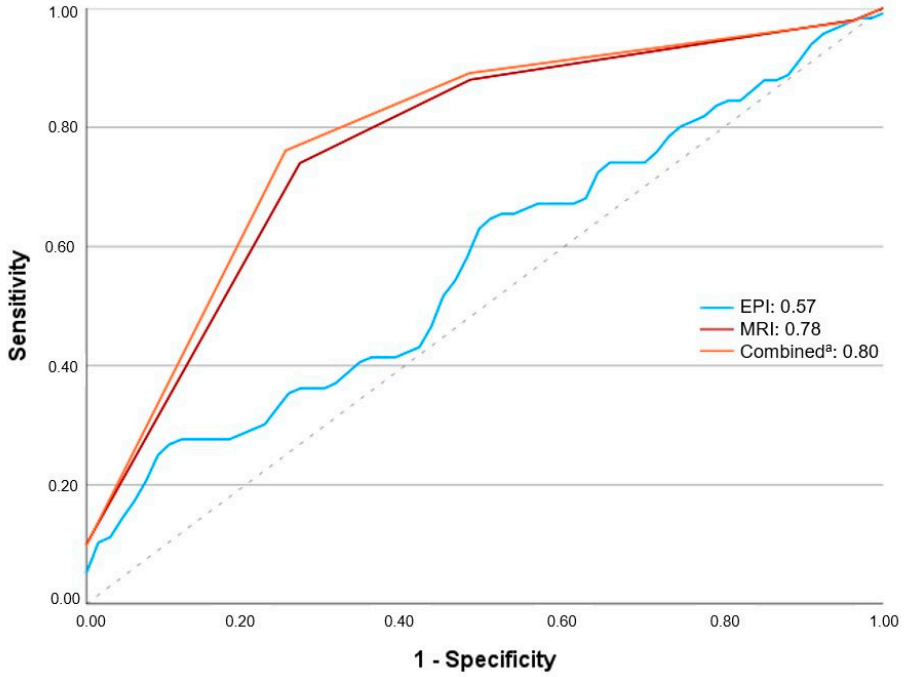


**Figure 1.** ROC curve analysis of EPI alone, mpMRI alone and combined testing using respective biopsy results. Abbreviations: ROC, Receiving Operating Characteristic; EPI, Exosome-based Prostate Intelliscore; MRI, Multiparametric Magnetic Resonance Imaging. [a] Combined testing used biopsy results for patients with EPI > 15.6 and available mpMRI PI-RADS score.

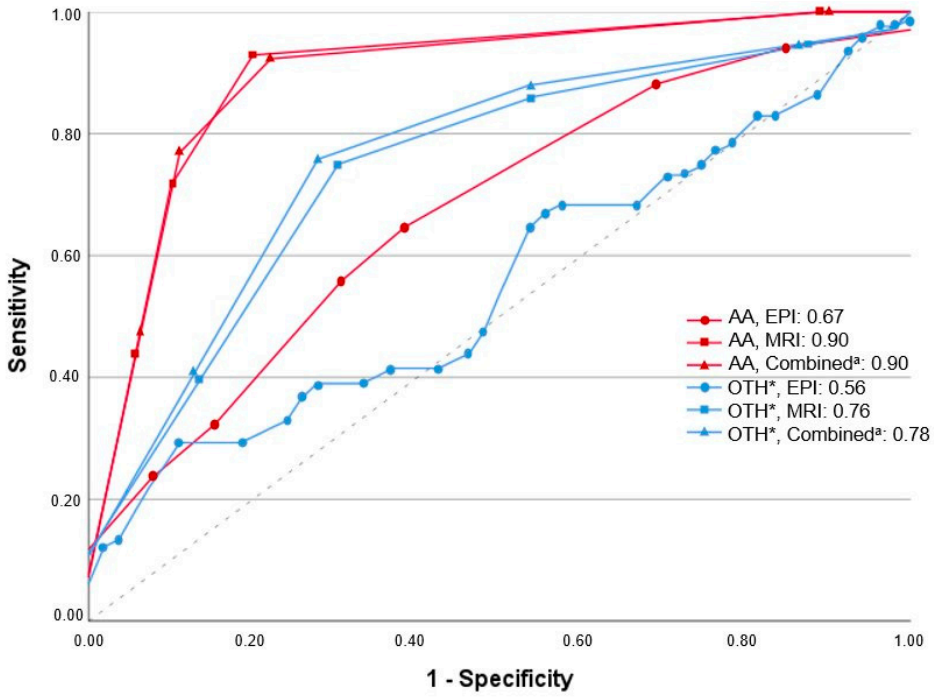


**Figure 2.** ROC curve analysis of EPI alone, mpMRI alone, and combined testing in patients of African American race versus other race. Abbreviations: ROC, Receiving Operating Characteristic; EPI, Exosome-based Prostate Intelliscore; MRI, Multiparametric Magnetic Resonance Imaging; AA, African American; OTH, other race. [a] Combined testing used biopsy results for patients with EPI > 15.6 and available mpMRI PI-RADS score. * Other race defined as non-African American race.

## 4. Discussion

There is currently limited evidence supporting the efficacy of EPI in tandem with mpMRI for risk stratification of clinically significant prostate cancer. We sought to characterize the utility of the two noninvasive metrics together with a goal to reduce unnecessary and invasive prostate biopsies. At the institution investigated, we have found the use of both EPI and mpMRI helps to inform shared decision-making, avoiding biopsies in 43% of the total patients. In addition to guiding the decision to proceed with a biopsy, the use of EPI with mpMRI increased the accuracy of identifying clinically significant prostate cancer. When combined, sensitivity increased from 91% and 90%, for EPI and mpMRI, respectively, to 96%. Overall diagnostic accuracy assessed by the ROC curve was slightly increased from 0.78 (95% CI, 0.70–0.87) to 0.80 (95% CI, 0.71–0.89) by the incidence of a positive EPI prior to mpMRI testing.

The prior literature supports the use of EPI as a valuable tool for risk stratification. Using a cutoff of >15.6 avoids 26% of all biopsies while only missing 7% of clinically significant prostate cancer [14]. Interestingly, our ROC findings (Figure 1) of a 0.57 AUC for EPI testing may support insignificance of increasing EPI value over the 15.6 threshold. EPI is also advantageously noninvasive in comparison to other liquid markers, requiring no prior DRE or other variables to calculate its score [2,4]. The use of EPI for detection of clinically significant prostate cancer has been previously shown to influence the biopsy recommendations made by urologists, and the subsequent patient decisions. Instances for disregarding negative EPI results are primarily associated with other findings, such as rising PSA or other concerning clinical findings [16]. Our study additionally demonstrates how mpMRI can be utilized as another noninvasive metric to further stratify risk in EPI-negative patients rather than proceeding with an invasive biopsy. A biopsy decision guided by mpMRI findings alone can lead to avoiding a primary biopsy in 27% of patients and correctly identifying 18% more clinically significant prostate cancer [21]. In our study, all EPI-negative patients with positive biopsy findings had prior elevated PSA (>10 ng/mL) or a positive PI-RADS score ($\geq$3).

Current evidence supports the use of liquid biomarkers prior to mpMRI in the decision to proceed with a biopsy. Initial evaluation with EPI or 4Kscore followed by mpMRI has shown reduction in unnecessary biopsies while missing minimal clinically significant prostate cancer [17,22]. While use of both maximizes overall test accuracy, the increased cost of noninvasive testing is an added factor [12]. This is weighed against the alternative cost of an invasive biopsy and the risk of complication [11,12]. Infectious complications of biopsies range from 1 to 17.5%, potentially causing hospitalization and additional hematuria, hematospermia, or lower urinary tract symptoms [11]. Regardless, the appropriate clinical course is often dependent on the patient and requires shared decision-making [3,4,24].

Current evidence indicates that men of African American race have earlier disease presentation, more aggressive disease, and higher rates of mortality than Caucasian men [25,26]. From 2012 to 2016, the prostate cancer specific mortality rate was 39.8 deaths per 100,000 in Black men versus 19 per 100,000 in White men [26]. In our study, we found test accuracy was highest when delineated by African American race with sensitivities of 94%, 93%, and 100% in EPI, mpMRI, and combined tests, respectively. ROC analysis showed additional improvement with respective AUC values of EPI 0.67 (95% CI, 0.48–0.87), mpMRI 0.90 (95% CI, 0.76–1.0) and combined 0.90 (95% CI, 0.75–1.0) in the African American population. Notably, there was statistical significance in the distribution of age and PSA in this group, with lower age (67 vs. 70 years old, $p$-value 0.005) and higher PSA (7.0 vs. 5.3 ng/mL, $p$-value 0.001) in the African American group. Prior evidence has indicated similar findings of younger age at diagnosis (63 vs. 66 years old) and higher PSA levels (6.7 vs. 6.2 ng/mL) than non-Hispanic White men [27]. With evidence of higher disease burden in this population, the relative effects on PPV and NPV in comparison to other populations must be considered. Ultimately, the findings within this study are encouraging to improve the detection and outcome of prostate cancer in the African American population.

As with any study, there should be an acknowledgement of this study's limitations. The retrospective nature of this study creates vulnerability to its findings and is subject to human error and bias in data collection, statistical calculation, analysis of results and loss of patient follow up. Being primarily based on data at a single mid-western university medical center, the results demonstrated here may not be generalizable.

Notably, in Table 5, the results for specificity of EPI, mpMRI and combined group were lower than expected. Calculations revealed specificities of 11%, 49%, and 2%, respectively. As specificity is used to categorize true negatives, retrospectively it is vulnerable to inaccuracy, as not all patients received a prostate biopsy. In patients who had a negative EPI, mpMRI or both, it is unlikely that clinical decision-making led to a prostate biopsy without an additional concerning factor such as elevated PSA, abnormal DRE or positive family history [16]. This is reinforced in Table 4 as only 26% of patients with negative EPI also received a prostate biopsy, with the majority having a prior elevated PSA, positive mpMRI, positive family history, abnormal DRE or combination of factors. This lack of confirmatory biopsies for low-risk patients leaves a question regarding the calculations, as to which true negatives are required. Furthermore, as data collection occurred at a single point, it must be considered that patients avoiding a biopsy in active surveillance could reach a shared decision for proceeding with a biopsy at a future date.

Future studies should optimize study design to provide a higher level of evidence for utilizing both EPI and mpMRI. Primarily, a prospective study design in which all patients receive a prostate biopsy is necessary to accurately define values such as sensitivity, specificity, positive predictive value, and negative predictive value. Future studies should utilize a larger sample size across several institutions to account for small events and make the results generalizable [28]. Optimal clinical practice can further be investigated by evaluating the additional economic cost of both noninvasive modalities.While a greater initial cost of testing, the overall cost of care should be evaluated with the respective decreased biopsy rates, overdiagnosis, and overtreatment. Clinical utility can be further investigated in combination with other metrics such as PSA, DRE, and family history [24,28].

While the results of the current study should inform more rigorous study design, the data collected show promising results. To date, there is limited evidence guiding the combined use of EPI and mpMRI in the detection of clinically significant prostate cancer. Here, we demonstrate additional evidence for improved diagnostic accuracy with the addition of EPI testing to mpMRI in the detection of prostate cancer. Furthermore, we demonstrate increased test accuracy in particularly susceptible populations such as those of African American race. These findings are encouraging for the future use of EPI and mpMRI in patients faced with a prostate biopsy decision.

## 5. Conclusions

We observed that the combined use of EPI and mpMRI resulted in the shared decision for biopsy avoidance in 43% of patients. Using both parameters increased overall sensitivity and diagnostic accuracy in detecting clinically significant prostate cancer. The best test performance was observed in the African American cohort. The retrospective nature of this study limits the level of evidence it can provide; however, it indicates promising results. Further study should prospectively utilize a larger patient population to assess clinical significance and thresholds for the biopsy decision. Identifying optimal testing modalities for men at risk for prostate cancer is crucial to providing accurate and cost-effective care. Regardless, a patient-centered approach is paramount to clinical decision-making in this population. The aim of reliably identifying clinically significant prostate cancer while avoiding an unnecessary biopsy remains a challenge in men with select elevated PSA.

**Author Contributions:** Conceptualization, N.K. and P.S.; data curation, N.K., J.L. and S.J.; formal analysis, N.K. and J.L.; investigation, N.K., J.L., S.J., C.L. and P.S.; methodology, N.K., B.S. and P.S.; project administration, N.K., C.L., N.N. and P.S.; supervision, J.L., N.N. and P.S.; validation, N.K., B.S. and P.S.; visualization, N.K.; writing—original draft, N.K.; writing—review and editing, N.K., B.S., N.N. and P.S. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Patient consent was waived due to the study involving no more than minimal risk.

**Data Availability Statement:** Data is unavailable due to terms of IRB agreement regarding protection of patient information.

**Conflicts of Interest:** The authors have no conflicts of interest to disclose.

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