ORIGINAL RESEARCH

# Reduced Rate of Repeated Prostate Biopsies Observed in ConfirmMDx Clinical Utility Field Study

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**Background:** The diagnosis of prostate cancer is dependent on histologic confirmation in biopsy core tissues. The biopsy procedure is invasive, puts the patient at risk for complications, and is subject to significant sampling errors. An epigenetic test that uses methylation-specific polymerase chain reaction to determine the epigenetic status of the prostate cancer–associated genes *GSTP1*, *APC*, and *RASSF1* has been clinically validated and is used in clinical practice to increase the negative predictive value in men with no history of prostate cancer compared with standard histopathology. Such information can help to avoid unnecessary repeat biopsies. The repeat biopsy rate may provide preliminary clinical utility evidence in relation to this assay's potential impact on the number of unnecessary repeat prostate biopsies performed in US urology practices.

**Objective:** The purpose of this preliminary study was to quantify the number of repeat prostate biopsy procedures to demonstrate a low repeat biopsy rate for men with a history of negative histopathology who received a negative epigenetic assay result on testing of the residual prostate tissue.

**Methods:** In this recently completed field observation study, practicing urologists used the epigenetic test called ConfirmMDx for Prostate Cancer (MDxHealth, Inc, Irvine, CA) to evaluate cancer-negative men considered at risk for prostate cancer. This test has been previously validated in 2 blinded multicenter studies that showed the superior negative predictive value of the epigenetic test over standard histopathology for cancer detection in prostate biopsies. A total of 5 clinical urology practices that had ordered a minimum of 40 commercial epigenetic test requisitions for patients with previous, cancer-negative biopsies over the course of the previous 18 months were contacted to assess their interest to participate in the study. Select demographic and prostate-screening parameter information, as well as the incidence of repeat biopsy, specifically for patients with a negative test result, was collected and merged into 1 collective database. All men from each of the 5 sites who had negative assay results were included in the analysis.

**Results:** A total of 138 patients were identified in these urology practices and were included in the analysis. The median age of the men was 63 years, and the current median serum prostate-specific antigen level was 4.7 ng/mL. Repeat biopsies had been performed in 6 of the 138 (4.3%) men with a negative epigenetic assay result, in whom no evidence of cancer was found on histopathology.

**Conclusion:** In this study, a low rate of repeat prostatic biopsies was observed in the group of men with previous histopathologically negative biopsies who were considered to be at risk for harboring cancer. The data suggest that patients managed using the ConfirmMDx for Prostate Cancer negative results had a low rate of repeat prostate biopsies. These results warrant a large, controlled, prospective study to further evaluate the clinical utility of the epigenetic test to lower the unnecessary repeat biopsy rate.

**Stakeholder Perspective, page 134**

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Prostate cancer is the most frequently detected cancer in men, and approximately 16% of men are diagnosed with prostate cancer during their lifetime.[1] Although the overall value of routine screening, resulting in approximately 1 million annual prostate biopsy procedures, has been recently questioned, the mortality

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## KEY POINTS

- Prostate cancer is the most often diagnosed cancer in men; its diagnosis is dependent on histologic confirmation with a core-tissue biopsy.
- As a result of the well-reported sampling errors using transrectal ultrasound–guided biopsies, many cancers are unsampled and hence undetected by histopathologic review.
- In the presence of persistent risk factors (eg, elevated PSA), repeat prostate biopsies are frequently used to detect occult cancer in men with previous negative findings, leading to unnecessary morbidity and increased healthcare costs.
- Previous studies on repeated biopsy procedures have shown that initial prostate biopsy histopathology has a 20% to 30% false-negative rate.
- Based on real-world data from 5 US urology practices, the use of the ConfirmMDx for Prostate Cancer test can help patients avoid unnecessary repeat biopsies and reduce healthcare waste and costs.
- Men who were managed based on the ConfirmMDx for Prostate Cancer test negative results had a <5% rate of repeat prostate biopsies, indicating a potential 10-fold reduction from previous rates.
- The ConfirmMDx for Prostate Cancer assay has been clinically validated to significantly improve the negative predictive value over histopathology to approximately 90%.

rate of the disease remains significant, accounting for 10% of all cancer-related deaths.[1-3] The clinical course of prostate cancer can range from indolent and self-contained to metastatic and lethal.[4]

Disease prognosis at the time of diagnosis is typically assessed by the tumor volume, serum prostate-specific antigen (PSA) level, clinical stage, and the use of the Gleason scoring system.[5] An accurate diagnosis followed by acute treatment or active surveillance techniques for patients with disease localized within the gland can be vital for good clinical outcomes.[4]

Sampling errors inherent with the random tissue collection of the biopsy procedure result in a false-negative rate of approximately 25% for standard-of-care histopathology.[5] Repeat biopsies are common in men with previous histopathologically negative findings, in an attempt to detect occult cancer that leads to considerable morbidity and adds costs to the healthcare system.[5]

### Clinical Background

The US Preventive Services Task Force recently published its conclusion discouraging routine PSA testing in the general population of US men as a result of the potential overtreatment of indolent disease.[6] Such screening, along with an annual digital rectal examination (DRE), however, has led to a significant reduction in the presentation of advanced cancer.[1,3,7] Urologists who treat patients with prostate cancer fear a resurgence of advanced cancer and higher mortality rates with the reduction of screening, resulting in an increase in healthcare costs to effectively treat patients with prostate cancer.[8]

Many at-risk men continue to be screened and evaluated for prostate cancer. When cancer is suspected, urologists typically perform a prostate biopsy, obtaining approximately 10 to 12 needle core tissue samples, per the current standard of care.[4,9]

As a result of the well-reported sampling errors using transrectal ultrasound methods, many cancers are undetected by histopathologic review.[10] Studies on repeated biopsy procedures indicate that initial prostate biopsy histopathology has a 20% to 30% false-negative rate.[11,12] This imprecision poses a diagnostic dilemma, often resulting in multiple repeat biopsies from the fear of missed cancer in men with persistent risk factors.[13,14] Although diminishing rates of cancers are detected during these invasive repeat procedures, a high rate of clinically significant (ie, a Gleason score ≥7) cancer found with a repeat biopsy (65%, 53%, and 52% in second, third, and fourth or more biopsies, respectively) has been reported.[15]

As a result, many men are exposed to the discomfort and risk of complications from a biopsy, such as infections, prostatitis, and anxiety.[16] Increasing rates of antibiotic resistance has also been reported, adding to the disease-associated risks and to morbidity.[2]

### Description of ConfirmMDx for Prostate Cancer

Molecular testing at both the DNA and RNA levels is improving cancer detection over standard techniques used in oncology. Although genetic screening predicts the lifelong risk of disease development in inherited germline cells requiring genetic counseling, epigenetic profiling of target organ tissue has been shown to be an important predictor of cancer presence.[17] The result of the epigenetic assay, used in this study, of the initial biopsies has been reported to enhance the negative predictive value over histopathologic review.[18,19]

In 2 multicenter, blinded studies, the high negative predictive value of this epigenetic test (ConfirmMDx for Prostate Cancer; MDxHealth, Inc, Irvine, CA) was clinically validated.[18,19] The assay is commercially available and uses multiplex methylation-specific polymerase chain reaction to measure the epigenetic status of prostate cancer–associated gene biomarkers *GSTP1*, *APC*, and *RASSF1* in residual cancer-negative prostate biopsy core tissue samples.[18,19] By detecting epigenetic abnormalities in a halo

**Table 1** Patient Demographics and Prostate-Related Findings

| Site | | 1 | 2 | 3 | 4 | 5 | All |
|---|---|---|---|---|---|---|---|
| Patients, N | | 29 | 19 | 18 | 26 | 46 | 138 |
| Age, yrs | Mean (SD) | 60.38 (9.41) | 65.87 (8.3) | 59.94 (7.77) | 59.12 (10.14) | 63.48 (7.73) | 61.7 (8.9) |
| | Median (range) | 59 (40-75) | 67 (52-82) | 60 (43-70) | 61 (44-78) | 65 (44-77) | 63 (40-82) |
| | ≥65 (%) | 11 (38) | 9 (60) | 5 (31) | 10 (38) | 22 (55) | 57 (45) |
| PSA at biopsy, ng/mL | Mean (SD) | 5.82 (6.81) | 6.69 (6.29) | 4.53 (2.23) | 8.16 (15.31) | 5.02 (3.25) | 5.95 (7.95) |
| | Median (range) | 4.85 (0.2-37.5) | 5.52 (0.78-30.4) | 4.47 (0.5-11.8) | 4.7 (0.4-81) | 4.37 (0.33-16.6) | 4.7 (0.2-81) |
| Current PSA, ng/mL | Mean (SD) | 4.25 (5.14) | 6.4 (6.02) | 3.7 (2.08) | 8.6 (14.37) | 6.02 (6.82) | 6.03 (8.45) |
| | Median (range) | 3.1 (0.2-24.5) | 4.43 (2.17-25.5) | 3.7 (0.5-7.3) | 5.1 (0.59-75.2) | 4.6 (0.33-42.91) | 4.43 (0.2-75.2) |
| DRE | Normal, N (%) | 17 (63) | 19 (100) | 13 (72) | 19 (73) | 34 (74) | 102 (75) |
| | Abnormal, N (%) | 10 (37) | 0 (0) | 5 (28) | 7 (27) | 12 (26) | 34 (25) |
| Histopathology | Normal, N | 28 | 15 | 18 | 26 | 46 | 133 |
| | Abnormal, N (%) | 1 (3.5) | 4 (21) | 0 (0) | 0 (0) | 0 (0) | 5 (3.7) |
| Repeated biopsy? | No | 27 | 19 | 17 | 24 | 45 | 132 |
| | Yes, N (%) | 2 (6.9) | 0 (0) | 1 (5.6) | 2 (7.7) | 1 (2.2) | 6 (4.3) |
| | Negative, N | 2 | 0 | 1 | 1 | 1 | 6 |
| | Positive, N | 0 | 0 | 0 | 0 | 0 | 0 |

DRE indicates digital rectal examination; PSA, prostate-specific antigen; SD, standard deviation.

around the tumor, which is shown to be associated with oncogenesis, these biomarkers aid in finding evidence of occult prostate cancer unseen by histopathology.[18-20]

This field effect, which is measured in adjacent benign-appearing biopsy core tissues is a strong independent predictor to diagnose prostate cancer in a subsequent biopsy, with a negative epigenetic result providing a higher negative predictive value (approximately 90%) than standard histopathology alone.[12,18,19] The test results from this epigenetic assay help guide urologists on decisions regarding the need for repeat biopsy for patients with a previous negative biopsy but who are still considered to be at risk for prostate cancer.

The goal of this study was to determine the prevalence of repeat prostate biopsies in patients managed by urologists ordering the test for patients with a previous histopathologically negative prostate biopsy who received a negative epigenetic test result. This study was conducted in urology practices that had ordered the test for a minimum of 40 patients as a preliminary examination of the clinical utility of the molecular diagnostic to reduce unnecessary repeat biopsy procedures.

## Methods

### *Study Design*

This study was conducted at 5 urology centers that had ordered the ConfirmMDx assay to help manage their patients with previous histopathologically negative prostate biopsies. Each center reported whether patients who had a negative assay result had undergone a repeat biopsy at the time of the analysis. The median patient follow-up time after the receipt of the assay results was 9 months, compared with a median of 7.3 months between repeat biopsies in a previous retrospective study.[18]

Physicians from urology practices ordering a minimum of 40 ConfirmMDx tests were asked to participate. An electronic spreadsheet was used to collect demographic and medical data from clinic records related to the initial biopsy and to any repeat biopsy.

No protected health information or Health Insurance Portability and Accountability Act identifiers were collected in this study. The study design was reviewed and granted a notice of exemption by the Quorum Review Institutional Review Board for all sites participating in this trial.

### *Collected Data Elements*

Men at each site were assigned a unique, confidential, study-specific identifier. The following demographic, prostate health, and biopsy outcome information was collected on electronic data collection forms for all patients who received an epigenetic assay–negative result:

- Age at the time of the initial negative biopsy

**Table 2** Repeated Biopsy Rates Stratified by Available Risk Factors[a]

| Risk factor | PSA at biopsy | PSA, current | DRE | Biopsy result | Age | ConfirmMDx |
|---|---|---|---|---|---|---|
| Low risk, % | 4.1 (2 of 49) | 0 (0 of 49) | 5.9 (6 of 102) | 4.5 (6 of 133) | 4.3 (5 of 117) | 4.3 (6 of 138) |
| High risk, % | 4.5 (4 of 88) | 8.6 (6 of 70) | 0 (0 of 34) | 0 (0 of 5) | 0 (0 of 9) | — |

*NOTE*: High risk is defined as serum PSA concentrations exceeding 4 ng/mL, abnormal DRE results, nonbenign histopathology of the initial biopsy, and age ≥75 years.
[a]Where data are available for patients in the study.
DRE indicates digital rectal examination; PSA, prostate-specific antigen.

- Race
- PSA level: preceding the negative biopsy and the most current value
- DRE: suspicious or nonsuspicious
- Date the negative epigenetic assay results were received by the treating physician
- Initial biopsy histopathology findings: benign or nonbenign histology
- Repeat biopsy: yes or no; if yes, histopathology findings of the repeat biopsy.

### *Patient Selection*

Geographically dispersed urologists who had ordered MDxHealth's ConfirmMDx testing for a minimum of 40 men with previous negative prostate biopsies over the 18 months preceding this analysis (which was conducted in January 2014), were contacted for their interest to participate in this study. The clinical staff at the individual urology practices recorded the desired data elements from hard copy and/or from electronic medical records onto an electronic spreadsheet of all patients who had received a negative assay result report. The completed electronic forms were forwarded to MDxHealth, where the forms were merged into an accumulated database for data summaries and analyses.

## Results

The 5 study sites reported findings for 18 patients to 46 patients per site, for a combined total of 138 patients with negative assay results. These 138 patients represent an unfiltered group of men with negative biopsy results from multiple urology clinics whose primary care urologists sent their biopsy tissue for testing with the commercial assay. By focusing on multiple centers with a sufficiently large volume, a representative sample was obtained, so that the encouraging results from this cohort can lead to the launch of a larger, controlled prospective trial to definitively answer the test's clinical utility in standard urology practice.

**Table 1** lists the patient demographics and prostate-specific and repeat biopsy findings for the 138 study participants. Patients had a mean age of approximately 63 years, covering a wide range (40-82 years), and 45% of them were aged ≥65 years. The mean PSA value across the men in the study at the time of the initial biopsy was 5.95 ng/mL, and the mean of the most recent PSA levels was 6.03 ng/mL. Of these men, 25% were reported to have had abnormal DRE findings and 5 had nonbenign, but not suspicious for cancer, histopathology reports.

Table 1 also shows the repeat biopsies performed. Of the 138 patients, 6 (4.3%) underwent the repeat procedure by the time of data collection. Of the 6 repeat biopsies, 1 patient had high-grade prostatic intraepithelial neoplasia detected on histopathologic review, and all of the men were cancer-free.

**Table 2** illustrates the repeat biopsy rates, which are stratified according to the different risk factors available to the urologist. PSA appears to be the only clear driving factor in the decision-making process. For 11 patients, the serum PSA concentrations were >10 ng/mL when measured after the initial biopsy, which appears to be the most important trigger for a repeat biopsy (2 of the 11 patients, 18%).

## Discussion

Prostate cancer differs in its clinical presentation and behavior. It can be an isolated lesion that can remain subclinical during a man's life, or it can develop into a heterogeneous, metastatic disease causing death. The advent of prostate cancer screening with factors such as annual serum PSA measurement and DRE could lead to a modest increase in overall survival in this patient population; however, it is currently part of a debate regarding what the extent of the improvement is.[3,7]

Recent medical guidelines (eg, by the National Comprehensive Cancer Network or American Urological Association) propose adjusted screening conventions to select men most likely to benefit because of the fear of overdiagnosis.[13,21] Although radical treatment (ie, prostatectomy or radiotherapy) of low-risk cancer (often defined as a Gleason score of 6) is not the best treatment option and is progressively being replaced by active surveillance programs, highly aggressive disease is still discovered at the time of diagnosis, leading to poor clinical patient outcomes.

The practicing urologist must remain vigilant to detect cancers at an earlier stage, when cure is most achievable.[21] On informed consultation with their physicians, many men elect to continue screening for prostate cancer, especially those who are considered to be at elevated risk as a result of their race, family history, or urinary symptoms.[21]

Prostate biopsy is a common procedure and is the standard of care for diagnosis. Under the current standard of care, high false-negative rates resulting from sampling errors lead to repeat biopsies in more than 40% of men who had initial negative findings, for fear of missed disease.[22] These repeated procedures most often again reveal a lack of detectable cancer, while incurring considerable costs and risks to the patient. This suggests that an improved method to better stratify risk in men with histopathologically negative prostate biopsies is needed.

The ConfirmMDx for Prostate Cancer assay has been clinically validated to significantly improve negative predictive value over histopathologic examination to approximately 90%.[18,19] The analytical cutoffs used for each of the assay's 3 cancer-associated biomarkers were established to maximize negative predictive value in that a negative test result can be used as an important contributing factor to improve the identification of men with sufficiently low risk for harboring occult prostate cancer, despite other clinical risk factors, who may avoid a repeat biopsy.

The current study was conducted to obtain a preliminary, real-world indication of the clinical utility of negative test results of the epigenetic assay in urologic practice. The patient cohort (N = 138) included a wide range of ages, with 45% of patients in the study aged ≥65 years. The results show that the repeat biopsy rate in this cohort was <5%, demonstrating a potential 10-fold reduction with the assay from the reported rate of repeat prostate biopsy, which provides justification for a prospective, randomized multicenter clinical utility trial.[22] During such a trial, the proposed substantial cost-savings, as determined by a budget impact model for the use of the assay for this indication, can also be further validated.[23]

## Limitations

Because the number of patients in this study is relatively small compared with the number of repeat biopsies performed annually, the results are only indicative of the potential that the epigenetic assay may have on patient management.

This observational study was conducted by physicians using a commercial assay to manage patients with histopathologically negative prostate biopsies. It was intended to assess preliminary evidence of its primary indication (ie, generating the hypothesis that negative epigenetic test findings reported to urologists impact patient management and are thus associated with a lower incidence of repeat procedures).

Although generalizations on the clinical utility outcomes of the assay based on a small, retrospective cohort should be made with caution, this study provides a strong indication that the assay may indeed have an impact to reduce the rate of unnecessary repeat biopsies.

An additional, large, prospective clinical utility trial is under development to further demonstrate the test's impact on clinical practice.

## Conclusions

The use of new molecular diagnostic technologies, such as this epigenetic test, can lead to better patient management than the current standard guidelines, and can reduce the overall healthcare costs by reducing unnecessary repeat prostate biopsies. The preliminary evidence of the clinical utility from this current study strongly supports this premise and warrants a larger, prospective trial. ■

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*Author Disclosure Statement*

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## STAKEHOLDER PERSPECTIVE

# Molecular Tests Can Help to Reduce Repeated Prostate Biopsies

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**PAYERS:** In their article in this issue, Wojno and colleagues conclude that the results of their small-scale study, with only 138 patients, warrant a prospective, larger-scale trial to confirm these results. Indeed, health plans and other payers should support the authors' conclusion to provide more definitive evidence on the ability of ConfirmMDx to reduce the number of repeated prostate biopsies to test for prostate cancer.

Molecular tests, such as ConfirmMDx, may enable the advent of personalized medicine in prostate cancer, which could reduce the cost of care through evidence-based, tailored approaches for individual care management. A robust, large-scale study with the conclusion that ConfirmMDx reduces the rate of repeated prostate biopsies would be a significant accomplishment in the efforts to reduce healthcare costs, as well as reduce potential patient complications related to unnecessary biopsies.

Furthermore, health plans may consider guideline development to use a negative predictive value test when the clinical path forward is unclear, such as in the case of a biopsy with a Gleason score of 5 or 6. It may not be necessary to run such a test for a patient with a Gleason score of ≤4 and a normal digital rectal examination (DRE) or a patient with a Gleason score of ≥7 and a suspicious DRE result. A guideline-based utilization with demonstrated change in clinician behavior would be of special interest. Payers should consider both the economic benefits and the benefits of improvement in quality of life for patients who avoid the need for repeated biopsies.

**PATIENTS/PROVIDERS:** As in other disease states, patients and providers should discuss the available data and experience (eg, details of the biopsy results, prostate-specific antigen history, family history, DRE results, and age) to determine the clinical course of action in the individual case. The US Preventive Services Task Force has recommended against routine testing for prostate cancer of otherwise healthy men.[1] The driving force behind this recommendation relates to the potential for unnecessary overtreatment of indolent disease, as well as to the complications related to biopsy, including infection and prostatitis. Therefore, patients and providers should welcome the promise of a molecular epigenetic test, such as ConfirmMDx, that has the potential to provide true confirmation of negative biopsy results; a confirmation that, in many cases, could preclude the need for repeated biopsies and potential complications, as well as relieve the patient's anxiety surrounding the question, "Do I have cancer?"

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