Evidence table

Authors, Design, Aim	Patient's characteristics	Outcomes	Conclusion, RoB (QUADAS-2)
Waterhouse et al., 2019 Design: Retrospective study Aim: To assess the performance of ConfirmMDx in African American (AA) men.	N=211 AA Patients were men undergoing repeat biopsy within 30 months from a negative index biopsy. Age: 43-86 yrs; PSA: 0.6-61.6 ng/mL; 60% had normal DRE. GS: 66% had GS of 6; 34% had GS ≥7 Clinical stage: 69% T1c On repeat bx results: 62% had no PCa, 38% had PCa (66% GS ≤6; 33% GS ≥7). Index test consisted of Multiple qMSP assay (MDxHealth). The reference standard was histopathology on repeat prostate bx.	**The clinical performance (detection of any PCa) included:** Sensitivity: 74.1% (63.1%-83.1%) Specificity: 60.0% (51.1%-68.5%) PPV: 53.6% (47.4%-59.6%) **NPV: 78.8%** (71.5%-84.6%) Sensitivity & specificity in this study were comparable to studies with predominantly Caucasian population. **Detection of high-grade PCa (GS ≥7):** Sensitivity: 77.8% (57.7%-91.4%) Specificity: 52.7% (45.2%-60.1%) PPV: 19.4% (15.8%-23.7%) **NPV: 94.2%** (88.7%-97.1%) No significant differences in sensitivity or specificity were observed between age groups (<55; 55-69; ≥70) The high NPV demonstrates that repeat biopsy can be avoided. A test with high NPV may be clinically useful. **2*2 tables:** Detection of any cancer at biopsy PCa pos / PCa neg CMDx pos: 60 / 52 / 112 CMDx neg: 21 / 78 / 99 81 / 130 Detection of high-grade cancer at biopsy HG PCa pos / HG PCa neg CMDx pos: 21 / 87 / 108 CMDx neg: 6 / 97 / 103 27 / 184	**Conclusion**: the study validates the use of ConfirmMDx to help guide repeat biopsy decision in AA. ConfirmMDx has a good performance in this AA population. Its high NPV shows that it may be clinically useful for classification of AA men who had an initial negative biopsy. **RoB**: High Patient selection: low Index test: Unclear (Were the index test results interpreted without knowledge of the results of the reference standard? Unclear) Reference standard: Unclear (Were the reference standard results interpreted without knowledge of the results of the index test? Unclear) Flow & timing: Low

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<td>Stewart et al., 2013

Design: retrospective study

(Methylation Analysis to Locate Occult Cancer (MATLOC study))

Aim: to demonstrate high NPV and clinical utility (by averting unnecessary biopsy)</td>
<td>The authors included 483 patients with two consecutive biopsies where the first biopsy was negative, and the repeat biopsy was positive (cases) or negative (controls);
Mean age 63 years (45-84);
PSA mean 7.61 (range 0.4 to 50 ng/ml);
Percentage of patients with normal DRE 73%;
Most patients had GS=6
Histopathology biopsy: benign 73%.
Patients were classified in two groups: Group 1, cases, with positive repeat biopsy result (n=87), and group 2 which have negative repeat bx referenced as controls (n=396).

The index test was the qMSP assay. The reference test was histopathology result from repeat prostate bx. PSA > 4 ng/ml was more frequent in controls than in cases.</td>
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<tr><th></th><th>Sensitivity (CI)</th><th>Specificity (CI)</th><th>NPV (CI)</th><th>PPV(CI)</th><th>Accuracy</th></tr>
<tr><td>3-gene model</td><td>68% (57%-77%)</td><td>64% (59%-69%)</td><td>90% (87%-93%)</td><td>29% (25%-33%)</td><td>65%</td></tr>
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DNA methylation was a significant independent predictor of cancer on repeat biopsy (OR 3.17, 95% CI 1.81–5.53, p <0.0001).
Atypical cells but not HGPIN were also predictor of cancer (OR 3.17 (95% CI 1.31–7.70)).
</td>
<td>Conclusion: The Findings show that the test has moderate sensitivity & specificity with high NPV and can predict repeat biopsy outcome. The test could decrease unnecessary repeat biopsy by 64%. The high NPV indicates a low false negative. The DNA methylation is an independent risk factor for detecting prostate cancer before repeat biopsy. The increased NPV could help avert unnecessary repeat biopsies.

Rob: High
Patient selection: High (Case control was not avoided)
Index test: unclear (Were the index test results interpreted without knowledge of the results of the reference standard? Unclear)
Reference standard: high (Is the reference standard likely to correctly classify the target condition? High risk)
Flow & timing: low
Applicability concerns: Low for Patient selection, Index Test, & reference standard.</td>
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Partin et al., 2014: Detection of Cancer Using Methylated Events in Negative Tissue (**DOCUMENT trial**)) Design: retrospective study Aim: To validate the performance of an epigenetic test.	N=350 patients Pt characteristics (n=320), mean age: 62 yrs, PSA (mean ng/mL): 6.1, % of normal DRE: 60%, Histopathology bx 1: No abnormality: 58%. All patients received repeat biopsy within 2 years; those with negative results were controls (n=228) and patients with positive results were cases (n=92). Index test was the multiplex methylation (MDxHealth, Irvine, California). Inclusion criteria was defined as a minimum of 8 cores per biopsy. The reference test was histopathology result on repeat prostate bx.	Sensitivity 62% (51%-72%), Specificity 64% (57%-70%), **NPV 88% (85%-91%)** The test was found to be the most significant independent predictor of patient outcome (OR 2.69, 95% CI 1.60-4.51) on repeat biopsy after controlling for age, PSA, DRE, first biopsy histopathological characteristics and race. Atypical cells were also found to be a significant predictor of patient outcome (OR, 2.37; P=0.0465). In a subgroup of African Americans (small sample size): Sensitivity 77% (95% CI 46–95) Specificity 66% (95% CI 46–82) **NPV 93% (85% CI 82–97)**	The findings have shown that the epigenetic test is a significant and independent predictor of prostate cancer detection in a repeat biopsy collected within 24 months. Its NPV is high and as result the test can help avoid unnecessary repeat biopsies if it is added to other known risk factors. Rob: High Patient selection: high (case control was not avoided) Index test: Low Reference standard: High (Is the reference standard likely to correctly classify the target condition? High risk) Flow & timing: Low Applicability concerns: Low for Patient selection, Index Test, & reference standard.
Van Neste et al., 2016 Design: retrospective study Aim: To assess the performance of a DNA-methylation assay, to predict men at risk of harboring high-grade cancer.	Cohorts from the MATLOC & DOCUMENT trials, appraised above, were combined (n=803 patients). Therefore, patients' characteristics are similar to those studies. All men had a negative index biopsy followed by either a positive (179 men) or negative (624 men) repeat biopsy. The index test & reference standard are identical to that of MATLOC & DOCUMENT trials. Patients were classified according to the histopathological outcome of the repeat biopsy: High risk (GS ≥7, n=67), indolent PCa (GS ≤6, n=106), Control (no PCa, n=)	**Overall** NPV (for finding low levels of DNA methylation) 89.2% for all cancers. PPV 28.2% for all cancers. None of these cancers were detected at the time of index biopsy. The assay had a significantly increased PPV (P < 0.001) compared to current clinical practice. **Regarding high-grade PCa detection (GS ≥7)**, NPV was 95.9%. DNA methylation was the strongest predictor of high-grade cancer (AUC 0.661 (0.572–0.751) p=0.001) upon repeat biopsy. **Risk score (DNA-methylation intensity and traditional clinical risk factors) AUC: 0.762 (0.679 – 0.844)**	The risk score may help to detect patients with high-grade cancer in comparison to PSA and PCPTRC. The risk of bias of the study is high. This is due to the exclusion of patients with GS 6, long duration between biopsies (>2 years), small sample size in high-grade cancer, conflict of interest in the form of financial interest between some authors and the laboratory.

	No significant differences in PSA, DRE, time between biopsies were reported. Histopathology significantly differ between groups. HGPIN predominated in the groups Age was significantly different in the groups (controls, GS≤6, GS≥7): 62.5/62.0, 63.3/64.0, 65.6/66.0 p<0.001.	Decision curve analysis: In comparison with PSA and PCPTRC (Prostate Cancer Prevention Trial Risk Calculator), there is a higher benefit that high-grade PCa was reported on repeat bx for risk score.	

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