Supplemental online content for:
Evaluation of New Tests and Interventions for Prostate Cancer Management: A Systematic Review

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J Natl Compr Canc Netw 2018;16(11):1340–1351

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### eTable 1. Summary of Interventions

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<th>Intervention/Manufacturer</th>
<th>Type of Intervention/Markers Measured</th>
<th>About the Intervention</th>
<th>Indication</th>
<th>Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHI/Beckman Coulter, Inc.</td>
<td>Blood-based immunoassay PSA, fPSA, p2PSA PHI score = p2PSA/fPSA ×3pPSA</td>
<td>PHI score is a continuous measure Patients are categorized as low (0–20.9), moderate (21.0–39.9), or high risk (&gt;40) Risk of cancer detection at biopsy estimated to be 8.7% for low-risk, 20.6% for moderate-risk, and 43.8% for high-risk</td>
<td>Used if PSA level 2–10 ng/mL (4–10 ng/mL FDA) + negative DRE results + age ≥50 y (FDA-approved for this indication)</td>
<td>1, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Used after negative biopsy and when there is continuous suspicion of PCa</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not in patients receiving 5α-reductase inhibitors</td>
<td></td>
</tr>
<tr>
<td>4Kscore test© ORKO Health, Inc.</td>
<td>Blood-based immunoassay 4 kallikrein markers: tPSA, PSA, intact PSA, hK2</td>
<td>4Kscore &gt;7.5% → predicted probabilities of 2.5%, 5.6%, 9.9%, and 16.4% of distant metastasis in 5, 10, 15, and 20 y, respectively 4Kscore ≤7.5% → predicted probabilities of 0%, 0.2%, 1%, and 1.8% of distant metastasis in 5, 10, 15, and 20 y, respectively Provides probability of finding high-grade PCa (GS ≥7) on biopsy</td>
<td>Men with an abnormal PSA level or DRE results, or clinical suspicion</td>
<td>1, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients with a prior negative biopsy and want a repeat biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not in patients who received 5α-reductase inhibitors in past 6 months</td>
<td></td>
</tr>
<tr>
<td>Prostarix©/Metabolon, Inc.</td>
<td>Urine-based 4 metabolites: sarcosine, alanine, glycin, glutamate</td>
<td>Prostarix PLUS risk score: Prostarix results × PSA level + TRUS-determined prostate volume Score (1–100): predicted likelihood of 5-y recurrence</td>
<td>Men with an abnormal PSA levels or DRE results, or clinical suspicion</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No validation studies</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Imaging of lesions</td>
<td>Determines which lesions to biopsy, rebiopsy, and treat Identifies men with insignificant disease who are ideal for AS Early detection of PCa Among patients diagnosed with PCa, determines which require treatment, which should receive adjuvant treatment, and treatment dose (PCA staging) Improves accuracy of biopsies</td>
<td>Men with no previous biopsy, with previous biopsy with negative results, after positive biopsy results</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>OncotypeDX© Genomic Health, Inc.</td>
<td>Tissue-based genomic test 17 genes (12 cancer-related + 5 reference genes)</td>
<td>Genomic Prostate Score (0–100) provides likelihood of favorable pathology Can be used on lesions as small as 1 mm</td>
<td>Very low-, low-, and intermediate-risk patients</td>
<td>2</td>
</tr>
<tr>
<td>ProLaris© Myriad Genetic Laboratories, Inc.</td>
<td>Tissue-based genomic test 46 genes (31 CCP + 15 housekeeping genes)</td>
<td>Estimates 10-y PCa-specific mortality risk and BCR Stratifies patients according to tumor aggressiveness</td>
<td>After biopsy: low/very low-risk patients → candidates for AS Post-RP: patients who may benefit from aggressive intervention at high risk of recurrence FDA-approved</td>
<td>2, 4</td>
</tr>
<tr>
<td>ProMark©/Metamark Genetics, Inc.</td>
<td>Tissue-based proteomic test 8 proteins</td>
<td>Predicts probability of adverse pathology at RP based on biopsy High score independently predicts unfavorable pathology at RP Predicts BCR in patients after RP Score between 0 and 1</td>
<td>Biopsy tissue–based prognostic assay for patients with biopsy GS 3 + 3 and 3+4 Low- and low-to-intermediate-risk patients</td>
<td>2, 4</td>
</tr>
<tr>
<td>Mi-Prostate Score (MIPS)© MLabs</td>
<td>Urine-based biomarker First urine catch post-DRE PSA level and PCA3 and TMPRSS2:ERG mRNAs</td>
<td>Low, intermediate, and high scores assigned according to levels of TMPRSS2:ERG and PCA3 in urine → frequency of PCa diagnosed in each of the groups, respectively: 21%, 43%, and 69% Probability of cancer based on biopsy</td>
<td>High specificity for detecting high-grade PCa (GS &gt;6) in low-risk patients</td>
<td>2</td>
</tr>
<tr>
<td>ProstaVysion®/Bostwick Laboratories</td>
<td>Tissue-based genomic test ERG fusion/translocation and loss of PTEN tumor suppressor gene</td>
<td>Predicts PCA-related death in low-risk patients/ future metastasis after RP PTEN loss linked with higher risk of BCR ERG associated with more aggressive phenotype</td>
<td>No validation studies</td>
<td>2</td>
</tr>
<tr>
<td>ConfirmMDx© MDx Health</td>
<td>Biopsy tissue-based genomic test Monitors the methylation states of APC, GSTP1, and RASSF1</td>
<td>Negative result: avoid repeat biopsy and monitor with routine screening Positive result: suspicious areas marked as positive providing repeat biopsy guidance on prostate map</td>
<td>Prior negative or HGPIN biopsy result (12-core biopsy within 24 months)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: AS, active surveillance; ASAP, atypical small acinar proliferation; BCR, biochemical recurrence; CCP, cell cycle progression; DRE, digital rectal examination; fPSA, free PSA; GS, Gleason score; hK2, human kallikrein 2; HGPIN, high-grade prostatic intraepithelial neoplasia; mtDNA, mitochondrial DNA; p2PSA, serum prostate-specific antigen isoform [–2]isoform proPSA; PCa, prostate cancer; PHI, Prostate Health Index; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; RP, radical prostatectomy; tPSA, total PSA; TRUS, transrectal ultrasound.

*Group 1: used for screening (before initial biopsy) to determine whether biopsy is necessary; Group 2: used after positive biopsy results to distinguish indolent vs aggressive disease and to determine which patients to treat; Group 3: used after negative (or indeterminate) biopsy results to determine when to rebiopsy; Group 4: used after an intervention to determine which patients require additional treatment.

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</table>
| **Progensa PCA3**<sup>a</sup> Gene-Probe Incorporated | Urine-based biomarker assay; first urine catch post-DRE; PSA + PCA3 mRNAs | Ratio of PCA3 mRNA copies/mL to PSA mRNA copies/mL, multiplied by 1,000
Predicts likelihood of positive biopsy result
Recommended threshold score: 25
Values ≥25 suggest cancer | Patients aged ≥50 y with negative diagnosis of PCa on biopsy analysis (≥1 previous biopsies) and elevated serum PSA level in whom a repeat biopsy is recommended (FDA-approved)
Not for patients on medications known to affect serum PSA levels | 3 |
| **Prostate Core Mitomic Test (PCMT)**<sup>a</sup> Mitomics | Tissue-based genomic test
mtDNA deletions | Negative result: patient at low risk of undiagnosed PCa
Positive result: patient at high risk of undiagnosed PCa | Patients with a prior negative biopsy and a PSA level >4.0 ng/mL, PSADT <3 mo, PSAV >0.4 ng/mL/y, or irregular DRE results, family history of PCa, African American race, or life expectancy >10 y<sup>a</sup>
Patients with a prior indeterminate biopsy (ASAP, HGPIN, atypia) | 3 |
| **NADiA ProsVue**<sup>a</sup> IRIS International, Inc. | Blood-based
Calculate PSA slope | PSA level ≤2 pg/mL/mo → reduced risk of clinical recurrence within 8 years post-RP | Useful for intermediate-risk patients who are candidates for adjuvant radiotherapy post-RP | 4 |
| **Decipher**<sup>a</sup> Genomedx Biosciences Inc. | Tissue-based genomic test
22 coding and noncoding RNAs | Reports probability of metastasis at 5 y after surgery and 3 y after PSA recurrence
High risk (>0.6): patients may benefit from adjuvant radiation
Low risk (<0.45): patients can be safely observed with PSA monitoring | Patients with adverse pathology postsurgery: pT3 or positive surgical margin or increasing PSA level
Candidates for radiation | 2, 4 |

Abbreviations: AS, active surveillance; ASAP, atypical small acinar proliferation; BCR, biochemical recurrence; CCP, cell cycle progression; DRE, digital rectal examination; fPSA, free PSA; GS, Gleason score; h2K, human kallikrein 2; HGPIN, high-grade prostatic intraepithelial neoplasia; mtDNA, mitochondrial DNA; p2PSA, serum prostate-specific antigen isoform [-2]proPSA; PCa, prostate cancer; PHI, Prostate Health Index; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; RP, radical prostatectomy; tPSA, total PSA; TRUS, transrectal ultrasound.

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### eTable 2. Study Characteristics

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<tr>
<th>Study</th>
<th>Type of Study</th>
<th>N</th>
<th>Outcomes</th>
<th>Results</th>
<th>Grade</th>
<th>Score* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Kscore</td>
<td>Benckx et al., 2010</td>
<td>269</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 492 biopsies avoided (49.2%) per 1,000 men with elevated PSA level using threshold of ≥20% Missed: 61 advised against biopsy (most low risk: 163; high risk: 12)</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Carlsson et al., 2013</td>
<td>392</td>
<td>Avoided overtreatment</td>
<td>Over-treatment avoided in 110 for every 1,000 men, but treatment delayed for 26 patients with aggressive disease using threshold of ≥30%</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Vickers et al., 2012</td>
<td>2,914</td>
<td>Decrease in unnecessary biopsy</td>
<td>Reduction in biopsy: 513 per 1,000 men using threshold of ≥20% Missed: 12 of 100 high-grade cancers</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Vickers et al., 2010</td>
<td>740</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 443/740 (60%) using threshold of ≥20% Missed: 31/152 low-grade cancers and 3/40 high-grade cancers</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Vickers et al., 2010</td>
<td>1,241</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 41% (of 1,000 patients) using threshold of ≥20% Missed: 60 of 259 cancers</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Braun et al., 2016</td>
<td>749</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 25% avoided Delayed treatment: 13 high-grade cancers Threshold: ≥8% risk for cancer</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Vickers et al., 2010</td>
<td>1,501</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 363/7,000 (36%) Missed: 47 (of which 4 were high-grade cancers)</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Lin et al., 2017</td>
<td>718</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 252 biopsies avoided (25.2%) per 1,000 men with elevated PSA levels using threshold of ≥20% Missed: 19 men were advised against necessary biopsy (high-grade cancers)</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Kone et al., 2015</td>
<td>611</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 64% reduction The higher the score, the greater the likelihood of performing a biopsy (P=0.001)</td>
<td>1, 3</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Gupta et al., 2010</td>
<td>925</td>
<td>Decrease in unnecessary biopsy</td>
<td>Reduction in biopsy: 817 biopsies avoided (82%) per 1,000 men using threshold of ≥20% Treatment reduction: 135 surgeries (14%) per 1,000 men Missed: 67 cancers</td>
<td>3</td>
<td>78.5</td>
</tr>
<tr>
<td>PHI</td>
<td>Filella et al., 2014</td>
<td>354</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 19% using cutoff of 31.94 Missed: 17 of 175 cancers (5 GS ≥7)</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Lazzeri et al., 2013</td>
<td>158</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 16.5% using cutoff of 25.5 Missed: 6/71 cancers would have been missed; 4 with GS 6 (3+3) and 2 with GS 7 (3+4)</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Ng et al., 2014</td>
<td>230</td>
<td>Decrease in unnecessary biopsy</td>
<td>Reduction in biopsy: 104/209 (45.2%) using cutoff of 27.6 Missed: 9.5%</td>
<td>1</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Lazzeri et al., 2013</td>
<td>646</td>
<td>Reduction in biopsy number</td>
<td>Reduction in biopsy: 15.5% of biopsies avoided using cutoff of 27.6; 52% avoided and 37.1% missed with cutoff of 41.5 Missed: 9.8%</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Foley et al., 2016</td>
<td>250</td>
<td>Stratification</td>
<td>PHI model showed best correlation between predicted probabilities and actual outcome (scatter plot)</td>
<td>1, 3</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Gnanapragasam et al., 2016</td>
<td>279</td>
<td>Decrease in repeat biopsy</td>
<td>PHI not useful in determining whether mpMRI will be positive 94 negative MRI results that included 21 GS ≥7 if PHI performed after mpMRI, only 1 of 21 were missed</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Hirama et al., 2014</td>
<td>67</td>
<td>Likelihood of reclassification</td>
<td>PHI significantly higher in the reclassification group among patients undergoing AS (P=0.010)</td>
<td>3</td>
<td>59</td>
</tr>
</tbody>
</table>

Abbreviations: AS, active surveillance; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-S, CAPRA Postoperative; CCP, cell cycle progression; CSM, cancer-specific mortality; EAU, European Association of Urology; GC, genomic classifier; GS, Gleason score; mpMRI, multiparametric MRI; NRI, net reclassification improvement; PHI, Prostate Health Index; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; RP, radical prostatectomy.

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*bScoring: >75%, excellent quality; 50%–75%, good quality; <50%, poor quality.

*cStudy performed to assess utility of 4Kscore after prostate cancer diagnosis, but this is not yet approved for clinical use.

(continued on next page)
Reduction in biopsy: 51.1% if restricting MR-guided biopsy to PI-RADS 4/5
Missed: 15 patients with intermediate-high-risk cancer on biopsy

Reduction in biopsy: 63%
Missed: 30% (7/23)

70% decrease in biopsy indication when using MRI before repeat biopsy
After comparing with repeat biopsy, 22% of those with PI-RADS 3, 75% with PI-RADS 4, and 100% with PI-RADS 5 had significant cancer

Reclassification: 47% of cases eligible for AS were reclassified to significant disease
MRI: understaged 4 vs 12 men (when matched with pathologic findings) (diagnosed + on AS)

Recall: AS, active surveillance; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-S, CAPRA Postsurgical; CCP, cell cycle progression; CSM, cancer-specific mortality; EAU, European Association of Urology; GC, genomic classifier; GS, Gleason score; mpMRI, multiparametric MRI; NRI, net reclassification improvement; PHI, Prostate Health Index; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; RP, radical prostatectomy.

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</tr>
</thead>
<tbody>
<tr>
<td>ProMark</td>
<td>Assay development and validation study</td>
<td>381 &amp; 256</td>
<td>Outcome of interest: reclassification measured as NRI</td>
<td>NRI: 0.34 for NCCN risk classification (P&lt;.00001; 95% CI, 0.20–0.48) and 0.24 for D’Amico risk classification (P&lt;.0001; 95% CI, 0.12–0.35)</td>
<td>2</td>
<td>80.76</td>
</tr>
<tr>
<td>OncotypeDX</td>
<td>Prospective clinical utility study</td>
<td>180</td>
<td>Change in management patterns + costs</td>
<td>Interventional treatment: 21% reduction in low-and very low-risk patients; Radiation and RP: decreased by 14% and 10%, respectively; Reclassification: 4.3% of very low-risk and 35.7% of low-risk patients reclassified as intermediate risk</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>Dall’Era</td>
<td>Retrospective chart review</td>
<td>211</td>
<td>Change in treatment recommendations</td>
<td>Interventional treatment: 24% reduction to AS</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Badani et al</td>
<td>Prospective study</td>
<td>24</td>
<td>Change in adjuvant and salvage treatment recommendations</td>
<td>Change in treatment: 43% of adjuvant, 53% of salvage; Interventional treatment: 27% (adjuvant) and 16% (salvage) reduction; 37% (adjuvant) and 61% (salvage) intensification</td>
<td>4</td>
<td>61</td>
</tr>
<tr>
<td>Badani et al</td>
<td>Multicenter prospective, decision-impact study</td>
<td>122</td>
<td>Change in adjuvant treatment recommendations</td>
<td>Reclassification: 51% of patients reclassified as low risk; Change in treatment: 31%; Interventional treatment: 40% reduction to observation, 20% increase</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>Michalopoulos et al</td>
<td>Prospective study</td>
<td>146</td>
<td>Change in clinical treatment decision post-RP; Effect on physicians' uncertainty</td>
<td>Reclassification: 60% of high-risk patients reclassified as low-risk; Change in treatment: 30.8%; Interventional treatment: 42.5% reduction to observation, 17.6% increase</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>Multicenter, prospective study</td>
<td>11</td>
<td>Change in adjuvant treatment recommendation</td>
<td>Change in treatment: 35% and 45% of treatment changed by radiation oncologists and urologists, respectively; High GC risk: urologists and oncologists recommended adjuvant treatment 91% or 89% of the time, respectively, vs 62% and 79% for those same cases before GC results</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>Cooperberg et al</td>
<td>Retrospective cohort</td>
<td>185</td>
<td>Reclassification</td>
<td>Reclassification: In 82 patients stratified to high risk based on CAPRA-S score ≥6, GC scores were likewise high risk for 33, among whom 17 had CSM events; GC reclassified the remaining 49 men as low to intermediate risk, among whom 3 CSM events were observed</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Den et al</td>
<td>Prospective observational study</td>
<td>2,342</td>
<td>Reclassification</td>
<td>Reclassification: 52%, 76%, and 40% of patients in CAPRA-S low-, intermediate-, and high-risk groups were reclassified, respectively</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>Ross et al</td>
<td>Retrospective case-cohort</td>
<td>260</td>
<td>Reclassification</td>
<td>Reclassification: 71%, 52%, and 19% of patients in CAPRA-S low-, intermediate-, and high-risk groups were reclassified, respectively</td>
<td>4</td>
<td>76.6</td>
</tr>
<tr>
<td>NADIA ProsVue</td>
<td>Prospective multicenter clinical trial</td>
<td>225</td>
<td>Reduction in interventional treatment</td>
<td>Interventional treatment: 63.4% reduction in secondary treatment recommendations (adjuvant radiation + androgen deprivation therapy)</td>
<td>4</td>
<td>70.5</td>
</tr>
</tbody>
</table>

Abbreviations: AS, active surveillance; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-S, CAPRA Postsurgical; CCP, cell cycle progression; CSM, cancer-specific mortality; EAU, European Association of Urology; GC, genomic classifier; GS, Gleason score; mpMRI, multiparametric MRI; NRI, net reclassification improvement; PHI, Prostate Health Index; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; RP, radical prostatectomy.

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eAppendix 1. Search Strategies

**Medline Search Strategy**

1. exp Prostatic neoplasms/
2. prostat*.hw. and exp Neoplasms/
3. (prostat* adj5 (adenoma* or adenocarcin* or mass or masses or cyst* or cancer* or tumor* or neo?plas* or carcinom* or oncolog* or sarcom*)).tw,kf.
4. 1 or 2 or 3
5. Animals/ not (Animals/ and Humans/)
6. 4 not 5
7. (PHI or prostat* health index*).tw,kf.
8. 6 and 7
9. (4Ksco* or 4K scor* or ("4" or four) adj3 (kallikrein* or Kallikurein*)).tw,kf.
10. 6 and 9
11. (Bostwick* or ProstaV*s* or Prosta V*s*).tw,kf.
12. ERG.tw,kf. and PTEN.tw,kf,hw.
13. 11 or 12
14. 6 and 13
15. Prostarix*.tw,kf.
16. (sarcosin* and alanin* and glycinc* and glutamat*).tw,kf,hw.
17. 15 or 16
18. 6 and 17
19. prolar*s*.tw,kf. or ((ccp or cycle cell proliferat*) adj3 (test* or score* or assay*)).tw,kf,hw.
20. 6 and 19
21. (oncotyp* or (onco adj2 typ*)).tw,kf.
22. 6 and 21
23. (metamar* or meta-mar* or promar* or pro-mar*).tw,kf.
24. 6 and 23
26. ((PCA3 or PCA 3 or gene 3) adj5 (test* or score* or assay*)).tw,kf.
27. 25 or 26
28. 6 and 27
29. (PCMT or mitom*).tw,kf.
30. 6 and 29

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eAppendix 1. Search Strategies (cont.)

31. (Confirm MDx* or ConfirmMDx*).tw,kf.
32. 6 and 31
33. [(genomedx or deciphertest* or deciphertm or decipherdx or deciphergc or decipher*) and (tm or test* or score* or gc or rna or biomark* or bio-mark* or genom* or assay* or dx)].tw,kf.
34. 6 and 33
35. (ProsV* or prostat* specific antigen slope*).tw,kf.
36. 6 and 35
37. (Mi-Prostat* or MiPS or (mi adj5 score*)].tw,kf.
38. 6 and 37
39. exp Magnetic Resonance Imaging/
40. (mri or (magnetic* adj3 resonanc*)).tw,kf.
41. 39 or 40
42. 6 and 41
43. exp Mass Screening/
44. (screen or screening).tw,kf.
45. 43 or 44
46. 42 and 45

Cochrane Search Strategy

1. (prostat* near/5 (adenoma* or adenocarcin* or mass or masses or cyst* or cancer* or tumo?r* or neo:plas* or carcinom* or onco-log* or sarcom*)):ti,ab,kw
2. (PHI or prostat* health index*):ti,ab,kw
3. 1 and 2
4. (4Kscor* or 4K scor* or (“4” or four) near/3 (kallikrein* or Kallikurein*))):ti,ab,kw
5. 1 and 4
6. (Bostwick* or ProstaV?s* or Prosta V?is*):ti,ab,kw
7. (ERG and PTEN):ti,ab,kw
8. 6 or 7
9. 1 and 8
10. Prostarix*:ti,ab,kw
11. (sarcosin* and alanin* and glycin* and glutamat*):ti,ab,kw
12. 1 and 11
13. prolar?s*:ti,ab,kw or ((ccp or cycle cell proliferat*) near/3 (test* or score* or assay*)):ti,ab,kw

(continued on next page)
eAppendix 1. Search Strategies (cont.)

14. 1 and 13
15. (oncotyp* or (onco near/2 typ*)):ti,ab,kw
16. 1 and 15
17. (metamar* or meta-mar* or promar* or pro-mar*):ti,ab,kw
18. 1 and 17
19. Progensa*:ti,ab,kw
20. ((PCA3 or PCA 3 or gene 3) near/5 (test* or score* or assay*)):ti,ab,kw
21. 19 or 20
22. 1 and 21
23. (PCMT or mitom*):ti,ab,kw
24. 1 and 23
25. (Confirm MDx* or ConfirmMDx*):ti,ab,kw
26. 1 and 25
27. ((genomedx or deciphertest* or deciphertm or decipherdx or deciphergc or decipher*) and (tm or test* or score* or gc or rna or biomark* or bio-mark* or genom* or assay* or dx)):ti,ab,kw
28. 1 and 27
29. (ProsV* or prostat* specific antigen slope*):ti,ab,kw
30. 1 and 29
31. (Mi-Prostat* or MiPS or (mi near/5 score*)):ti,ab,kw
32. 1 and 31
33. (mri or (magnetic* adj3 resonanc*)):ti,ab,kw
34. (screen or screening):ti,ab,kw
35. 1 and 33 and 34

Embase Search Strategy

1. exp prostate tumor/
2. prostat*.hw. and exp neoplasm/
3. (prostat* adj5 (adenoma* or adenocarcin* or mass or masses or cyst* or cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*)):tw,kw.
4. 1 or 2 or 3
5. (exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not human/

(continued on next page)
eAppendix 1. Search Strategies (cont.)

6. 4 not 5

7. (PHI or prostat* health index*).tw,kw.

8. 6 and 7

9. (4Kscor* or 4K scor* or ("4" or four) adj3 (kallikrein* or Kallikurein*))).tw,kw.

10. 6 and 9

11. (Bostwick* or ProstaV*s* or Proста V*s*).tw,kw.

12. ERG.tw,kw. and PTEN.tw,kw,hw.

13. 11 or 12

14. 6 and 13

15. Prostarix*.tw,kw.

16. (sarcosin* and alanin* and glycín* and glutamat*).tw,kw,hw.

17. 15 or 16

18. 6 and 17

19. prolar*s*.tw,kw. or ((ccp or cycle cell proliferat*) adj3 (test* or score* or assay*)).tw,kw,hw.

20. 6 and 19

21. (oncotyp* or (onco adj2 typ*)).tw,kw.

22. 6 and 21

23. (metamar* or meta-mar* or promar* or pro-mar*).tw,kw.

24. 6 and 23


26. ((PCA3 or PCA 3 or gene 3) adj5 (test* or score* or assay*)).tw,kw.

27. 25 or 26

28. 6 and 27

29. (PCMT or mitom*).tw,kw.

30. 6 and 29

31. (Confirm MDx* or ConfirmMDx*).tw,kw.

32. 6 and 31

33. ((genomedx or deciphertest* or deciphertm or decipherdx or deciphergc or decipher*) and (tm or test* or score* or gc or rna or biomark* or bio-mark* or genom* or assay* or dx)).tw,kw.

(continued on next page)
eAppendix 1. Search Strategies (cont.)

34. 6 and 33
35. (ProsV* or prostat* specific antigen slope*).tw,kw.
36. 6 and 35
37. (Mi-Prostat* or MiPS or (mi adj5 score*)).tw,kw.
38. 6 and 37
39. nuclear magnetic resonance imaging/
40. (mri or (magnetic* adj3 resonanc*)).tw,kw.
41. 39 or 40
42. 6 and 41
43. screening test/
44. (screen or screening).tw,kw.
45. 43 or 44
46. 42 and 45

Web of Science Search Strategy

41. 39 AND 40 AND 1
40. TS=(screen or screening)
39. TS=(mri or (magnetic* NEAR/3 resonanc*))
38. 37 AND 1
37. TS=(Mi-Prostat* or MiPS or (mi NEAR/5 score*))
36. 35 AND 1
35. TS=(ProsV* or prostat* specific antigen slope*)
34. 33 AND 1
33. TS=((genomedx or deciphertest* or deciphertm or decipherdx or deciphergc or decipher*) and (tm or test* or score* or gc or rna or biomark* or bio-mark* or genom* or assay* or dx))
32. 31 AND 1
31. TS=(Confirm MDx* or ConfirmMDx*)
30. 29 AND 1
29. TS=(PCMT or mitom*)

(continued on next page)
eAppendix 1. Search Strategies (cont.)

28. 27 AND 1
27. 26 OR 25 OR 24 OR 23
26. TS=((gene 3) NEAR/5 (test* or score* or assay*))
25. TS=((PCA 3) NEAR/5 (test* or score* or assay*))
24. TS=((PCA3) NEAR/5 (test* or score* or assay*))
23. TS=Progensa*
22. 21 AND 1
21. TS= (metamar* or meta-mar* or promar* or pro-mar*)
20. 19 AND 1
19. TS= (oncotyp* or (onco NEAR/2 typ*))
18. 17 AND 1
17. 16 OR 15 OR 14
16. TS=((“cycle cell proliferat*”) NEAR/3 (test* or score* or assay*))
15. TS=((ccp) NEAR/3 (test* or score* or assay*))
14. TS=prolar?s*
13. 12 AND 1
12. 11 OR 10
11. TS= (sarcosin* and alanin* and glycin* and glutamat*)
10. TS=Prostarix*
9. 8 AND 1
8. 7 OR 6
7. TS=(ERG and PTEN)
6. TS=(Bostwick* or ProstaVys* or Prosta Vys* or ProstaVis* or ProstaVis*)
5. 4 AND 1
4. TS= (4Kscore* or 4K scor* or (“4” or four) NEAR/3 (kallikrein* or Kallikurein*))
3. 1 AND 2
2. TS=(PHI or “prostat* health index*”)
1. TS=(prostat* NEAR/5 (adenoma* or adenocarcin* or mass or masses or cyst* or cancer* or tumo*r* or neo?plas* or carcinom* or oncolog* or sarcom*))
eAppendix 2. Data Extraction Sheet

Name of reviewer:
Date:
Study ID (first author, year):
Notes:

| Article title: | 
| Type of study: |
| 1. Randomized controlled clinical trial/survey/observational...? |
| 2. Was the study designed to evaluate the clinical utility of a new prognostic test, or was it a secondary analysis of data collected for other purposes? |
| 3. Funding source: |
| 4. To what phase does the study belong? Phase 1, screening; phase 2, after positive biopsy; phase 3, after negative biopsy; phase 4, add treatment |
| 5. What was the testing scenario? (Is there in the study a comparison between cases and controls? Did the 2 groups have similar characteristics?) |

| Study population |
| 6. Country and year where the study was conducted: |
| 7. Number of subjects enrolled: |
| 8. Number of subjects completed the study: |
| 9. Duration of study: |
| 10. Characteristics of subjects: |
| 11. Inclusion/exclusion criteria: |
| 12. Were the patients selected by the physician or randomly assigned? |
| 13. Did the sample represent patients that would be tested in clinical practice? |
| 14. Is there a concern for selection bias (systematic differences between baseline characteristics of the groups that are compared), explain: |

(continued on next page)
eAppendix 2. Data Extraction Sheet (cont.)

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. What is the used intervention?</td>
</tr>
<tr>
<td>16. Were investigators/physicians blinded to the test results?</td>
</tr>
<tr>
<td>(i.e., when they gave their first recommendation, they didn’t know about test results)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. What are the outcomes studied?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. How were the outcomes assessed?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
</table>
## eAppendix 3. Quality Appraisal Tool

Name of reviewer:  
Date:  
Study ID (first author, year):  
Notes:

Scoring procedure: 0 if “not clear” or “not a relevant item” or “not good quality,” 1 for “good quality,” 2 for “excellent quality”

<table>
<thead>
<tr>
<th>Article title</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of study</strong></td>
<td></td>
</tr>
<tr>
<td>1. Was the study designed to evaluate the clinical utility of the new prognostic test or was it a secondary analysis of data collected for other purposes?</td>
<td></td>
</tr>
<tr>
<td>2. Were there conflicts of interest? (0 if there is a conflict/2 if no conflict)</td>
<td></td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td></td>
</tr>
<tr>
<td>3. Was the clinical population clearly described including inclusion and exclusion criteria and subject participation?</td>
<td></td>
</tr>
<tr>
<td>4. How were the patients assigned to the chosen intervention? Were they selected by the physician or randomly assigned?</td>
<td></td>
</tr>
<tr>
<td>5. Is there a concern for selection bias (systematic differences between baseline characteristics of the groups that were compared)?</td>
<td></td>
</tr>
<tr>
<td>6. Did the sample represent patients that would be tested in clinical practice?</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
</tr>
<tr>
<td>7. Were the prognostic tests clearly described and conducted using a standardized, reliable, and valid method?</td>
<td></td>
</tr>
<tr>
<td>8. Was the test used and interpreted the same way by all sites/studies including any indeterminate test results? (ie, did they do and interpret as standards/manufacturer says)</td>
<td></td>
</tr>
<tr>
<td>9. Were the investigators blinded to the test results?</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>10. Was the outcome being predicted clearly defined?</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
**eAppendix 3. Quality Appraisal Tool (cont.)**

<table>
<thead>
<tr>
<th>Outcome assessment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Was the outcome being predicted ascertained using a standardized, reliable, and valid method? (eg, if there is a change in treatment, did a third party assess the change?)</td>
<td></td>
</tr>
<tr>
<td>12. Did participants in the sample group have a common starting point for follow-up with respect to the outcome of interest, including any treatments that could affect the outcome being predicted? (ie, Did the patients receive any treatment? Intervention that could affect the results/outcomes [eg, digital rectal examination timing, 5-α-reductase inhibitors]? Were all the patients from the same phase or were the patients who had the test from low-risk group and those who didn’t from high-risk group, which could lead to overestimation because high-risk groups are less likely to change treatment?)</td>
<td></td>
</tr>
<tr>
<td>13. Is there a concern for performance bias? (Systematic differences between groups in the care that is provided or in exposure to factors other than the interventions of interest?) Is there a concern for detection bias (systematic differences between groups in how outcomes are determined)?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14. How complete was the follow-up of subjects, and were losses to follow-up related to the test results or the outcome being predicted? Was the duration of follow-up adequate? (If no follow-up in a study in which there was no need for follow-up, then the answer is 0/not applicable)</td>
<td></td>
</tr>
<tr>
<td>15. Is there a concern for attrition bias (systematic differences between groups in withdrawals from a study; eg, data not available or exclusions)?</td>
<td></td>
</tr>
<tr>
<td>16. Is there a concern for reporting bias (systematic differences between reported and unreported findings; eg, are both significant and nonsignificant differences reported?)</td>
<td></td>
</tr>
</tbody>
</table>