Chapter 3.2

NHMRC Evidence Statement Form for Clinical Question 8: If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?

### NICE question 8.1: In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy?


#### 1. Evidence base (number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)

**NICE review of studies of prognostic factors at initial negative biopsy that may predict prostate cancer at re-biopsy**

NICE reviewed 25 studies of age, 27 of PSA level, 18 of free-to-total PSA (ftPSA), nine of PSA density, ten of PSA velocity, 18 of DRE, 12 of prostatic intraepithelial neoplasia (PIN) or high grade prostatic intraepithelial neoplasia (HGPIN), six of atypical small acinar proliferation (ASAP), one of atypical glands suspicious for carcinoma (AGSC), 12 of biomarker PCA3, two of family history, and one of ethnicity assessed at initial biopsy as prognostic for prostate cancer at re-biopsy. All were either level II or level III prognostic or diagnostic accuracy studies. The NICE review rated one study as of moderate quality and the remainder as of low or very low quality; the main weaknesses being that the prognostic factor of interest influenced whether patient underwent repeat biopsy in many of the studies and that many of the models did not include important confounding factors such as age, free-to-total PSA, and prostate volume.

**Grade D**

Studies found on repeating NICE review search strategy and published after the cut-off date for the NICE review and before 1st March 2014

One additional level II and two level III prognostic or diagnostic accuracy studies were found (ElShafei et al 2013; Gittelman et al 2013; Stewart et al 2013). All were judged to be at high risk of bias in predicting prostate cancer at re-biopsy. The one study that assessed diagnostic accuracy (of one prognostic factor, gene methylation status; Stewart et al 2013) was judged to be at risk of bias in this assessment. The prognostic factors assessed by these three studies were: ElShafei et al (2013) – Age, PSA, ftPSA, PSAd, PIN, HGPIN, ASAP, family history, ethnicity; Gittleman et al (2013) – Age, family history, ethnicity; Stewart et al (2013) – Age, PSA, DRE, HGPIN, DNA methylation.

<table>
<thead>
<tr>
<th>Grade</th>
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<tr>
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Grade D

2. Consistency (if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)

Age

The NICE review found odds ratios (ORs) of 1.01-1.10 per year increase in age in 14 studies of the relationship of age (as a continuous variable) with prostate cancer at re-biopsy examined in multivariate models that adjusted for potential confounders such as different PSA measures, HGPIN, ASAP, DRE and prostate volume; three were statistically significant (p<0.05). This review found three additional studies that reported results from multivariate models, two with ORs of 1.01 per year of age as a continuous variable, p>0.05 in each case (Gittelman et al 2013 and Stewart et al 2013), and one with an OR of 1.47 (95%CI 1.10-1.97) for comparison of the 75th with 25th percentiles of age as a continuous variable (ElShafei et al 2013). There is consistent evidence of a weak positive association between age and detection of cancer at re-biopsy.

Grade B

Total PSA at first biopsy

The NICE review found ORs of 0.93-1.04 per ng/mL increase in PSA in 14 studies of the relationship of PSA as a continuous variable with prostate cancer at re-biopsy examined in multivariate models; three were statistically significant. Two studies reported multivariate adjusted results for PSA in categories; none were statistically significant. Sensitivity and specificity were not consistent for similar PSA levels between six studies and showed no clear trend with increasing cut-off level. One additional study reported a multivariate adjusted OR of 1.59 for a PSA of <10 relative to ≥10 ng/mL (p=0.18; Stewart et al 2013). A second additional study did not report multivariate adjusted results for PSA (ElShafei et al 2013). In summary there is moderately consistent evidence of a weak positive association between total PSA and detection of cancer at re-biopsy. Test performance characteristics were not consistent.

Grade C

Ratio of free PSA to total PSA (ftPSA) at first biopsy

The NICE review found odds ratios (ORs) of 0.87-1.40 per unit increase in ftPSA in 8 studies of the relationship of ftPSA as a continuous variable with prostate cancer at re-biopsy examined in multivariate models; four were statistically significant (3 for an inverse association and 1 for a direct association). Three studies reported multivariate adjusted ORs comparing categories of ftPSA; in each case the OR was <1 for the higher category relative to the lower category but none was statistically significant. Sensitivity and specificity were not consistent for similar ftPSA levels between five studies and showed no clear trend with increasing cut-off level. One additional study did not report multivariate adjusted results for ftPSA (ElShafei et al 2013). In summary there was inconsistent evidence of an inverse association of ftPSA with cancer at re-biopsy. Test performance characteristics were not consistent.
**Grade D**

**PSA density (PSAd) at first biopsy**
The NICE review found statistically significant results in 4 of 5 studies of the relationship of PSAd as a continuous or categorical variable with prostate cancer at re-biopsy examined in multivariate models. Where reported the ORs were 1.005 (95% CI 0.998-1.012) per unit of PSAd as a continuous variable and 2.3 (95% CI 1.4-4.0) and 2.34 (p=0.012) for a PSAd of >0.15 relative to less than this value. Test performance characteristics were reported for only one study (sensitivity 66%, specificity 60%). One additional study did not report multivariate adjusted results for PSAd (ElShafei et al 2013). In summary, there was moderately consistent evidence of a positive association of PSAd with cancer at re-biopsy in five studies.

**Grade C**

**PSA velocity (PSAv) at first biopsy**
The NICE review found statistically significant results in 3 of 5 studies of the relationship of PSAv as a continuous or categorical variable with prostate cancer at re-biopsy examined in multivariate models. Where reported the ORs were 1.34 (95% CI 1.03-1.74) and 1.58 (95% CI 1.06-2.35) per unit of PSAv as a continuous variable. Sensitivity and specificity showed no clear trend with increasing cut-off level and demonstrated low overall diagnostic accuracy in four studies. There were no additional studies of PSAv. In summary, there was moderately consistent evidence of a positive association of PSAv with cancer at re-biopsy in five studies. Test performance characteristics were not consistent.

**Grade C**

**DRE at first biopsy**
The NICE review found odds ratios (ORs) of 0.4-6.75 for abnormal relative to normal DRE in 13 studies of its relationship with prostate cancer at re-biopsy examined in multivariate models; five were statistically significant with ORs of 2.63-4.61 (reported for only three of the five studies). Eight studies reported low overall diagnostic accuracy; most reporting low sensitivity (0-55.9% with six <30%) but high specificity (56.3-95.9% with five >85%). One additional study found an OR of 1.36 (p=0.30) from a multivariate model (Stewart et al 2013). In summary there is inconsistent evidence of positive association between abnormal DRE and detection of cancer at re-biopsy. There was moderately consistent evidence of low sensitivity and high specificity.

**Grade C**

**High grade prostatic intraepithelial neoplasia (HGPIN) at first biopsy**
The NICE review found eight studies of HGPIN with multivariate models that reported ORs of 0.13 to 3.2 for prostate cancer at re-biopsy (there was, though, only one study with an OR <1); four were statistically significant. Five studies reported inconsistent test performance characteristics of the presence of HGPIN at initial biopsy. The NICE review also found two studies of PIN, which reported univariate results only; one reported a statistically significant association of PIN with prostate cancer at re-biopsy and the other did not. Two additional studies reported ORs of 1.87 (1.23-2.85) (ElShafei et al 2013) and 1.25 (p=0.5; Stewart et al 2013) for the association of HGPIN with prostate cancer at re-biopsy. There was moderately consistent evidence for the association of HGPIN with cancer at re-biopsy. Test performance was inconsistent.

Grade C

Atypical small acinar proliferation (ASAP)/atypical glands suspicious for carcinoma (AGSC) at first biopsy
The NICE review found five studies that examined the relationship between the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma and the risk of prostate cancer at re-biopsy in multivariate models. All reported statistically significant associations (p<0.05). One study that was reported twice (more participants in the second report) reported multivariate adjusted OR of 20.7 (95% CI 4.45-96.4; p<0.001) in the first report and 17.7 (p<0.001) in the second. The other four studies reported ORs ranging between 2.97 and 3.65. Two studies that assessed diagnostic accuracy for the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma at initial biopsy both reported low sensitivity but high specificity.

The updated review found one additional study that examined the relationship between the presence of atypical small acinar proliferation/atypical glands suspicious for carcinoma and the risk of prostate cancer at re-biopsy. It reported an OR of 1.92 (95% CI 1.07-3.46).

Grade A

PCA3 at first biopsy
The NICE review found three studies that reported multivariate adjusted associations of PCA3 with prostate cancer at re-biopsy; the association was statistically significant in each case. One study reported an OR of 1.02 (95%CI 1.00-1.03) per unit of PCA3 as a continuous variable; another, an OR of 3.01 (95%CI 1.74-5.23) for a PCA3 value of >30 relative to <30; and another, ORs of 9.44 (95%CI 5.15-17.31) and 9.29 (95%CI 5.11-16.89) respectively for PCA3 cut-offs at 39 and 50. Sensitivity and specificity were not consistent in a total of 12 studies in which it had been measured and showed no clear trend with increasing cut-off level; indicating low overall diagnostic accuracy. No additional studies addressed PCA3. There was consistent evidence in three studies for the association of PCA3 with prostate cancer at re-biopsy. Test performance was inconsistent.
DNA methylation in first biopsy

One additional study reported on the association with prostate cancer on re-biopsy of hypermethylation of three marker genes combined, *GSTP1, APC and RASSF1*, evaluated in tissue from the first biopsy (Stewart et al 2013). The OR for cancer on re-biopsy was 3.17, 95%CI 1.81-5.53, adjusted for age, PSA, DRE, and histopathology of first biopsy (benign, atypical cells, HGPIN). The sensitivity of the test was 68% and specificity 64%.

Family history of prostate cancer

Both of two studies included in the NICE review found family history to be a significant predictor of prostate cancer at re-biopsy in multivariate models (OR of 3.1, 95%CI 1.2-8.0, reported from one study). Two additional studies observed ORs of 1.33 (95%CI 0.81-2.18) (ElShafei et al 2013) and 0.92 (95%CI 0.50-1.72) (Gittelman et al 2013) in multivariate models. There was inconsistent evidence in four studies of an association of family history with prostate cancer on re-biopsy.

Ethnicity

The NICE review reported on one study, which found an OR of 0.8 (95%CI 0.4-1.6) for prostate cancer at re-biopsy in those of Caucasian ethnic origin relative to those of other ethnic origins in a multivariate model. Two additional studies observed ORs of 1.21 (95%CI 0.63-2.31) (ElShafei et al 2013) and 0.58 (95%CI 0.23-1.45) (Gittelman et al 2013) in US men of black ethnicity relative to non-black in multivariate models. There was consistent evidence in three studies of lack of association of ethnicity with prostate cancer on re-biopsy.

3. Clinical impact

See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Grade</th>
<th>ASAP</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>Very large</td>
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<td>B</td>
<td>Substantial</td>
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<td>C</td>
<td>Moderate</td>
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Grade C DRE, ASGC

Grade D Age, PSA, ftPSA, PSAd, PSAv, HGPIN, PCA3, DNA methylation, family history, ethnicity

4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report

The NICE review noted that there were six studies (16%) in which there were differences between the study populations and patients likely to be tested in practice. Two of the additional studies were done in US populations (both including African American men, 13.5% of population in ElShafei et al 2013 and 8.4% in Gittelman et al 2013), and the third was done in the UK and Belgium.

Grade B

5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)

Most of the prognostic factors studied are likely to be measured in Australian men having an initial prostate biopsy for suspected prostate cancer.

Grade B

Other factors (Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).

The NICE guideline development group (GDG) noted that it considered the outcome of diagnostic accuracy to be the most important as it would show which prognostic factors were significant predictors of cancer. The GDG also took specific account of the following limitations of the evidence when making its recommendations: the time between biopsies was unclear in many studies and sometimes more than 1 year; several studies excluded important potential confounding factors from their statistical models; the way tests were performed and the way results were interpreted was poorly reported; and the reference standard depended on the index test result for several studies.

EVIDENCE STATEMENT MATRIX

Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account.

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Evidence base</td>
<td>D</td>
<td>Level IV studies or Level II to Level III studies/SRs with a high risk of bias</td>
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</tbody>
</table>
| 2. Consistency | A-D | A – All studies consistent – ASAP  
B – Most studies consistent and inconsistency can be explained – age  
C – Some inconsistency, reflecting genuine uncertainty around question – total PSA, PSA density, PSA velocity, DRE, HGPIN, PCA3, ethnicity  
D – Evidence is inconsistent – ftPSA, family history  
NA – Not applicable (one study only) – AGSC, DNA methylation |
|----------------|-----|------------------------------------------------------------------|
| 3. Clinical impact | B-D | B – Substantial – ASAP  
C – Moderate – DRE, ASGC  
D – Slight/restricted – Age, PSA, ftPSA, PSAd, PSAv, HGPIN, PCA3, DNA methylation, family history, ethnicity |
| 4. Generalisability | B | Evidence directly generalisable to target population with some caveats |
| 5. Applicability | B | Evidence applicable to Australian healthcare context with few caveats |
**Evidence statement:**

**Age:** There is consistent evidence that each additional year of age at an initial negative biopsy predicts a 1-10% greater risk of prostate cancer at re-biopsy. **Ethnicity:** There is consistent evidence in three studies (two including African American men) that ethnicity at an initial negative biopsy is not associated with prostate cancer at re-biopsy. **Family history of prostate cancer:** There is inconsistent evidence in four studies that family history of prostate cancer at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, with high specificity but low sensitivity. **DRE:** There is moderately consistent evidence that an abnormal DRE at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, with high specificity but low sensitivity. **Total PSA:** There is little evidence that a higher total PSA at an initial negative prostate biopsy predicts a higher risk of prostate cancer at re-biopsy. **Ratio of free to total PSA:** There is inconsistent evidence that a higher f/t PSA% at an initial negative prostate biopsy predicts a lower risk of prostate cancer at re-biopsy. **PSA density:** A moderately consistent association of PSA density at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results. **PSA velocity:** A moderately consistent association of PSA velocity at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results. **Atypical small acinar proliferation:** There is consistent evidence that a finding of ASAP at an initial negative biopsy predicts with high specificity but low sensitivity a higher risk of prostate cancer at re-biopsy. **High-grade PIN:** There is moderately consistent evidence that high-grade PIN at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, but with low diagnostic accuracy. **PCA3:** The three studies that adjusted for potential confounding found significantly positive associations of PCA3 at an initial negative biopsy with prostate cancer at re-biopsy. However, the sensitivity and specificity PCA3 for prostate cancer at re-biopsy were not consistent in 12 studies in which they were measured and showed no clear trend with increasing cut-off level. **DNA methylation:** The only available study found that methylation of three marker genes in tissue from an initial negative biopsy was a moderately strong predictor of prostate cancer at re-biopsy.

The additional studies identified in the update review (those published after the NICE systematic review and before 1 March 2014) did not materially alter the evidence on which the recommendations in the NICE guideline were based. Therefore we have chosen to adapt the NICE 2014 recommendations with minimal changes. The NICE guideline recommended that clinicians should advise men whose initial biopsy is negative for prostate cancer that there is still a risk that prostate cancer is present, and that the risk is higher if any of the following conditions apply: the initial biopsy showed high-grade prostatic intraepithelial neoplasia, the initial biopsy showed atypical small acinar proliferation, or their digital rectal examination before the initial biopsy was abnormal.
### RECOMMENDATION

What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

<table>
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<th>GRADE OF RECOMMENDATION</th>
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Advise men whose initial biopsy is negative for prostate cancer that they should continue to be followed up.

Monitor more closely for those with abnormal findings on pre-biopsy digital rectal examination, and for those whose biopsy findings included either atypical small acinar proliferation or high-grade prostatic intra-epithelial neoplasia.

In addition to further PSA testing and digital rectal examination, consider prostate imaging with investigations that can help to localise the site of cancer within the prostate, and repeat biopsy using a targeted approach.

### CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

None.

### PRACTICE POINTS

Points of guidance used to support evidence-based recommendations, where the subject matter is outside of the scope of search strategy, and which were formulated based on expert opinion using a consensus process.

None.
Unresolved issues

**UNRESOLVED ISSUES**
If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.

The predictive value of histopathological features reported by the pathologist reviewing the initial biopsy.

Implementation of recommendation

**IMPLEMENTATION OF RECOMMENDATION**
Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Will this recommendation result in changes in usual care?</td>
<td>NO</td>
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<tr>
<td>Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant changes to usual care.</td>
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<tr>
<td>Are there any resource implications associated with implementing this recommendation?</td>
<td>NO</td>
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<tr>
<td>Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not have any important resource implications.</td>
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<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
<td>NO</td>
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<tr>
<td>Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant change the way care is organised.</td>
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<tr>
<td>Are the guideline development group aware of any barriers to the implementation of this recommendation?</td>
<td>NO</td>
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No barriers to the implementation of these recommendations are envisaged.
**NHMRC Evidence Statement Form for Clinical Question 8:** If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?

**NICE question 8.2:** In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?


1. **Evidence base** *(number of studies (quantity), level of evidence and risk of bias (quality) in the included studies – see body of evidence tables in report)*

**NICE review:** NICE systematically reviewed studies reporting the diagnostic yield of the following after a negative prostate biopsy: review of initial biopsy, repeat TRUS biopsy, multiparametric MRI-targeted biopsy, extended/saturation transrectal or transperineal biopsy, enhanced ultrasound targeted biopsy, and elastography targeted biopsy.

The NICE systematic review included case series (level IV evidence) as well as comparative studies. The primary comparison of different types of investigations, that being MRI targeted rebiopsy and saturation biopsies, was drawn from a meta-regression analysis of essentially case series (level IV evidence) data (Nelson et al 2013). Evidence on multiparametric MRI targeted biopsy in addition to standard biopsy came from a systematic review (Mowatt et al 2013) which included case series studies and four additional recent studies. These four recent studies, included three sequential sampling studies (Arsov et al 2012, Portalez et al 2012, Vourganti et al 2012) of level II evidence and one case series study of level IV evidence (Lee et al 2012). Evidence on extended/saturation biopsy came from 35 case series level IV studies and four cohort studies. NICE systematically reviewed 7 studies on repeat standard TRUS biopsy including data from control arms of cohort studies (level IV evidence) and five studies including 3 case series that reported on the use of contrast enhanced ultrasound. One study compared elastosonography rebiopsy and contrast enhanced ultrasound rebiopsy however no relevant data could be extracted. Another study compared the initial diagnosis (performed by consultant pathologists) with a reference standard diagnosis by consultant pathologists with a special interest in uropathology. NICE assessed the risk of bias using the QUADAS-2 checklist. Namely, risk of bias in patient selection (was the sample representative, was the selection

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criteria clearly described) and risk of bias in the index test (was the repeat biopsy protocol described in sufficient detail). Risk of bias was deemed as low in the majority of studies.

**Grade D**

**NICE review update:** The literature search was extended to include studies published up to 1st March 2014. The update review was restricted to studies that directly compared different post negative biopsy investigations, e.g. sequential sampling studies or randomised controlled trials (level II evidence). Eight additional level II evidence sequential sampling studies were found (Salomon et al 2014; Abd-Alazeez et al 2014; Costa et al 2013; Tang et al 2013; Sonn et al 2013; Pepe et al 2013; Cornelis et al 2013; Yerram et al 2012). One study examined the addition of real-time elastography targeted biopsies to TRUS biopsy (Salomon et al 2014), while the other studies examined the addition of multiparametric MRI (including 3T MRI) targeted prostate biopsy to random or systematic biopsy. For consistency, we extracted data from studies in the NICE systematic review, including three of the four level II mpMRI studies (Lee et al 2012; Portalez et al 2012; Vourganti et al 2012). All eight update studies were judged to be at moderate risk of bias using a modified QUADAS-2 quality appraisal tool.

**Grade C**

2. **Consistency** *(if only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)*

Based on the meta-regression by Nelson et al 2013, the NICE review reported an estimated prostate cancer detection of 37.6% using MRI targeted biopsy in addition to non-targeted biopsy, 36.8% detection rate using transperineal saturation biopsy and 30.0% detection rate using transrectal saturation biopsy.

**Multiparametric MRI targeted biopsy**

The NICE review reported that the Mowatt et al 2013 systematic review estimated 4-21% of cancers would be missed if only men with mpMRI lesion(s) were re-biopsied. The three additional studies included in the NICE review showed that the addition of mpMRI targeted biopsies to standard biopsies improved cancer detection rates by 14.3% to 42.6% points. Six of the seven more recent studies reported in the NICE update review, showed more modest improvements of 5.1% to 26.3% points. One of the most recent studies showed no improvement (Abd-Alazeez et al 2014). The variability in the magnitude of these improvements may be in part explained by the variation in the extent of the standard biopsy (6-32 biopsy cores), type of mpMRI and number of targeted cores, and also the study
 Grade B

**Extended/saturation biopsy**
NICE found that cancer detection rate appears to increase with the number of re-biopsy cores, although there is variability between studies in the reported rates. Their findings are based on the pooling of results from primarily case series studies; pooled cancer detection rates were approximately 20% for repeat TRUS biopsy (10-12 biopsy cores), 20% for TRUS extended biopsy (12-14 biopsy cores), 30% for TRUS saturation biopsy (median of 24 biopsy cores) and 40% for transperineal saturation biopsy (median of 29 biopsy cores). The pooled proportion of detected cancers considered clinically significant (according to the individual study definitions) was 27% for repeat TRUS 10-12 biopsy cores, 60% for TRUS extended biopsy, 57% for TRUS saturation biopsy, and 62% for transperineal saturation biopsy.

 Grade C

**Enhanced ultrasound targeted biopsy**
NICE reported a cancer detection rate of 30% (13/44) for Power Doppler enhanced ultrasound based on pooled data from two small studies (Remzi *et al* 2004, Morelli *et al* 2009) and a rate of 20.8% (117/562) for Colour Doppler enhanced ultrasound based on pooled data from two studies. Taverna *et al* 2011 compared Colour Doppler ultrasound with or without SonoVue against TRUS grey-scale 13-core systematic biopsy sampling, finding no differences in cancer detection rates between groups (29% verse 28% verse 31%).

 Grade C

**Elastography targeted biopsy**
NICE included one small study published as an abstract only which did not report any comparative information (Morelli *et al* 2009). One study identified in the NICE update reported an 8.2% point improvement (31.4% vs 39.2%) with the addition of elastography in a group of 449 patients (Salomon *et al* 2014).
**Review of initial biopsy**  
NICE reported that a study of 2516 non-screened men found that 1.2% of biopsies initially classified as benign were changed to cancer on review, 1.5% of biopsies with an initial HGPIN diagnosis were changed to cancer on review and for biopsies an initial diagnosis of suspicious for malignancy the figure was 4.9% (Oxley et al 2011). Of those biopsies which were initially positive, 0.4% were changed to benign and 0.1% to suspicious.

**Grade NA**

**3. Clinical impact**  
See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

<table>
<thead>
<tr>
<th>Multiparametric MRI targeted biopsy</th>
<th>A</th>
<th>Very large</th>
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<tbody>
<tr>
<td>Enhanced ultrasound targeted biopsy</td>
<td>B</td>
<td>Substantial</td>
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<tr>
<td>Saturation or extended biopsy</td>
<td>C</td>
<td>Moderate</td>
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<td>Slight/Restricted</td>
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**Grade B**

**Multiparametric MRI targeted biopsy**  
Adding mpMRI targeted biopsies to standard biopsies improved cancer detection rates by 0% to 5.1% points when compared with standard biopsies with >20 cores (Abd-Alazeez et al 2014; Pepe et al 2013) and by 6.4% to 14.3% using various different or unspecified types of mpMRI in 4 of 5 studies compared with 12 core biopsy (Sonn et al 2013; Cornelis et al 2013; Yerram et al 2012; Vourganti et al 2012) In the fifth study using a 12 core standard biopsy, the improvement was 42.6% using T2W + DWI mpMRI (Lee et al 2012).

**Grade D**

**Enhanced ultrasound targeted biopsy**  
NICE reported that the one study examining the effect of adding enhanced ultrasound (Colour Doppler) targeted biopsy to a TRUS grey-scale 13-core systematic biopsy, found a 2-3% point improvement (Taverna et al 2011).

**Grade D**

**Saturation or extended biopsy**  
Increasing the number of biopsy cores increased cancer detection rates. Transrectal 12-14 core biopsies had cancer detection rates of 15% to 25%, whereas transrectal saturation biopsies (median core number ~24) had cancer detection rates of 11%-45% and transperineal saturation biopsies (median core number ~28) reported cancer detection rates of 23%-72%.

The NICE review also pooled data for complications related to repeat saturation biopsy. The most common complication was haematuria, occurring in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of...
men undergoing transperineal biopsy. Rectal bleeding was a complication in 1.2% of men undergoing transrectal biopsy. Urinary retention was more common amongst men undergoing transperineal saturation biopsy (6.8%) whereas acute prostatitis was more common amongst men undergoing transrectal biopsy (3.9%).

**Grade C**

**Elastography targeted biopsy**
The addition of elastography targeted biopsies to a TRUS 10 core biopsy increased cancer detection rate by 8.2% points (Morelli et al 2009).

**Grade D**

**Review of initial biopsy**
Review of initial biopsy reclassified 1.2% of benign biopsies as cancerous and 0.4% of positive biopsies were reclassified to benign (Oxley et al 2011).

**Grade C**

<table>
<thead>
<tr>
<th>4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nearly one third of the included studies were from US/Canadian populations with, no more 25% of the included men African American. The remainder of the studies were predominantly from European countries, with only 4 studies from Asian countries.</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability relates directly to the availability of MRI facilities, expertise in interpretation of findings and the ability to pay for the investigations. At present, prostate MRI is not reimbursed by Medicare, although this may change. Detailed cost-benefit analyses are awaited to help guide endorsement.</td>
</tr>
<tr>
<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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</tbody>
</table>
**Other factors** *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)).*

Availability and affordability, especially for non-insured patients, may change in the future.

**EVIDENCE STATEMENT MATRIX**

*Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account.*

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence base</td>
<td>C, D</td>
<td>C – One or two Level III studies with low risk of bias or Level I or II studies with a moderate risk of bias – Update of the NICE review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D – Level IV studies or Level I to III studies/SRs with a high risk of bias – NICE review</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>B, C, NA</td>
<td>B – Most studies consistent and inconsistency can be explained – Multiparametric MRI targeted biopsy,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C – Some inconsistency, reflecting genuine uncertainty around question – Extended/saturation biopsy, Enhanced ultrasound biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA – Not applicable (one study only) – Elastography and review of initial biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C – Moderate – Extended/saturation biopsy, Review of initial biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D – Slight/Limited – Enhanced ultrasound targeted biopsy, Elastography targeted biopsy</td>
</tr>
<tr>
<td>4. Generalisability</td>
<td>C</td>
<td>Evidence not directly generalizable to the target population but could be sensibly applied</td>
</tr>
<tr>
<td>5. Applicability</td>
<td>B</td>
<td>Evidence applicable to Australian healthcare context with caveats</td>
</tr>
</tbody>
</table>
**Evidence statement:**

**Multiparametric MRI targeted biopsy**
Studies included in the NICE systematic review found that compared with 12 core biopsy protocols adding multiparametric MRI (T2W+ DWI +DCE) targeted biopsies improved cancer detection rates by 14.3 % points and adding T2W + DWI multiparametric MRI improved cancer detection rates by 42.6 percentage points.

For men with positive findings on multi parametric MRI, adding multiparametric MRI targeted biopsies to 12-core biopsies improved cancer detection rates by 6.4, 10.1, 14.3 and 45.2 percentage points.

A single study from the updated NICE systematic review showed that a repeat saturation biopsy on its own had a cancer detection rate of 35.9%. Adding 3–4 multiparametric MRI targeted biopsies increased the cancer detection rate by an additional 5.1 percentage points.

**Enhanced ultrasound targeted biopsy**
Studies included in the NICE systematic review found that adding enhanced ultrasound targeted biopsy to a TRUS grey-scale schematic biopsy resulted in cancer detection rates similar to those using the TRUS grey-scale schematic biopsy method alone.

**Saturation or extended biopsy**
Studies included in the NICE systematic review found that increasing the number of biopsy cores increased cancer detection rates. Transrectal 12-14 core biopsies had a cancer detection rate of 15-25%. Transrectal saturation biopsies had a cancer detection rate of 11-45%, and transperineal saturation biopsies had a cancer detection rate of 23-72%. The most common complication was haematuria reported in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of men undergoing transperineal biopsy.

**Elastography targeted biopsy**
Studies included in the NICE systematic review found no relevant evidence.
NICE update review found that the addition of elastography-targeted biopsies to a TRUS 10-core biopsy increased cancer detection rate by 8.2 percentage points.

**Review of initial biopsy**
A study included in the NICE systematic review found that review of initial biopsy reclassified 1.2% of benign biopsies as cancerous and 0.4% of positive biopsies to benign.
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound-guided biopsy to determine whether another biopsy is needed.

Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the following risk factors are present:
- atypical small acinar proliferation on initial biopsy
- abnormal digital rectal examination before the initial biopsy
- high-grade prostatic intra-epithelial neoplasia on initial biopsy

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation can be given.

None.

Multiparametric MRI should be used only in centres with experienced radiologists appropriately trained in the use of multiparametric MRI to aid urologists in the management of individual patients.
Clinicians and other staff performing multiparametric MRI should do so in accordance with appropriate standards and guidelines for its use.
The recommendations for multiparametric MRI apply only to its use in patients who have already undergone biopsy. Primary healthcare professionals should not order multiparametric MRI in the initial investigation of suspected prostate cancer in men with raised PSA levels.
Advise patients not undergoing repeat biopsy after a normal multiparametric MRI that there is a 10-15% chance of missing a significant cancer and that further follow-up is recommended.
For men at average risk for prostate cancer whose initial biopsy is negative for prostate cancer, and who have a life expectancy of less than 7 years (e.g. due to their age or due to other illness), advise that no further action is recommended unless they develop symptoms that suggest prostate cancer.
Unresolved issues

**UNRESOLVED ISSUES**

*If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*

The following issues remain unresolved:

- Whether the transrectal and transperineal biopsy approaches differ according to effectiveness in cancer detection, comparability of biopsy findings with subsequent prostatectomy findings, or rates of adverse outcomes.
- Comparative complication rates for various biopsy schemes. Few studies reported complication rates for various biopsy schemes and these were mainly immediate outcomes. Data for long-term follow-up findings were difficult to match to biopsy pattern.
- The role of multiparametric MRI, given that it cannot identify all prostate tumours, including all clinically significant tumours.

Implementation of recommendation

**IMPLEMENTATION OF RECOMMENDATION**

*Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*

<table>
<thead>
<tr>
<th>Will this recommendation result in changes in usual care?</th>
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</thead>
<tbody>
<tr>
<td>The use of multiparametric MRI after an initial biopsy would affect the patient’s pathway through the healthcare system and would alter the way clinical decisions are made about further biopsies.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are there any resource implications associated with implementing this recommendation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation of the recommendation for the use of multiparametric MRI would lead to an increase in referrals for this imaging procedure before clinical decisions are made about further biopsies and would therefore increase the cost of care, but may reduce the number of further biopsies. If a man chooses to have multiparametric MRI after a negative biopsy, this will incur significant costs, which may not be offset by the reduced need for biopsies.</td>
</tr>
<tr>
<td>Question</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
</tr>
<tr>
<td>Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant change the way care is organised.</td>
</tr>
<tr>
<td>Is the guideline development group aware of any barriers to the implementation of this recommendation?</td>
</tr>
<tr>
<td>At present, facilities for performing multiparametric MRI and expertise in its interpretation are limited to major metropolitan centres.</td>
</tr>
<tr>
<td>The cost of this imaging procedure may be a deterrent for some men. There is currently no Medicare Item number for multiparametric MRI in assessment of the prostate. However, the Prostate Cancer Foundation of Australia is collaborating with the Australian Government Department of Health, the Urological Society of Australia and New Zealand, and The Royal Australian and New Zealand College of Radiologists to establish item numbers for multiparametric MRI.</td>
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</tbody>
</table>