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RAPID RECOMMENDATIONS

Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline

Kari A O Tikkinen,1 2 Philipp Dahm,3 Lyubov Lytvyn,4 Anja F Heen,5 Robin W M Vernooij,6 Reed A C Siemieniuk,4 Russell Wheeler,7 Bill Vaughan,8 Ahaw Cletus Fobuzi,9 10 Marco H Blanker,11 Noelle Junod,12 Johanna Sommer,13 Jérôme Stinnemann,16 Manabu Yoshimura,15 Reto Auer,16 17 Helen MacDonald,18 Gordon Guyatt,4 Per Olav Vandvik,5 Thomas Agoritsas4 14 19

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This BMJ Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. BMJ Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and The BMJ. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences, and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact The BMJ for permission to reuse content in this article.

What is the role of prostate-specific antigen (PSA) screening in prostate cancer? An expert panel produced these recommendations based on a linked systematic review.1 The review was triggered by a large scale, cluster randomised trial on PSA screening in men without a previous diagnosis of prostate cancer published in 2018 (box 1).2 It found no difference between one-time PSA screening and standard practice in prostate cancer mortality but found an increase in the detection of low risk prostate cancer after a median follow-up of 10 years.

Although the results of this study suggest screening is not worthwhile, several guidelines advocate offering screening in some cases. The study was much larger than previous studies, and existing trials had published more extended follow-up results, and the BMJ Rapid Recommendations team felt these merited a new appraisal of the body of evidence. This guideline aims to promptly and transparently translate potentially practice-changing evidence to usable recommendations for clinicians and patients, based on the GRADE framework and following standards for trustworthy guidelines.

The panel suggests against systematic PSA screening (weak recommendation). The panel members judged that most men will decline screening because the benefit is small and uncertain and there are clear harms. However, there is likely considerable variation in values and preferences. Men with family history of prostate cancer, African descent or of lower socioeconomic status, having higher baseline risk of prostate cancer death, may be more likely to choose PSA screening. Shared decision-making is needed for men considering screening.

Box 2 shows all of the articles and evidence linked in this Rapid Recommendation package. The main infographic provides an overview of the absolute benefits and harms of PSA screening. The table at the end of the article shows any evidence that has emerged since the publication of this guideline.

Current practice
Prostate cancer is one of the most common cancers in men and is the leading cause of cancer death in 24 countries, ranking eighth globally, sixth in high income countries, and 12th in low income countries.3 Prostate cancer screening is with a PSA blood test. A raised PSA level can be a sign of prostate cancer but can also occur

WHAT YOU NEED TO KNOW

- PSA testing has increased the number of men diagnosed with and treated for prostate cancer, but many of these men would never have experienced any symptoms or death from prostate cancer
- This guideline makes a weak recommendation against offering systematic PSA screening based on an updated systematic review. The recommendation is weak because there may be a small, though uncertain, benefit of screening on prostate cancer mortality
- Men who place more value on avoiding complications from biopsies and cancer treatment are likely to decline screening. In contrast, men who put more value in even a small reduction of prostate cancer mortality (such as men at high baseline risk because of family history or African descent, or those concerned to rule out the diagnosis) may opt for screening
- Shared decision making is needed for men considering screening to make a decision consistent with their individual values and preferences. However, clinicians need not feel obligated to systematically raise the issue of PSA screening with their patients

Box 1 Results of the CAP Randomized Clinical Trial4
This cluster-randomised trial of 419 582 British men was published in March 2018. After a median follow-up of 10 years, there was no significant difference in prostate cancer-specific mortality in men receiving care by general practices randomised to a single PSA screening intervention compared with men receiving care by practices randomised to standard practice without screening. The detection of low risk prostate cancer cases was higher in the PSA screening group. Although the trial had limitations, such as low adherence to PSA testing in the intervention arm (36%) and a follow-up of only 10 years, its findings do not support the use of single PSA testing for population based screening.

The Rapid Recommendations executive felt this new study—taken together with extended follow-up data from existing trials—required a new appraisal of the body of evidence for patients and clinicians.
We suggest against systematic PSA-based screening for prostate cancer. Either option is reasonable. Shared decision making is needed for men considering screening.
### RAPID RECOMMENDATIONS

#### Comparison of benefits and harms - all evidence

<table>
<thead>
<tr>
<th></th>
<th>With screening</th>
<th>No important difference</th>
<th>With no screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 10 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>128</td>
<td>No important difference</td>
<td>129</td>
</tr>
<tr>
<td>Prostate cancer mortality</td>
<td>3</td>
<td>No important difference</td>
<td>3</td>
</tr>
<tr>
<td>Incidence of cancer (any stage)</td>
<td>39</td>
<td>7 fewer</td>
<td>32</td>
</tr>
<tr>
<td>Incidence of localized cancer</td>
<td>26</td>
<td>7 fewer</td>
<td>19</td>
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<tr>
<td>Incidence of advanced cancer</td>
<td>11</td>
<td>No important difference</td>
<td>13</td>
</tr>
<tr>
<td><strong>Within 1 month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy-related complications</td>
<td>Fewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer treatment complications</td>
<td>Fewer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Evidence quality: Events per 1000 people

- Moderate
- Low

#### Comparison of benefits and harms - selected evidence at lower risk of bias

<table>
<thead>
<tr>
<th></th>
<th>With screening</th>
<th>No important difference</th>
<th>With no screening</th>
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<td><strong>Within 10 years</strong></td>
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<td>129</td>
</tr>
<tr>
<td>Prostate cancer mortality</td>
<td>3</td>
<td>No important difference</td>
<td>3</td>
</tr>
<tr>
<td>Incidence of cancer (any stage)</td>
<td>50</td>
<td>18 fewer</td>
<td>32</td>
</tr>
<tr>
<td>Incidence of localized cancer</td>
<td>33</td>
<td>14 fewer</td>
<td>19</td>
</tr>
<tr>
<td>Incidence of advanced cancer</td>
<td>10</td>
<td>3 fewer</td>
<td>13</td>
</tr>
<tr>
<td><strong>Within 1 month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Biopsy-related complications</td>
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<td>Cancer treatment complications</td>
<td>Fewer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Evidence quality: Events per 1000 people

- Moderate
- Low

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#### Key practical issues

**Screening**
- PSA testing is done with a regular blood sample

**If biopsy is required**
- Usually taken through rectum guided by ultrasound
- Antibiotics given before procedure
- Takes about 5-10 minutes
- Local anaesthesia or sedation given before procedure
- May have to stop blood thinners before procedure

#### Men at higher risks
- Family history of prostate cancer
- African descent
- Poorer socio-economic groups

Men with these characteristics carry a higher incidence of prostate cancer, and could be at higher risk of dying of prostate cancer. It remains uncertain whether the impact of screening is similar in these higher risk men in comparison to men at lower risk.

#### Values and preferences

There is considerable variability among men's values and preferences regarding prostate cancer screening. Men who place a high value in avoiding complications from biopsies and subsequent treatment are likely to decline screening. In contrast, men who place a higher value in even a small reduction of prostate cancer mortality may opt for screening. Higher risk patients may be more likely to seek screening because they may worry more about prostate cancer and want to rule out the diagnosis.

#### Lower Urinary Tract Symptoms (LUTS)
- Slow stream
- Sensation of incomplete emptying
- Increased urinary frequency

LUTS symptoms like these are common complaints in adult men that can have a major impact on quality of life and substantial economic burden. The aetiology of LUTS is multifactorial, benign prostatic enlargement, due to hyperplasia, being the major cause. Evidence to date indicates that men with LUTS are at no higher risk of prostate cancer than men without LUTS.

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Among 1000 men with PSA screening, more presented with complications due to prostate biopsies:
- Blood in semen: 94
- Pain: 43
- Fever: 19
- Blood in urine: 67
- Hospitalized for sepsis: 1

Among 1000 men with PSA screening, more presented with complications due to cancer treatment:
- Erection not firm enough for intercourse: 25
- Urinary incontinence: 3

RAPID RECOMMENDATIONS

Box 2 | Linked articles in this BMJ Rapid Recommendation cluster

- Summary of the results from the Rapid Recommendation process
- Systematic review and meta-analysis of all available randomised trials that assessed PSA based screening for prostate cancer
- Systematic review of the values and preference of men considering PSA screening
- MAGICapp (https://app.magicapp.org/public/guideline/n32gkl)
- Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included patient partners (men at risk of prostate cancer), general practitioners, general internists, urologists, epidemiologists, methodologists, and statisticians. They determined the scope of the question that the recommendation should address and what outcomes are most important to patients considering screening.

No person had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 1 on bmj.com).

The panel identified eight critical outcomes needed to inform the recommendations: all-cause mortality; prostate cancer mortality; incidence of prostate cancer diagnoses (all stages); incidence of localised cancer (stage I and II); incidence of advanced cancer (stage III and IV); complications from biopsies (such as bleeding, pain, infections, and hospital readmissions), complications from prostate cancer treatment (such as urinary incontinence and erectile dysfunction); and quality of life. The panel also identified three additional patient-important outcomes: false positive rates (men with elevated PSA levels who will have negative biopsy); false negative rates (men with a normal PSA result who will subsequently be diagnosed with cancer), and the anxiety and uncertainty related to concerns about having prostate cancer. The panel asked that potential subgroups effects be explored according to age, screening interval, family history, being of African descent, and being of lower socioeconomic level. They also asked for a sensitivity analysis of the effect of screening restricted to trials at lower risk of bias.

To inform the recommendation, the panel members requested two systematic reviews, on the following questions:

- What are the benefits and harms of PSA screening versus no screening?
- What evidence describes the values and preference of men considering PSA screening?

Two parallel teams conducted these systematic reviews, which are linked to this publication.

The panel met to discuss the evidence and formulate a recommendation. They followed the BMJ/Rapid Recommendation procedures for creating a trustworthy recommendation, including use of the GRADE approach to interpret the evidence and create recommendations (see appendix 2 on bmj.com).

The panel considered the balance of benefits, harms, and burdens of PSA screening; the quality of the evidence for each outcome; and typical and expected variations in patient values and preferences, as well as feasibility and acceptability. Recommendations can be strong or weak, for or against a course of action. The recommendations take a patient-centred perspective which de-emphasises public health, societal, and health payer point of view.

due to a non-cancerous enlargement or inflammation of the prostate.3 Many men have a raised PSA level without having cancer (that is, false positive results). Conversely, a substantial number of men with a low PSA level will subsequently be diagnosed with prostate cancer (false negative results).

Investigations after raised PSA

If PSA is raised, the test is usually repeated. Men with persistently elevated PSA levels typically undergo a transrectal, ultrasound-guided, core-needle biopsy of the prostate to test for prostate cancer (see main infographic). If cancer is detected in the biopsied tissue, management options include surgery, radiation therapy, hormonal treatment, active surveillance, or watchful waiting. Diagnostic imaging studies such as ultrasonography, magnetic resonance imaging (MRI), bone scan, and computed tomography, are often also performed, especially in men presenting with higher risk disease, to check for disease spread.

Screening controversy

For many reasons, PSA screening remains controversial. Advocates often base their opinions on the European Randomised study of Screening for Prostate Cancer (ERSPC), which suggests that screening may reduce the long term risk of prostate cancer-specific mortality by at least 9% (relative reduction).3 They also note that substantial observational evidence indicates a reduction in advanced disease and reduction in prostate cancer mortality, which they attribute to the introduction of PSA screening.3 Opponents of PSA screening highlight the indolent natural course of prostate cancer, citing systematic reviews that reported little or no impact of PSA screening on overall and prostate cancer-specific mortality.3 Opponents also suggest that the harms and burden from overdiagnosis and overtreatment resulting in unnecessary prostate biopsies and impaired urinary, sexual, and bowel function as side effects of surgery or radiation therapy outweigh the uncertain and modest benefits.

Current guidelines on PSA testing

Guidelines vary in their recommendations on PSA testing (see table 1). The Canadian Task Force on Preventive Health Care recommends against PSA screening for men aged 55 to 69 years.6 However, the US Preventive Services Task Force recently changed its guidance to say that “the
decision about whether to be screened for prostate cancer should be an individual one, without clearly suggesting for or against screening; previously it recommended against screening in that group. National Cancer Center Network (NCCN) guidelines (which represents cancer centres in the USA) recommends initiating PSA screening at age 45 years. Guidelines from the American Urological Association (AUA) and European Association of Urology (EAU) recommend a discussion about PSA screening with patients.

Uptake of PSA testing
The incidence of prostate cancer has dramatically increased over the last quarter century. This has been associated with widespread use of prostate specific antigen (PSA) testing detecting early stage prostate cancers. There is wide variation in the adoption of prostate cancer screening. In the UK, about 39% of men aged 45-69 years have undergone PSA testing in the past 10 years. In Sweden 23% of men aged 50-69 had a PSA test in the previous 12 months and 58% in the previous 10 years. Although the rates of screening have declined during the past decade in the US, up to half of US men aged 60-74 undergo screening each year. Also, as many as 33% of elderly US men with competing medical comorbidities at high risk of dying from other cause underwent screening, and twice as many of these men recalled discussing the potential benefits rather than harms of screening. African-Americans were less likely to have been screened than non-African US men. Overall, two thirds of men reported no past discussion with physicians about the advantages, disadvantages, or scientific uncertainty and no shared decision making about prostate cancer screening.

The evidence
The updated systematic review on the benefits and harms of PSA screening pools data from five randomised controlled trials (with ERSPC comprising eight European countries), which enrolled a total of 721,718 men (with 419,582 included in the latest CAP trial).1

Main characteristics and limitations of the trials
Figure 2 provides an overview of the trials' characteristics and the patients included. All trials had methodological limitations. In the CAP trial only 36% of men randomised to the screening arm actually underwent PSA testing (that is, low adherence to screening), while about 10-15% in the non-screening arm were actually tested (that is, contamination). CAP also differed from other large scale trials in that it used one-time screening, whereas others used repeated screening with intervals varying from annual to every two years or more.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial conducted in the US lacked allocation concealment, and rates of PSA testing in the non-screening arm exceeded 50%, possibly as high as 80%. The European Randomised Study of Screening for Prostate Cancer (ERSPC) was conducted in eight European countries. There was probably inadequate allocation concealment, and there are concerns that groups may have received different quality of treatment for prostate cancer (performance bias). Nevertheless, the systematic review authors judged the ERSPC trial to be the one that was probably least affected by bias. Based on a predefined sensitivity analysis, the BMJ Rapid Recommendations panel decided to appraise both the summary of the whole

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Table 1 | Major guideline recommendations on PSA screening*

<table>
<thead>
<tr>
<th>Organisation, last published update</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Services Task Force, 2018</td>
<td>Provide information about potential benefits and harms of screening for men aged 55-69 years. Recommend against screening for men aged ≥70 years.</td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care, 2014</td>
<td>Recommend against routine screening. Weak recommendation in men aged 55-69, and strong in other ages.</td>
</tr>
<tr>
<td>American Cancer Society, 2016</td>
<td>Provide information about uncertainties, risks, and potential benefits of screening to enable informed decision making. Recommend screening discussions for: • Men aged 50 years who are at average risk (expected to live at least 10 more years) • Men aged 45 years who are at high risk (African-Americans, and men with a first degree relative with prostate cancer diagnosed at ≥75 years old) • Men aged 60 years who are at very high risk (more than one first degree relative with prostate cancer diagnosed at ≥75 years old).</td>
</tr>
<tr>
<td>American Academy of Family Physicians, 2012</td>
<td>Adopted the US Preventive Services Task Force 2012 recommendation, which recommended against screening.</td>
</tr>
<tr>
<td>American Urological Association, 2015</td>
<td>Shared decision making for men aged 55-69 years. Recommend routine screening in men aged ≤60 years or those with life expectancy ≤10-15 years.</td>
</tr>
<tr>
<td>American College of Physicians, 2015</td>
<td>Shared decision making for men aged 50-69 years. Recommend against screening in men aged ≥70 years or those with life expectancy ≤10 years, and those who had not had informed discussion.</td>
</tr>
<tr>
<td>US National Comprehensive Cancer Network, 2018</td>
<td>Offer screening to men aged 45-75 years. Begin discussing PSA screening with African-American men several years earlier than white men. Continue screening beyond 75 years old with caution in healthy patients with little or no comorbidity.</td>
</tr>
<tr>
<td>European Association of Urology, 2018</td>
<td>Recommend against PSA testing without prior counselling on potential risks and benefits. Offer an individualised, risk-adapted strategy for early detection to well informed men with good performance status and life expectancy ≥10-15 years. Recommend screening for men aged ≥50 years, and ≥45 years for men with positive family history or African-American ethnicity. Recommend against routine screening for men with life expectancy ≤15 years.</td>
</tr>
<tr>
<td>European Society for Medical Oncology, 2015</td>
<td>Recommend against population based screening.</td>
</tr>
<tr>
<td>UK National Screening Committee, 2016</td>
<td>Recommend against systematic population screening.</td>
</tr>
</tbody>
</table>

*These guidelines have not taken account of the new evidence captured in our Rapid Recommendations.
### RAPID RECOMMENDATIONS

#### DATA SOURCES

**NUMBER OF TRIALS**: 5  
**NUMBER OF PARTICIPANTS**: 721,718

#### TRIAL CHARACTERISTICS

| Screening frequency          |  
|------------------------------|---|
| One-time PSA screening       | 2  
| Annual PSA screening         | 2  
| PSA screening at least every 2–4 years | 1  

Digital rectal examination (DRE) performed in addition to PSA

| DRE and PSA screening | 3  
| PSA only screening    | 2  

| Follow-up duration       |  
|--------------------------|---|
| Reported 10 year follow up | 1  
| Reported 11 year follow up | 1  
| Reported 13 year follow up | 1  
| Reported 15 year follow up | 1  
| Reported 20 year follow up | 1  

#### PARTICIPANT CHARACTERISTICS

**NUMBER OF PATIENTS ENROLLED**

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>Med</th>
<th>Max</th>
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<tbody>
<tr>
<td>Thousands</td>
<td>408,825</td>
<td>76,683</td>
<td>408,825</td>
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**MEAN AGE† at baseline**

<table>
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<th>Age (years)</th>
<th>Min</th>
<th>Med</th>
<th>Max</th>
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<tr>
<td>45</td>
<td></td>
<td>59</td>
<td>80</td>
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**ADHERENCE**

Proportion of participants in the screening arm who actually underwent PSA testing

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>24%</td>
<td>74%</td>
<td>85%</td>
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</table>

**CONTAMINATION ‡**

Proportion of participants in the non-screening arm who actually underwent PSA testing

<table>
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<th>Med</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>31%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**MEN WITH FAMILY HISTORY**

Distribution reported in only 2 studies

**MEN OF AFRICAN DESCENT**

Distribution reported in only 1 study

#### FUNDING

- 4 trials reported non-industry funding
- 1 trial reported limited industry funding*

#### PATIENT PARTNERSHIP

- No patient involvement reported in trial designs

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* Swedish arm of ERSPC trials received funding from Abbott Pharmaceuticals
† Age distribution reported in only 2 studies
‡ Estimated, not directly measured in all except one study

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**Fig 2** Characteristics of patients and trials included in systematic review of the use of the prostate-specific antigen (PSA) test for prostate cancer screening.†
RAPID RECOMMENDATIONS

Evidence suggests that different men judge the benefits and harms of PSA testing and its consequences differently. The linked systematic review on the values and preferences of men considering PSA screening included studies that reported quantitative data on the degree of benefits (such as reduction in mortality risk) that men would require and degree of harms (such as increase in risk of incontinence) that men would be willing to accept under PSA screening.

The studies used different methodologies and varied considerably in how their outcomes were reported. One study showed that men were willing to forego screening with a benefit of 2% on prostate cancer mortality if it increases their probability of avoiding unnecessary biopsies by 10% or avoiding unnecessary treatment by 10%. In another study, men were willing to accept between 65 and 233 per 10,000 unnecessary biopsies to avoid one per 10,000 prostate cancer deaths. These results varied with age: men in their 50s were willing to accept more unnecessary biopsies than men in their 40s or in their 60s.

The review also included six studies in which men were specifically investigated whether the men’s values and preferences differed among men with a family history of prostate cancer, men of African descent, or men of lower socioeconomic class.

Death and cancer diagnosis
PSA screening may increase the detection of prostate cancer (7 more per 1000 men (95% confidence interval 1 to 15 more) at 10 years), particularly of localised cancer (7 more per 1000 men (2 to 15 more)). But the data show no difference in prostate cancer mortality. Overall confidence in these estimates across these outcomes was low because of risk of bias as well as the inconsistency of findings across studies.

When focusing on studies at lower risk of bias—ERSPC trials—the panel was confident that over a 10 year period:

- PSA screening probably has little or no effect on death
  - All-cause mortality (0 fewer per 1000 men (95% CI 3 fewer to 3 more))
  - Prostate cancer mortality (1 fewer per 1000 (1 to 0 fewer))
  - Prostate cancer mortality is similar at longer periods of up to 18 years of follow-up (1 to 2 fewer per 1000 men)

The review also included six studies in which men were presented with decision aids showing outcomes such as prostate cancer diagnosis and prostate cancer mortality. Willingness to undergo screening varied from 37% in a study displaying a reduction in mortality of 10 per 1000 men to 44% in a study displaying a reduction in mortality of 7 per 1000. The review found no studies that specifically investigated whether the men’s values and preferences differed among men with a family history of prostate cancer, men of African descent, or men of lower socioeconomic class.
RAPID RECOMMENDATIONS

- PSA screening probably increases diagnosis of prostate cancer
  - Detection of any prostate cancer (18 more per 1000 men (16 to 20 more))
  - Detection of localised cancer (14 more per 1000 (13 to 16 more))
  - But it probably results in a small decrease in detection advanced prostate cancer (3 fewer per 1000 (4 to 2 fewer)).

The panel was also confident that:
- About two thirds of men offered a biopsy because of an elevated PSA result will have normal biopsy results and no prostate cancer (that is, false positive results of PSA screening)
- About 15% of men with a normal PSA result will subsequently be diagnosed with prostate cancer; with about 2% of men with a normal PSA result diagnosed with advanced cancer (that is, false negative results of PSA screening)
- Each biopsy bears a substantial risk of side effects and serious complications, including blood in semen (93%), blood in urine (66%), pain (44%), fever (18%), and admission to hospital for sepsis (1-2%).

Thus, considering that about one in seven men who undergo PSA screening will have an elevated PSA result and most of them will undergo biopsy (about 85%) in the CAP and ERSPC trials, see appendix 3 on bmj.com):
- Among a hypothetical population of 1000 men, about 94 more will present with blood in the semen with PSA screening, 67 more with blood in the urine, 45 more with pain, 19 more with fever, and 1 more hospitalised for sepsis, due to a prostate biopsy
- The panel acknowledges uncertainty in these projected estimates, as they were based on modelling and several assumptions in the rates of biopsies and cancers detected in men that were screened and in those who were not. These are likely to vary across clinical contexts and diagnostic strategies. For example, new approaches (including genetic or biomarkers, risk stratification tools, and MRI-guided biopsy) have the potential for avoiding biopsies in men with non-progressive and slowly progressive cancer, and thus diminish the likelihood of harm from their complications when entering screening through PSA testing. However, the impact of such modalities on patient-important outcomes remains uncertain.

Harms linked to management of prostate cancer
The panel was confident in the complications rates reported for treatments of prostate cancer, in particular:
- Urinary incontinence (pad use at 6 years after treatment) was present in 17% of men who had surgery, 4% who had radiotherapy, and 8% of men under active surveillance
- Erections not firm enough for intercourse were present in 83% of men who had surgery, 73% who had radiotherapy, and 70% under active surveillance.

Thus,
- Applying these numbers to a hypothetical 1000 men, about three more will present with urinary incontinence (any pad use) and 25 more will have an erection not firm enough for intercourse due to treatment for prostate cancer diagnosed through PSA screening (see appendix 3). Once again, the panel has low confidence in these projected estimates, as they are based on several assumptions depending on the particular context and required data modelling. New diagnostic strategies could also shift the proportions of men who enter active surveillance rather than radical surgery or radiotherapy.

Quality of life
The panel was less confident about the impact of screening on the overall quality of life or the anxiety of having cancer:
- There was no difference in quality of life between men who undergo PSA screening and those who do not. But this comparison was available only in a subset of men from one of the trials (n=1088, more details through the MAGICapp within the main infographic).
- There is no randomised evidence comparing PSA screening with non-screening in regard to the anxiety related to a cancer diagnosis. A large cohort study in Sweden among 4.3 million men showed an increased risk of suicide (relative risk 2.6 (95% CI 2.1 to 3.0)) and cardiovascular events (1.3 (1.3 to 1.3)) during the first year after diagnosis. A US cohort study with 343,000 men showed no increased risk of suicide during the first year after the widespread use of PSA screening (after 1993) but an increased risk of cardiovascular death during the first month after diagnosis (adjusted relative risk 1.55 (1.3 to 1.8)). Thus it remains uncertain whether screening results in changes in anxiety about cancer.

Adapting the offer for men at higher risk of prostate cancer and death
The linked systematic review did not find a relative subgroup effect by age: the effects of screening are consistent across age strata. Age of men enrolling in the studies ranged from 45 to 80 years, with most aged 50-69 years. The panel believes the evidence thus applies to men regardless of age. However, any possible benefit of screening is likely to become negligible as life expectancy decreases due to age or comorbidities.

There were no randomised data on whether screening efficacy differed in those with a family history of prostate cancer, men of African descent, or men from lower socioeconomic levels. It remains uncertain whether the relative effect of screening is similar to that in the general population. However, these factors are associated with higher incidence of prostate cancer and higher risk of prostate cancer death in observational studies, as well as in follow-up publications of the trials included in the linked review (Finnish and Swiss arms from the
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ERSPC trial and the PLCO trial). Using evidence from these trials, we adapted the baseline risk in our summary of findings, using the same studies at lower risk of bias (that is, ERSPC data). In these studies, family history was assessed by self reporting in a questionnaire and defined positive if a man reported that his father or at least one brother had been diagnosed with prostate cancer. For race or ethnicity, non-Hispanic black men were compared with non-Hispanic white men. Level of education was used as a proxy for socioeconomic status, and men with primary education only were defined as having a low level of education and men with secondary or tertiary education defined as having high level of education.

For men of African descent, over a 10 year period:
• The baseline risk of developing prostate cancer of any stage is likely higher than that of the general population (estimated at about 51 per 1000 men diagnosed), and PSA screening probably increases their detection of any stage cancer by a larger magnitude than in the general population (29 more per 1000 men (95% CI 26 to 32 more))
• Baseline risk of prostate cancer mortality is likely also higher than in the general population of men considering screening (estimated at about 7 per 1000 men dying at 10 years). However, PSA screening had a similar small effect in reducing prostate cancer mortality in absolute terms (1 fewer per 1000 (2 to 1 fewer)).

For men with family history, over a 10 year period:
• As for men with African descent, the baseline risk of developing prostate cancer is likely higher than in the general population (estimated at about 50 per 1000 men diagnosed with any stage prostate cancer; and about 25 per 1000 are localised cancers). PSA screening probably increases their detection of any stage cancer (29 more per 1000 (26 to 31 more)) as well as localised cancers (19 more per 1000 (17 to 21 more))
• These baseline risk estimates are based on studies that defined family history as positive if a man reported that his father or at least one brother had been diagnosed with prostate cancer. These baseline risk estimates may increase with increasing number of relatives diagnosed with prostate cancer.

For men with lower level of education, over a 10 year period:
• There was limited data on how much more these men were at higher baseline risk. Using lower level of education as a proxy of lower socioeconomic status, we estimated that baseline risk of prostate cancer mortality was higher (about 4 per 1000 men dying at 10 years) as well as all-cause mortality (about 196 per 1000 men)
• The absolute effect of PSA screening is overall comparable to that in the other subgroups, with a small reduction in prostate cancer mortality (about 1 fewer per 1000 men (1 to 0 fewer))
• PSA screening probably has little or no effect on all-cause mortality (about 4 fewer per 1000 (10 to 0 fewer)).

Values and preferences
The panel, including the patient partners, felt that this variability in values and preferences contributes to a weak recommendation. The recommendation against screening reflects a belief that most men would value avoiding complications from biopsies and subsequent treatment because the reduction in prostate cancer and death from screening is small and uncertain. Prostate cancer will often, though not always, remain indolent.

Men who place a high value on avoiding complications from biopsies and subsequent treatment are likely to decline screening. In contrast, men who place a higher value on even a small reduction of prostate cancer may opt for screening. Several panel members felt that higher risk patients—such as patients with family history of cancer or of African descent—may be more likely to seek screening because they may worry more about prostate cancer and want to rule out the diagnosis.

For men considering screening, shared decision making is critical to ensure that their decision is in line with their own values and preferences. The evidence summarised in this Rapid Recommendation is available in MAGICapp as decision aids that can support shared decision making (https://app.magicapp.org/public/guideline/n32gkl).

Practical issues and other considerations
Figure 3 outlines the key practical issues. PSA testing can be performed on any normal blood sample, but prostate biopsies and their follow-up have important implications for daily life.

Lower urinary tract symptoms (slow urine stream, sensation of incomplete emptying, increased urinary frequency) are common complaints in adult men that can have a major impact on quality of life. Benign prostatic enlargement is the major cause. Evidence to date indicates that men with these complaints are not at increased risk of prostate cancer.

For men who chose to undergo PSA testing, the optimal frequency of screening remains unknown. Figure 2 summarises the frequency used in the different trials, yet the accompanying systematic review did not find any significant subgroup effect of the effect of screening based on these different frequencies. Given that the ERSPC data are likely at lower risk of bias, PSA screening every four years—rather than, say, every year or only once in a lifetime—may be the optimal interval.

Costs and resources
Results from a recent cost-effectiveness study modelled for the US suggested that screening between the ages of 55 and 69 years combined with active surveillance for low risk men could only be cost-effective at a $100 000 threshold if the screening frequency remains low (every four years) and active surveillance is offered to all men with low risk prostate cancer (that is, Gleason score ≤6 and stage ≤T2a). Strategies with shorter screening intervals or in which immediate treatment is offered to all men were not cost-effective. Although the Rapid Recommendations panel focused on the patients’ priorities rather than those of society, our recommendation is compatible with these findings.
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### PRACTICAL ISSUES

<table>
<thead>
<tr>
<th></th>
<th>PSA testing</th>
<th>Biopsy</th>
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<tbody>
<tr>
<td><strong>MEDICATION ROUTINE</strong></td>
<td>Blood sample, often taken at GP/family physician</td>
<td>May have to stop blood thinners before prostate biopsy procedure</td>
</tr>
<tr>
<td><strong>TESTS &amp; VISITS</strong></td>
<td>PSA testing is done with a regular blood sample</td>
<td>Prostate biopsy is usually taken through rectum guided by ultrasound</td>
</tr>
<tr>
<td></td>
<td>Waiting for prostate biopsy results can be stressful</td>
<td>Takes about 5-10 minutes</td>
</tr>
<tr>
<td><strong>PROCEDURE &amp; DEVICE</strong></td>
<td>PSA testing is done with a regular blood sample</td>
<td>Antibiotics and local anaesthesia/sedation given before procedure</td>
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<tr>
<td></td>
<td>Prostate biopsy is normally done in outpatient clinic/hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate biopsy is usually taken through rectum guided by ultrasound</td>
<td></td>
</tr>
<tr>
<td><strong>RECOVERY &amp; ADAPTATION</strong></td>
<td>Minimal discomfort associated with the blood draw</td>
<td>Allow for some recovery time dependent on adverse effects after prostate biopsy</td>
</tr>
<tr>
<td><strong>COORDINATION OF CARE</strong></td>
<td>Waiting for PSA results can be stressful</td>
<td>Need for someone to drive you home after prostate biopsy procedure</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS, INTERACTIONS &amp; ANTIDOTE</strong></td>
<td>Some drugs (finasteride, dutasteride) can lower PSA levels</td>
<td>Prostate biopsy often leads to soreness, blood in semen, urine and stool for days to weeks</td>
</tr>
<tr>
<td><strong>PHYSICAL WELL-BEING</strong></td>
<td>Cost depends on health policy and health insurance; usually not expensive</td>
<td>Prostate biopsy procedure can be uncomfortable</td>
</tr>
<tr>
<td><strong>EMOTIONAL WELL-BEING</strong></td>
<td>Avoid vigorous exercise or physical activities after prostate biopsy</td>
<td>Waiting for prostate biopsy results can be stressful</td>
</tr>
<tr>
<td><strong>COSTS &amp; ACCESS</strong></td>
<td>Need to take time off work for PSA testing</td>
<td>Blood in semen and pain in pelvic area can impact sexual life after prostate biopsy</td>
</tr>
<tr>
<td><strong>EXERCISE &amp; ACTIVITIES</strong></td>
<td>Avoid ejaculation in the 2 days prior to PSA testing, as this may result in false positive elevation</td>
<td>Need to take time off work to do prostate biopsy procedure</td>
</tr>
<tr>
<td><strong>SOCIAL LIFE &amp; RELATIONSHIPS</strong></td>
<td>Avoid vigorous exercise (such as cycling) in the 2 days prior to PSA testing, as this may result in false positive elevation</td>
<td>Should not drive directly after prostate biopsy procedure if sedation is given</td>
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**Fig 3** | Practical issues about use of prostate-specific antigen (PSA) testing and biopsy for prostate cancer screening

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Uncertainties for future research
Recent evidence suggests that incorporating MRI in the investigation of those with a positive PSA test result decreases the false positive rate, and thus the number of patients undergoing unnecessary biopsies, and may also increase the accuracy of biopsies in those who do have prostate cancer. The Rapid Recommendations panel considered addressing this issue in the guideline, but the impact of MRI on long term outcomes of prostate cancer incidence, mortality, and complications of treatment remains uncertain. Sophisticated decision modelling might shed light on this issue, but the panel decided not to conduct such an analysis because of logistic and feasibility considerations, and because the panel’s review of the evidence suggests that modelling would introduce further uncertainties regarding the impact of MRI on patient-important outcomes.

Key research question to inform decision makers and future guidelines include

- Could new screening and diagnostic techniques reduce the harms and burden of the diagnostic procedure by better identifying non-progressive and slowly progressive cancer from cancer that is likely to become symptomatic and affect quality or length of life? These strategies may include genetic markers or biomarkers, risk stratification tools, or MRI guided biopsy. For example, two recent high quality studies on MRI guided biopsy have shown encouraging results of MRI to reduce overdiagnosis. But the impact of this strategy on long term, patient-important outcomes (such as prostate cancer incidence, mortality, and complications of treatment) remains uncertain.

- For men opting for screening, what would be the ideal age range and screening interval? Randomised trials varied in their offer of a one-off or repeated PSA testing and it remains uncertain which strategy is more suitable.

- What is the impact of screening on men at higher baseline risk (men with a family history of cancer, of African descent, and of lower socioeconomic status)? Are their values and preferences different from those of men in the general population?

Updates to this article
The final table shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on the extent it is expected to alter the recommendation.

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Transparency: KAD Tikkinen and T Agostinas affirm that the manuscript is an honest, accurate, and transparent account of the recommendation being reported, that no important aspects of the recommendation have been omitted, and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

4 Østergaard ML, Krogh-Jespersen A, Brodersen J. Do men with lower urinary tract symptoms have an increased risk of advanced prostate cancer? BMJ 2018;361:k1202. 10.1136/bmj.k1202. pmid:29724877.
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