**Supplementary File 2: GRADE Evidence to Decision framework for a coverage decision**

An interactive version of this framework that includes more subgroup information is available at: <http://ietd.epistemonikos.org/#/frameworks/54cb63812b3867639eed4bff/question>

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*Interactive Evidence to Decision Framework* ***Date:*** *Jan 2015*

**3. Should we stop covering opportunistic screening for prostate cancer in asymptomatic men?**

(Coverage decision)

**QUESTION**

***Question details***

**Patients**: Asymptomatic men aged 50 or older

**Intervention:** Opportunistic screening with prostate specific antigen (PSA)

**Comparison:** No screening

**Main outcomes:** All-cause mortality, prostate cancer specific mortality, prostate cancer diagnosis (number of men diagnosed with prostate cancer), harms, quality of life

**Setting:** The National Health Service in Italy

**Perspective:** Regional Health Authority

***Background***

Prostate cancer is common and a leading cause of morbidity and mortality in men. It rarely leads to early, reliable warning signs or symptoms while still confined to the prostate gland. Effective early detection and treatment strategies in asymptomatic men could potentially provide a large benefit to many men. Screening aims to identify cancers at an early stage, thereby increasing the chances of successful treatment (resulting in improvements in survival and quality of life). However, many men will live with asymptomatic prostate cancer until they die from other causes. Detecting cancers that will never cause symptoms or death is referred to as overdiagnosis. Consequences of overdiagnosis include the negative effects of unnecessary labelling, the harms of unneeded tests and treatments, and the wasted resources.

**ASSESSMENTS**

***Problem***

**Is the problem a priority?**

Judgment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | [ ] No | [ ] Probably No | xProbably Yes | [ ] Yes |

Research evidence

Prostate cancer is the most commonly diagnosed cancer and the third leading cause of death in men in high-income countries. Advanced age is the primary risk factor: more than 75% of all prostate cancers are diagnosed in men aged 65 years and over.

The vast majority of men with prostate cancer have no symptoms and their tumours are detected by routine testing. Lower urinary tract symptoms due to benign prostatic obstruction are common in elderly men and may result in increased concentrations of prostate specific antigen (PSA) but are not associated with an increased prostate cancer incidence. For most men prostate cancer is slow growing and does not result in clinical signs or symptoms during their lifetime.

***Desirable effects***

**How substantial are the desirable anticipated effects?**

Judgment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | [ ] Trivial | xSmall | [ ] Moderate | [ ] Large |

Research evidence

Summary of findings: PSA screening for prostate cancer in asymptomatic men aged 50 or older

[(See an interactive version here)](http://isof.epistemonikos.org/#finding/54d4f9c3f30d0c1d86385ccc)



***Undesirable effects***

**How substantial are the undesirable anticipated effects?**

Judgment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | xLarge | [ ] Moderate | [ ] Small | [ ] Trivial |

Research evidence

See summary of findings table above.

***Certainty of the evidence***

**What is the overall certainty of the evidence of effects?**

Judgment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| [ ] No included studies | [ ] Very low | [ ] Low | xModerate | [ ] High |

Research evidence

See summary of findings table above.

***Values***

**Is there important uncertainty about how much people value the main outcomes?**

Judgment

|  |  |  |  |
| --- | --- | --- | --- |
| [ ] Important uncertainty | [ ] Possibly important uncertainty | xProbably no important uncertainty | [ ] No important uncertainty |

Research evidence

A 2012 study (de Bekker-Grob 2012) aimed at determining men’s preferences for prostate cancer screening found that men were willing to trade-off some risk reduction of prostate cancer related death to be relieved of the burden of biopsies or unnecessary treatments. Increasing knowledge on overdiagnosis and overtreatment, especially for men with lower educational level, is warranted to prevent unrealistic expectations from screening. The study results are based on a discrete choice experiment conducted among a representative sample of 1000 men (55-75 years old).

A 2008 study (Sanda 2008) aimed at identifying determinants of health-related quality of life after primary treatment of prostate cancer and measuring the effects of such determinants on satisfaction with the outcome of treatment. They prospectively collected outcomes reported by 1201 patients and 625 spouses or partners at multiple centers before and after radical prostatectomy, brachytherapy, or external-beam radiotherapy and evaluated factors associated with changes in quality of life within study groups and determined the effects on satisfaction with the treatment outcome. Each prostate-cancer treatment was associated with a distinct pattern of change in quality-of-life domains related to urinary, sexual, bowel, and hormonal function. These changes influenced satisfaction with treatment outcomes among patients and their spouses or partners.

***Balance of effects***

**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**

Judgment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | xFavors the comparison | [ ] Probably favors the comparison | [ ] Does not favor either the intervention or the comparison | [ ] Probably favors the intervention | [ ] Favors the intervention |

Research evidence

See table values of the main outcomes of interest, and summary of findings table above.

***Resources required***

**How large are the resource requirements (costs)?**

Judgment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | [ ] Large costs | xModerate costs | [ ] Negligible costs or savings | [ ] Moderate savings | [ ] Large savings |

Research evidence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Total population** **(age range)** | **N° of patients** | **N° of PSA performed** | **% patients** | **Single cost €** | **Total costs €** |
| 50-59 | 36 781   | 6 302   | 8 754   | 17.1   | 7.41   | 64 867   |
| 60-69 | 26 975   | 9 058   | 14 631   | 33.6   | 7.41   | 108 416   |
| 70-79 | 22 461   | 11 133   | 20 275   | 49.6   | 7.41   | 150 238   |
| >79 | 13 038   | 5 929   | 10 716   | 45.5   | 7.41   | 79 406   |
| **> 50** | **99 255** | **32 422** | **54 376** | **32.7** | 7.41   | **434 781** |

In this table both symptomatic and asymptomatic men are included.

Other possible costs related to PSA screening are: biopsies (50 € each), specialists’ visits (30 € each), treatment (3000 € each), complications’ treatments (200 € each).

Data are for 2013 from Roma E Italian Local Health Authorithies (population of 537,002 inhabitants).

***Certainty of evidence of required resources***

**What is the certainty of the evidence of resource requirements (costs)?**

Judgment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| [ ] No included studies | [ ] Very low | [ ] Low | xModerate | [ ] High |

Research evidence

The data about costs derives from Local Health Authorithies database with the analysis of actual patient information.

***Cost-effectiveness***

**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**

**Judgment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | xFavors the comparison | [ ] Probably favors the comparison | [ ] Does not favor either the intervention or the comparison | [ ] Probably favors the intervention | [ ] Favors the intervention |

Research evidence

Shteynshlyuger (2011) evaluated the cost-effectiveness of prostate specific antigen screening using data from the European Randomized Study of Screening for Prostate Cancer protocol extrapolated to the United States. They used Surveillance, Epidemiology and End Results (SEER) Medicare data and a nationwide sample of employer provided estimates of costs of care for patients with prostate cancer. The lifetime cost of screening with prostate specific antigen, evaluating abnormal prostate

specific antigen and treating identified prostate cancer to prevent 1 death from prostate cancer was $5,227,306 based on the European findings and extrapolated to the United States. If screening achieved a similar decrease in overall mortality as the decrease in prostate cancer specific mortality in the European study, screening would cost $262,758 per life-year saved. The study authors used a cost-effectiveness threshold of $100,000/LYS (that can be considered high), suggesting that opportunistic PSA screening for prostate cancer is not good value for money.

Shin S (2014)  performed a cost-utility analysis on the adoption of PSA screening program among men aged 50-74-years in Korea from the healthcare system perspective. PSA screening was not cost-effective. Several data sources were used for the cost-utility analysis, including general health screening data, the Korean Central Cancer Registry, national insurance claims data, and cause of mortality data from the National Statistical Office. The net benefits of PSA screening were estimated to be very low. The incremental cost effectiveness ratio (ICER) was about 94 million KRW (approximately $76,140) per QALY.

Pataky R (2014) evaluate the cost-effectiveness of PSA screening, with and without adjustment for quality of life, for the British Columbia (BC) population. They adapted an existing natural history model using BC incidence, treatment, cost and mortality patterns. The modeled mortality benefit of screening derives from a stage-shift mechanism, assuming mortality reduction consistent with the European Study of Randomized Screening for Prostate Cancer. After utility adjustment, all screening strategies resulted in a loss of quality-adjusted life years (QALYs); however, this result was very sensitive to utility estimates.

***Equity***

**What would be the impact on health equity?**

Judgment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | [ ] Reduced | [ ] Probably reduced | xProbably no impact | [ ] Probably increased | [ ] Increased |

Research evidence

No evidence found.

***Acceptability***

**Is the intervention acceptable to key stakeholders?**

Judgment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| [ ] Don't know | [ ] Varies | [ ] No | [ ] Probably No | xProbably Yes | [ ] Yes |

Research evidence

No evidence found.

Additional considerations

PSA screening for men over 50 is used widely in Italy. Stopping coverage might not be acceptable for some:

* men who already had screening
* men who ask for screening because they know that it was a routine examination in the past
* men with a family history of prostate cancer

***Feasibility***

**Is the intervention feasible to implement?**

Judgment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   [ ] Don't know | [ ] Varies | [ ] No | [ ] Probably No | xProbably Yes | [ ] Yes |

Research evidence

No evidence found.

Additional considerations

Clinicians might potentially continue to order PSA tests for asymptomatic men and provide an incorrect reason for testing or suggest that patients pay out-of-pocket.

**CONCLUSIONS**

***Type of decision***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| xDo not cover | [ ] Cover with evidence development | [ ] Cover with price negotiation | [ ] Restricted coverage | [ ] Cover |

Research evidence

None

***Decision***

Stop covering opportunistic PSA screening for asymptomatic men.

***Justification***

Opportunistic PSA screening in asymptomatic men aged 50 or older probably has no benefits in terms of mortality or quality of life and has a number of undesirable effects, including bleeding, bruising, short-term anxiety, and overdiagnosis and overtreatment, which can lead to erectile dysfunction and incontinence, infections, and blood loss requiring transfusion.

Detailed justification

|  |
| --- |
| Desirable effects: No evidence of efficacy on mortality.Undesirable effects: Undesirable effects of PSA screening include minor and major adverse events such as bleeding, bruising, short-term anxiety, overdiagnosis and overtreatment, erectile dysfunction and incontinence, infections, blood loss requiring transfusion, pneumonia. |

***Restrictions***

No restrictions.

***Implementation considerations***

Patient information should be provided and reasons for not screening should be communicated clearly to eligible men.

***Monitoring and evaluation***

The use of PSA screening in asymptomatic men should be monitored.

**EVIDENCE PROFILE**

**Author(s):** Parmelli E, Amato L, Brunetti M, Saitto C.
**Date:** Jan 2015
**Question:** Should prostate cancer opportunistic screening be used for asymptomatic men?
**Settings:** The National Health Service in Italy
**References:** Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database of Systematic Reviews 2013, Issue 1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Evidence assessment** | **No of patients** | **Effect** | **Certainty (quality) of the evidence** | **Importance** |
|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Prostate cancer opportunistic screening** | **Control** | **Relative(95% CI)** | **Absolute** |
| **All-cause mortality** |
| 4 | randomized trials | serious1 | no serious inconsistency | no serious indirectness | no serious imprecision | none | 22833/125024 (18.3%) | 35790/169832 (21.1%) | RR 1.00 (0.96 to 1.03) | 0 fewer per 1000 (from 1 more to 1 more) | MODERATE | CRITICAL |
| **Prostate cancer-specific mortality** |
| 5 | randomized trials | serious2 | no serious inconsistency | no serious indirectness | no serious imprecision | none | 698/156157 (0.45%) | 1318/185185 (0.71%) | RR 1.00 (0.86 to 1.17) | 0 fewer per 1000 (from 1 fewer to 1 more) | MODERATE | CRITICAL |
| **Prostate cancer diagnosis** |
| 4 | randomized trials | serious1 | serious3 | no serious indirectness | no serious imprecision | none | 11929/125024 (9.5%) | 11536/169832 (6.8%) | RR 1.30 (1.02 to 1.65) | 20 more per 1000 (from 1 more to 44 more) | LOW | IMPORTANT |

1 Risk of bias was ’high’ or ’unclear’ for allocation concealment in 3 studies; ’high’ or ’unclear’ for random sequence generation in 2 studies; ’low’ for blinding in all 4 studies; ‘ unclear’ for incomplete outcome data in 2 studies; ’unclear’ for selective reporting in 1 study; and ’high’ or ’unclear’ for other bias in 2 studies.
2 Risk of bias was ’high’ or ’unclear’ for allocation concealment in 4 studies; ’high’ or ’unclear’ for random sequence generation in 3 studies; ’unclear’ for blinding of outcome assessment in 1 study; ’unclear’ for incomplete outcome data in 2 studies; ’unclear’ for selective reporting in 2 studies; and ’high’ or ’unclear’ for other bias in 3 studies.
3 I2 = 98%; Chi2 = 162.78 (P <0.00001)

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