Appendix 2: GRADE Basis of Recommendation Decision Table for screening for prostate cancer with prostate specific antigen

Questions: 1. What is the evidence that screening for prostate cancer with prostate-specific antigen decreases prostate cancer-specific and all-cause morbidity and/or mortality? 2. What is the evidence that treatment of early stage or screen-detected prostate cancer decreases prostate cancer-specific and all-cause morbidity and/or mortality?		
Populations: 1. Asymptomatic males at risk of prostate cancer 2. Men treated for screen-detected or early-stage prostate cancer		
Interventions: 1. Screening with prostate specific antigen 2. Treatment with radical prostatectomy, radiation therapy, hormonal therapy, cryotherapy, or high-intensity focused ultrasonography		
Setting (if relevant): Primary care		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Quality of evidence (QoE) for screening studies *Is there high or moderate quality of evidence* Yes☒ No ☐	**QoE for benefits of screening:** Moderate There are six trials of varying quality; three trials had a lower risk of bias and were used for this recommendation. Two found a positive effect of screening on prostate cancer-specific mortality, while one found no effect. **QoE for harms of screening:** Very Low The proportion of overdiagnosed prostate cancer cases ranges from 40-56% of cases diagnosed. The false positive rate ranges from 11-20% of men screened, depending on	Key reasons for downgrading or upgrading: **QoE for benefits of screening:** Reasons for downgrading: 1 - Serious risk of bias (only two studies provided description of random sequence generation and one described allocation concealment). 2 - Serious inconsistency in effect across studies of prostate cancer-specific mortality (domain not downgraded for all-/other-cause mortality studies). 3: Imprecision of effect estimates (RR), and includes the no effect value of 1. **QoE for harms of screening:** Evidence for harms of screening came from modeling or

	PSA level, and harms related to biopsy range from 1-24% of men who have biopsies, depending on type of harm.	uncontrolled observational studies, which are categorized as very low quality evidence.
Quality of evidence (QoE) for treatment studies *Is there high or moderate quality of evidence* Yes☐ No ☒	**QoE for benefits of treatment:** Very Low to High Prostatectomy: High quality evidence from trials and low quality evidence from observational studies indicate the risk of prostate cancer-specific mortality is reduced following prostatectomy. Trials reported no effect on all-cause mortality, while cohort studies show an effect. Radiation therapy: Low to very low quality evidence from observational studies indicate that the risk of both prostate cancer-specific and all-cause mortality are reduced following treatment with radiation therapy. Hormone therapy: Low quality evidence from observational studies found of an increased risk of prostate cancer-specific mortality following use of hormonal therapy, whereas 4 low quality observational studies found no effect on all-cause mortality. Combination therapy: Low quality evidence from observational studies found combined hormonal and radiation therapies decreased both prostate-specific and all-cause mortality. **QoE for harms of treatment:** Very Low to High Prostatectomy: High quality evidence from two trials and low quality evidence from four observational studies showed an increased risk of urinary incontinence following treatment with prostatectomy. Five low quality observational studies suggest an increased risk of erectile	Key reasons for downgrading or upgrading: **QoE for benefits of treatment:** There were no serious concerns for any domain of the prostatectomy or hormone therapy studies. There was serious inconsistency in the measures of effect of radiation therapy on prostate cancer-specific mortality, thus these observational studies were downgraded to very low quality. The same concerns were not shared for all-cause mortality. **QoE for harms treatment:** Reasons for downgrading the evidence were largely due to concerns over inconsistency across studies, and imprecision in the estimates of effect. Evidence from RCTs on the effect of prostatectomy on erectile and bowel dysfunction were downgraded due to imprecision and inconsistency, while the RCT that measured the effect of radiation therapy on urinary incontinence was downgraded due to imprecision. The evidence for post-surgical harms and mortality following prostatectomy were downgraded due to serious risk of bias.

	dysfunction, but two low quality trials found a null result. Very low and low quality evidence from observational studies and trials did not find an effect of prostatectomy on bowel dysfunction. Very low and low quality observational studies found that quality of life was improved following prostatectomy in 9 of 10 measured domains. Radiation therapy: There is moderate quality evidence from one trial of an increased risk of urinary incontinence following radiation therapy, but evidence from four very low quality observational studies found a null effect. Six low quality observational studies found an increased risk of erectile dysfunction with this treatment, and no effect on bowel dysfunction. There was no effect on quality of life after radiation therapy. Hormone therapy: Evidence from three low quality observational studies indicates increased risk of erectile dysfunction. There was no effect on quality of life after hormone therapy, with the exception of a decreased score on the physical component. Combination therapy: Low quality evidence found that risk of bowel and erectile dysfunction was increased.	
Balance of benefits and harms *Is there certainty that the benefits outweigh the harms?* Yes☐ No ☒	Of the two low risk of bias studies considered for this guideline, one demonstrated a benefit of screening on prostate cancer-specific mortality, while one did not. Further, there is evidence of harms related to screening, including overdiagnosis, false positive test results and major biopsy-related harms. Therefore, there is no certainty that the benefits outweigh the harms. While the evidence suggests that treatment of early stage	Is the baseline risk for benefit similar across subgroups? Yes☐ No☒ Baseline risk varies because of different baseline rates of opportunistic screening across RCTs. Should there be separate recommendations for subgroups based on risk levels? Yes☐ No☒

	or screen-detected prostate cancer with prostatectomy reduces prostate cancer-specific mortality, this treatment carries harms such as urinary incontinence. There is moderate certainty that the prostate cancer mortality benefit from PSA screening through 14 years is at best small in magnitude (13 per 10,000 with ERSPC data) while there is also at least moderate certainty that harms including false positives, biopsy related complications, overdiagnosis and overtreatment are frequent, serious and often persistent. The small benefit in screening was demonstrated in the 55 – 69 year age group, whereas no benefit is reported in under 55 years of age and over 69 years of age.	Click here to enter text. Is the baseline risk for harm similar across subgroups? Yes☐ No☒ Level of overdiagnosis varies by age and frequency of screen, and the false positive rate varies by baseline PSA level. Should there be separate recommendations for subgroups based on harms? Yes☐ No☒
Values and preferences *Is there confidence in the estimate of relative importance of outcomes and patient preferences?* Yes☒ No ☐	Research has shown that many men view screening positively but as many of these men are also unaware of the benefits and potential harms it is difficult to determine what informed preferences would be.	Perspective taken: Patient Source of values and preferences: Relative value of importance of outcomes determined by the guideline panel. Patient preferences were determined by literature review. Source of variability, if any: Some variability in patient preferences for screening Method for determining values satisfactory for this recommendation? Yes☒ No☐ All critical outcomes measured? Yes☒ No☐
Resource implications *Are the resources worth the expected net benefit?* Not Applicable	Cost was not considered in developing this recommendation statement.	

Overall strength of recommendation: **WEAK – 55 – 69 years** **STRONG – under 55 years; 70 years and older**	In the absence of conclusive evidence demonstrating the effectiveness of screening with the PSA test to reduce mortality from prostate cancer, and in view of clear evidence for harm, the CTFPHC does not recommend such screening.
Remarks and values and preference statement	Physicians should discuss the harms and benefits of screening with patients who request screening so that men can make informed screening decisions that are consistent with their values and preferences. Physicians should discuss screening with men aged 55 to 69 years who they believe may place value on a small uncertain benefit of screening and are not concerned with the potential harms, as they may wish to choose screening.

Appendix to: Bell N, Connor Gorber S, Shane A, et al.; Canadian Task Force on Preventive Health Care. Recommendations on screening for prostate cancer with the prostate-specific antigen test. *CMAJ* 2014. DOI:10.1503/cmaj.140703.