Appendix A: The benefits, harms, and cost-effectiveness of age-based and risk-stratified screening for prostate cancer with MRI

Thomas Callender[1], Caroline M Moore[2,3], Elena Frangou[2], Mark Emberton[2,3], Nora Pashayan[1]

[1]Department of Public Health and Primary Care, University of Cambridge, UK

[2]Division of Surgical and Interventional Science, University College London

[3]Department of Urology, University College London Hospitals Trust

[4]MRC Clinical Trials Unit, University College London

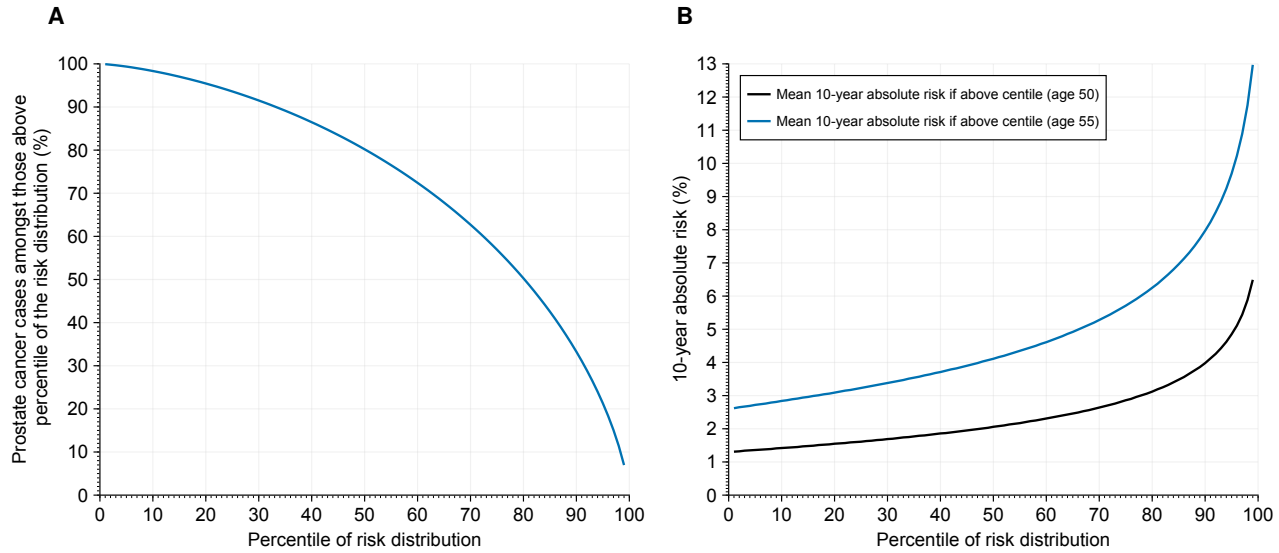
Appendix Contents

Appendix Figures

Appendix Tables

Appendix Methods

Polygenic risk



Appendix Figure A.1: Subfigure A shows the percentage of prostate cancers expected amongst those above each centile of the polygenic risk distribution. For example, 80% of prostate cancers are expected to occur amongst those above the 50th percentile of the risk distribution. Subfigure B shows the mean 10-year absolute risk of prostate cancer by percentile of the risk distribution from the age of 50 (black) and 55 (blue). The average 10-year risk of prostate cancer doubles from 1.3% to 2.6% between the age of 50 and 55, but lifetime risks remain approximately equal at 15%. Correspondingly, a risk-based screening programme from age 55 that uses a 3.5% 10-year absolute risk threshold is screening those from the approximately 35th centile (subfigure B) and so could be expected to include approximately 90% of men who will go on to develop prostate cancer in their lifetime (subfigure A). The same 10-year absolute risk threshold applied to a screening programme starting at age 50 involves screening those men at the approximately 85th centile (subfigure B), and would include 43% of men who will go on to develop prostate cancer in their lifetime (subfigure A).

In Table A.1, we show the proportion of cases and the relative risks of prostate cancer above and below each centile of the polygenic risk distribution. In risk-based screening analyses, we apply the relative risks to incidence rates in relevant cohorts. Age-specific 10-year and lifetime absolute risks of prostate cancer were calculated using Devcan software [1].

Appendix Table A.1: Polygenic risk distribution

Percentile of risk distribution	Proportion above centile (%)	Cases amongst those above centile (%)	RR of PCa diagnosis if above centile	RR of Pca diagnosis if below centile	10-year absolute risk at age 55 if above centile (%)	10-year absolute risk of PCa at age 55 if below centile (%)	Lifetime absolute risk of PCa at age 55 if above centile (%)	Lifetime absolute risk of PCa at age 55 if below centile (%)
1	99	99.93	1.01	0.10	2.62	0.26	15.34	1.54
2	98	99.81	1.02	0.11	2.65	0.30	15.47	1.74
3	97	99.68	1.03	0.13	2.67	0.33	15.61	1.91
4	96	99.53	1.04	0.14	2.69	0.35	15.75	2.06
5	95	99.37	1.05	0.14	2.72	0.38	15.88	2.19
6	94	99.19	1.05	0.15	2.74	0.40	16.02	2.32
7	93	98.99	1.06	0.16	2.76	0.42	16.16	2.44
8	92	98.79	1.07	0.17	2.79	0.44	16.3	2.55
9	91	98.57	1.08	0.18	2.81	0.46	16.44	2.66
10	90	98.34	1.09	0.18	2.84	0.47	16.58	2.77
11	89	98.10	1.1	0.19	2.86	0.49	16.72	2.87
12	88	97.85	1.11	0.20	2.89	0.51	16.87	2.97
13	87	97.59	1.12	0.20	2.91	0.53	17.01	3.07
14	86	97.31	1.13	0.21	2.94	0.54	17.16	3.17
15	85	97.03	1.14	0.21	2.96	0.56	17.31	3.26
16	84	96.73	1.15	0.22	2.99	0.57	17.46	3.36
17	83	96.43	1.16	0.23	3.01	0.59	17.61	3.45
18	82	96.11	1.17	0.23	3.04	0.61	17.76	3.54
19	81	95.79	1.18	0.24	3.06	0.62	17.91	3.63
20	80	95.45	1.19	0.24	3.09	0.64	18.07	3.72
21	79	95.10	1.20	0.25	3.12	0.65	18.23	3.80
22	78	94.75	1.21	0.26	3.15	0.67	18.39	3.89
23	77	94.38	1.22	0.26	3.17	0.68	18.55	3.98
24	76	94.00	1.23	0.27	3.20	0.70	18.72	4.06
25	75	93.61	1.24	0.27	3.23	0.71	18.88	4.15
26	74	93.21	1.25	0.28	3.26	0.72	19.05	4.24
27	73	92.80	1.26	0.28	3.29	0.74	19.22	4.32
28	72	92.38	1.28	0.29	3.32	0.75	19.40	4.41
29	71	91.95	1.29	0.30	3.35	0.77	19.57	4.49
30	70	91.51	1.30	0.30	3.38	0.78	19.75	4.58
31	69	91.06	1.31	0.31	3.41	0.80	19.93	4.66
32	68	90.60	1.32	0.31	3.44	0.81	20.12	4.75
33	67	90.12	1.34	0.32	3.47	0.83	20.30	4.84
34	66	89.63	1.35	0.32	3.51	0.84	20.49	4.92
35	65	89.14	1.36	0.33	3.54	0.86	20.69	5.01
36	64	88.63	1.37	0.34	3.57	0.87	20.88	5.09
37	63	88.11	1.39	0.34	3.61	0.89	21.08	5.18
38	62	87.58	1.40	0.35	3.64	0.90	21.29	5.27
39	61	87.03	1.41	0.35	3.68	0.92	21.49	5.36
40	60	86.47	1.43	0.36	3.71	0.93	21.70	5.44
41	59	85.91	1.44	0.36	3.75	0.95	21.92	5.53
42	58	85.32	1.46	0.37	3.79	0.96	22.14	5.62
43	57	84.73	1.47	0.38	3.82	0.98	22.36	5.71
44	56	84.12	1.49	0.38	3.86	0.99	22.59	5.80
45	55	83.50	1.50	0.39	3.90	1.01	22.82	5.89
46	54	82.87	1.52	0.39	3.94	1.02	23.05	5.98
47	53	82.22	1.53	0.40	3.98	1.04	23.29	6.07
48	52	81.56	1.55	0.41	4.03	1.05	23.54	6.16
49	51	80.88	1.57	0.41	4.07	1.07	23.79	6.26
50	50	80.19	1.58	0.42	4.11	1.09	24.05	6.35
51	49	79.49	1.60	0.42	4.16	1.10	24.31	6.45
52	48	78.77	1.62	0.43	4.20	1.12	24.58	6.54

Continued on the next page

Appendix Table A.1: Polygenic risk distribution, continued

Percentile of risk distribution	Proportion above centile (%)	Cases amongst those above centile (%)	RR of PCa diagnosis if above centile	RR of Pca diagnosis if below centile	10-year absolute risk at age 55 if above centile (%)	10-year absolute risk of PCa at age 55 if below centile (%)	Lifetime absolute risk of PCa at age 55 if above centile (%)	Lifetime absolute risk of PCa at age 55 if below centile (%)
53	47	78.03	1.64	0.44	4.25	1.14	24.85	6.64
54	46	77.28	1.65	0.44	4.30	1.15	25.13	6.74
55	45	76.51	1.67	0.45	4.35	1.17	25.42	6.84
56	44	75.73	1.69	0.46	4.40	1.19	25.72	6.94
57	43	74.93	1.71	0.46	4.45	1.20	26.02	7.04
58	42	74.11	1.73	0.47	4.50	1.22	26.33	7.14
59	41	73.27	1.75	0.48	4.56	1.24	26.65	7.24
60	40	72.41	1.77	0.48	4.61	1.26	26.98	7.35
61	39	71.54	1.80	0.49	4.67	1.28	27.31	7.45
62	38	70.65	1.82	0.50	4.73	1.29	27.66	7.56
63	37	69.73	1.84	0.50	4.79	1.31	28.02	7.67
64	36	68.80	1.87	0.51	4.86	1.33	28.39	7.78
65	35	67.84	1.89	0.52	4.92	1.35	28.77	7.90
66	34	66.86	1.92	0.53	4.99	1.37	29.16	8.01
67	33	65.86	1.94	0.53	5.06	1.39	29.56	8.13
68	32	64.83	1.97	0.54	5.13	1.41	29.98	8.24
69	31	63.78	2.00	0.55	5.20	1.43	30.41	8.37
70	30	62.71	2.03	0.56	5.28	1.45	30.86	8.49
71	29	61.61	2.06	0.57	5.36	1.47	31.33	8.61
72	28	60.48	2.09	0.58	5.44	1.50	31.81	8.74
73	27	59.32	2.13	0.58	5.53	1.52	32.31	8.87
74	26	58.13	2.16	0.59	5.62	1.54	32.84	9.00
75	25	56.91	2.20	0.60	5.71	1.56	33.38	9.14
76	24	55.65	2.23	0.61	5.81	1.59	33.95	9.28
77	23	54.37	2.27	0.62	5.91	1.61	34.55	9.42
78	22	53.04	2.31	0.63	6.02	1.64	35.18	9.57
79	21	51.68	2.36	0.64	6.13	1.66	35.84	9.71
80	20	50.28	2.40	0.65	6.25	1.69	36.53	9.87
81	19	48.83	2.45	0.66	6.37	1.71	37.26	10.03
82	18	47.34	2.50	0.67	6.51	1.74	38.03	10.19
83	17	45.79	2.56	0.68	6.65	1.77	38.85	10.36
84	16	44.20	2.61	0.69	6.80	1.80	39.73	10.53
85	15	42.55	2.68	0.70	6.96	1.83	40.66	10.71
86	14	40.84	2.74	0.72	7.13	1.86	41.66	10.89
87	13	39.06	2.81	0.73	7.31	1.90	42.74	11.08
88	12	37.20	2.89	0.74	7.51	1.93	43.91	11.28
89	11	35.27	2.97	0.76	7.73	1.97	45.18	11.49
90	10	33.25	3.06	0.77	7.97	2.00	46.58	11.71
91	9	31.13	3.17	0.79	8.23	2.04	48.13	11.94
92	8	28.89	3.28	0.80	8.53	2.08	49.85	12.19
93	7	26.52	3.41	0.82	8.86	2.13	51.80	12.44
94	6	24.00	3.56	0.84	9.24	2.18	54.04	12.72
95	5	21.29	3.73	0.86	9.69	2.23	56.65	13.02
96	4	18.35	3.93	0.88	10.23	2.28	59.78	13.34
97	3	15.10	4.19	0.90	10.89	2.34	63.66	13.70
98	2	11.41	4.52	0.93	11.75	2.41	68.72	14.11
99	1	6.97	4.99	0.96	12.97	2.50	75.84	14.59

Polygenic risk distribution given a variance of 0.72. At age 55, the average 10-year risk is 2.6% and the average lifetime risk is 15.2%.

Abbreviations: RR, relative risk. PCa, prostate cancer.

Appendix Table A.2: Model inputs

Parameter	Value (95% CI)	Source
Life table		
Mean sojourn time with MRI screening (years)	9.73 (9.66–9.79)	[a]
Mean sojourn time with PSA screening (years)	13.30 (13.26–13.35)	[a]
Relative reduction in prostate cancer-specific mortality with MRI or PSA screening	0.80 (0.67–0.93)[b]	[2]
Episode sensitivity	59%	[3]
Screening & diagnostic pathway		
PSA screening tests positive (%)	16.8% (16.6%–17.0%)	[4]
Positive PSA test leading to a biopsy (%)	67% (55%–77%)	[5]
MRI screening tests positive (%)	17.6% (14.0%–21.3%)	[6]
Costs, £ GBP		
PSA test	16 (7–28)	[7, 8]
Multiparametric MRI	198 (91–345)	[9]
Screening MRI	129 (60–225)	[9]
Transrectal ultrasound guided biopsy	755 (350–1,317)	[9]
Staging costs	567 (262–987)	[9]
Radical prostatectomy	11,258 (5,196–19,611)	[9]
Radical radiotherapy	7,749 (3,574–13,502)	[7, 8]
Chemotherapy	2,586 (1,194–4,512)	[9–11]
Brachytherapy	2,197 (1,014–3,830)	[7, 8]
Androgen deprivation therapy[c]	804 (371–1,401)	[7, 8]
Active surveillance[c]	6,366 (2,937–11,104)	[8, 12]
End of life costs	11,074 (886–33,546)	[8, 13]

[a] Derivation shown in Table A.3

[b] Time-varying, with a run-in period to reach maximal effect of 10-years and waning after screening ends (see assumptions in Table A.3).

[c] Total cost per cancer diagnosis (i.e. not yearly cost)

Abbreviations: MRI, magnetic resonance imaging; PSA, prostate specific antigen; CI, confidence intervals; GBP, British Pounds Sterling.

Appendix Table A.3: Assumptions

Assumption	Description
Mean sojourn time (MST)	In base case analyses of a screening programme between the ages of 55 and 69 years, our estimates of MST were: • 9.73 (95% CI: 9.66–9.79) years for MRI alone; and, • 13.30 (95% CI: 13.26–13.35) years for PSA. These estimates correspond to the following proportions of screen-detected cancers detected at a clinically significant stage: 34% with PSA [3] and 68% with MRI screening [14]. We used age-specific sojourn times of Gleason 6 (clinically insignificant) cancers and Gleason $\geq$7 (clinically significant) cancers, based on analyses from the Prostate Testing for Cancer and Treatment (ProtecT) study. We calculated MST values for different screening scenarios based on a weighted sum of the proportion of screen-detected cancers diagnosed by stage. In scenario analyses, we explored overall MST values from 7 and 14 years.
Relative mortality reduction with screening	In our base case, we assumed that the relative prostate-cancer-mortality reduction with an MRI-based screening programme could be at least that of a PSA-based programme [2]: 0.80 (95% CI: 0.67–0.93). In our analyses, this is the maximal effect of screening, reached after a run-in period of 10 years and with gradual waning as screening ends, in keeping with ERSPC [2, 4] (see Appendix B Figure B.9 for cumulative mortality with and without screening). Screening is considered to impact cancer-specific mortality by detecting cancers at an earlier stage when their prognosis may be improved. No data exist for an MRI-based screening programme so we used a relative risk estimate for transparency. The relative mortality reduction was varied between 0.7 and 0.9 in scenario analyses. We do not assume that polygenic risk is associated with death from prostate cancer and so do not adjust mortality rates.
Episode sensitivity	As the sensitivity of an MRI-based screening episode is unknown, we assumed that an MRI-based programme could be at least equivalent to a PSA-based programme (with a PSA cut-off of 3ng/ml [3]). We varied episode sensitivity between 20% and 70% in scenario analyses.

Age-specific incidence and mortality data in the absence of screening

We used average 2017–2019 prostate cancer incidence and death data by 5-year age-group for those in England [15]. To translate rates by 5-year age-group into age-specific background rates (in the absence of screening), we fitted polynomial regression models of log rates against the midpoint age in each 5-year age-group. The final models used 3rd degree polynomials for prostate cancer incidence and mortality rates and a 2nd degree polynomial for mortality from other causes (Table A.4).

Cancer incidence with screening

The natural history of prostate cancer involves a progression from an asymptomatic preclinical period to symptomatic clinical detection. The mean time between when a cancer could be detected by screening and when it would naturally progress to symptomatic presentation – is known as the mean sojourn time (MST).

The number of cancers on a prevalent (first) screen depends on the background pre-clinical incidence rate, λ_1, the sensitivity of a screening episode, S, and the pre-clinical screen-detectable period, the MST [16]:

$$\text{Prevalent screen} = \lambda_1 \cdot S \cdot MST \tag{A.1}$$

The incidence rate at subsequent screens can be estimated using the following equation derived by Duffy et al. [17] from Day and Walter [18]:

$$\text{Incident screen} = \frac{pS\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{(\lambda_2 - \lambda_1)(1 - (1 - S)e^{-\lambda_2 t})} \tag{A.2}$$

where screening uptake is denoted by p and the screening interval by t. We use a simplifying assumption for both equations 1 and 2 that λ_1 can be approximated to the background clinical incidence of prostate cancer, I. Under the assumption that the transition hazard between preclinical and clinical disease follows an exponential distribution, the transition from pre-clinical to clinical (symptomatic) disease – the inverse of the MST – is denoted by λ_2.

Interval cancers at time, t, since the last screen depend on the age-specific background incidence of prostate cancer, screening sensitivity and the inverse of the MST (λ_2), and were estimated as [19]:

$$\text{Interval cancers } (t) = I(1 - S) + IS\Big(t + \frac{e^{-\lambda_2 t} - 1}{\lambda_2}\Big) \tag{A.3}$$

Mean sojourn time

Using the age-specific values in Table A.5, we calculated a single age-specific weighted sum MST for each screening round based on the proportion expected to be diagnosed at different Gleason scores with screening. To account for uncertainty in these estimates, we modelled the MST from a Gamma distribution with a variance of 1.

Appendix Table A.4: Mean incidence and mortality rates from prostate cancer and other causes in England 2017–2019

Age	Incidence rate	Mortality rate (prostate cancer)	Mortality rate (other causes)
40	0.000017	0.000001	0.001465
41	0.000026	0.000001	0.001567
42	0.000038	0.000001	0.001678
43	0.000055	0.000002	0.001799
44	0.000079	0.000003	0.001931
45	0.000110	0.000003	0.002074
46	0.000151	0.000005	0.002231
47	0.000205	0.000006	0.002403
48	0.000274	0.000008	0.002590
49	0.000360	0.000010	0.002795
50	0.000466	0.000013	0.003020
51	0.000596	0.000017	0.003266
52	0.000751	0.000022	0.003536
53	0.000933	0.000028	0.003834
54	0.001145	0.000035	0.004160
55	0.001388	0.000044	0.004520
56	0.001662	0.000055	0.004916
57	0.001965	0.000068	0.005352
58	0.002298	0.000084	0.005834
59	0.002657	0.000103	0.006367
60	0.003039	0.000125	0.006956
61	0.003441	0.000152	0.007607
62	0.003856	0.000183	0.008329
63	0.004280	0.000219	0.009130
64	0.004706	0.000262	0.010019
65	0.005129	0.000311	0.011007
66	0.005542	0.000367	0.012105
67	0.005940	0.000433	0.013328
68	0.006316	0.000507	0.014691
69	0.006667	0.000592	0.016211
70	0.006987	0.000689	0.017908
71	0.007274	0.000799	0.019805
72	0.007525	0.000923	0.021928
73	0.007739	0.001063	0.024305
74	0.007914	0.001221	0.026969
75	0.008051	0.001397	0.029959
76	0.008151	0.001595	0.033318
77	0.008215	0.001816	0.037094
78	0.008246	0.002062	0.041344
79	0.008246	0.002337	0.046133
80	0.008219	0.002642	0.051533
81	0.008167	0.002982	0.057630
82	0.008095	0.003359	0.064520
83	0.008005	0.003778	0.072314
84	0.007901	0.004244	0.081140
85	0.007788	0.004761	0.091144
86	0.007667	0.005334	0.102496
87	0.007542	0.005972	0.115390
88	0.007417	0.006680	0.130050
89	0.007294	0.007468	0.146737

Appendix Table A.5: Age-specific mean sojourn time

Age group	Mean Sojourn Time (Gleason 6)	Mean Sojourn Time (Gleason ≥ 7)
50-54	13.88	6.88
55-59	15.68	5.65
60-64	16.53	6.19
65-69	19.9	6.69
70-74	19.9	6.69

Age-specific values by Gleason score from the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) study [22, 23]

PSA-based screening: In the European Randomized Study of Screening for Prostate Cancer (ERSPC) study, 28% of cancers were detected at a clinically significant Gleason grade and 72% would be considered clinically insignificant based on their Gleason score [20]. A PSA-based prostate cancer screening programme implemented today could be expected to use multiparametric MRI prior to biopsy, following current diagnostic protocols, such that the proportion diagnosed at a clinically insignificant stage would be lower than in the ERSPC. Using estimates from the Cochrane review by Drost and colleagues [21], we reduced the proportion of cancers detected at an insignificant stage by 8%. This gave us values of $0.72 - (0.72 \cdot 0.08) = 66\%$ detected at a clinically insignificant and 34% detected at a clinically significant.

MRI-based screening: The proportion who might be diagnosed at a clinically significant or insignificant stage remains uncertain for a screening programme that used a screening MRI as the primary screening test. We used estimates from the Imperial Prostate 1 Prostate Cancer Screening Trial Using Imaging (IP1-PROSTAGRAM) [6] study to anchor our assumptions. IP1-PROSTAGRAM involved an approximately 15 minutes-long non-contrast screening MRI. Amongst those who had a Prostate Imaging-Reporting and Data System (PIRADS)-2.1 score of 3-5, 14 of the 21 cancers detected on biopsy were considered clinically significant (67%, 95% confidence intervals [CI]: 45% to 83%). Restricting a positive scan to those with a PIRADS-2.1 score of 4-5 led to 69% (95% CI: 44% to 86%) being detected at a clinically significant stage. We used a mid-point estimate of 68%.

Life table specification

We used a life-table approach to model screening and no screening strategies. We initially used a population mortality rate, adjusted for the relative impact of screening where appropriate, to determine expected deaths amongst the screened and non-screened cohorts (see equations, algorithms, and code available at `https://github.com/callta/mri-screening-prostate` for more details).

Using a population-based mortality rate allows us to model the population-level efficacy of prostate cancer screening amongst those who receive the intervention. In other words, we can use this to establish the numbers of cancer deaths in the screened arm under different relative mortality reduction with screening. But a population-level mortality rate doesn't allow us to disentangle deaths amongst those whose cancer was screen-detected or not. For a given screening interval and episode sensitivity, different mean sojourn times will mean that a different number of interval cancers could be expected between screening modalities (PSA or MRI). To better account for this, we calculated prostate cancer case hazards for cancers that are screen-detected and not screen detected.

We generated case hazards, taking into account lead time and the impact of different parameter combinations (e.g. mean sojourn time), by dividing the age-specific number of person-years of cancer by the number of prostate cancer deaths. Once we had calibrated this value for non-screen-detected cancers, we subsequently derived the case hazard for those whose cancer was screen-detected.

This allows us to determine the relative reduction in deaths specifically amongst those with a screen-detected cancers that is required to achieve a population-level efficacy (i.e. when considering both screen-detected and interval cancers, where the denominator is correspondingly greater). As an illustration, let us imagine that anyone diagnosed with cancer will die from their cancer and that there are 1,000 deaths from cancer in a cohort over a period of time. Were this cohort to undergo screening, we might expect only 800 deaths from cancer (i.e. a 20% relative reduction). The 200 deaths prevented must occur amongst those with a screen-detected cancer. So, if only 250 cancers were detected by screening, the relative mortality reduction amongst those who have a screen-detected cancer would be 80%.

Overdiagnosis

We derived the age-specific proportion of screen-detected cancers overdiagnosed by screening strategy using the lead time approach [16, 24, 25] (Table A.6) and applied this to the age-specific number of screen-detected cancers. The lead time approach assumes that a cancer would have gone on to be clinically diagnosed if the individual had lived long enough, such that the numbers shown to be overdiagnosed in this analysis can reasonably be considered as a lower estimate.

We present estimates using the lead time approach to set a minimum floor on the percentage of screen-detected cancers likely to be overdiagnosed. This is because, with uptake and compliance set to 100% coupled with strategies where screening is restricted to those at very high risk, overdiagnosis can become negative with the excess incidence approach. In other words, such screening strategies might lead to fewer overdiagnosed than no screening. In theory, it could be possible that a risk-stratified programme restricted to those at very high risk with perfect adherence and uptake might reduce overdiagnosis relative to no screening, as currently ad hoc screening does occur that will inevitably cause overdiagnosis that we are not otherwise accounting for. To calculate overdiagnosis using excess cumulative incidence from our tables, subtract the incident prostate cancers by screening strategy from those that occur with no screening.

Appendix Table A.6: Age-specific percentage of screen-detected cancers overdiagnosed

Age	PSA screen-detected cancers overdiagnosed (%)	MRI screen-detected cancers overdiagnosed (%)
50	10.64	7.11
51	11.39	7.70
52	12.10	8.25
53	12.90	8.87
54	13.72	9.52
55	16.01	9.74
56	16.90	10.38
57	17.97	11.21
58	19.18	12.19
59	20.36	13.14
60	23.14	15.50
61	24.40	16.56
62	25.72	17.67
63	27.09	18.86
64	28.42	19.98
65	35.10	24.92
66	36.67	26.38
67	38.30	27.92
68	39.79	29.30
69	41.44	30.88

Age-specific values by screening modality (PSA or MRI) for base-case analyses averaged over 10,000 simulations. For example, 9.74% of cancers that were detected through screening with MRI at age 55 could be expected to be overdiagnosed. The percentage of screen-detected cancers overdiagnosed varies by the MST. Correspondingly, these values were recalculated in relevant scenario analyses in which the MST was varied.

Utilities

We used age-stratified EQ-5D-5L scores for the general population from the 2018 Health Survey for England [26]. As these were available in five-yearly age groups, we used polynomial regression (with age as a second-degree polynomial) to interpolate yearly values (Appendix Table A.7). We calculated an average utility decrement for those with prostate cancer, considering:

- The age-specific distribution of cancer stage at diagnosis (average 2017-2019 from NHS Digital [27]);
- the proportions receiving active surveillance or radical therapy by stage [28]; and
- the expected median survival based on age at diagnosis [29].

We considered radical therapy and active surveillance to have utility decrements of 0.789 and 0.88, respectively. The utility decrement of active surveillance assumes 55% of those having active surveillance transition to radical therapy, as in the ProtecT study.

The 2024 NHS Cancer Quality of Life Survey provides stage-specific EQ-5D-5L scores of individuals with prostate cancer 18 months after their diagnosis (Appendix Table A.8) [30]. This survey has been completed by approximately 50% of all individuals with a prostate cancer diagnosed in England since autumn 2021.

We assumed that a diagnosis of prostate cancer would only attract a utility decrement relative to background for ten years. Tan and colleagues, using comprehensive data from the UK Clinical Practice Data Link (CPRD), estimated median survival after a prostate cancer diagnosis of 11 years [29]. Unsurprisingly, there were significant differences by age at diagnosis, with median survival of approximately 18 years if diagnosed between the ages of 60-69, 10 years if diagnosed between 70-79, and <5 years if diagnosed from 80 onwards [29].

Appendix Table A.7: Age-specific stage at diagnosis and average utility values

	Stage at diagnosis (%)					
Age	1	2	3	4	Background utility	Utility with prostate cancer
50	0.324	0.398	0.128	0.150	0.825	0.808
51	0.324	0.398	0.128	0.150	0.822	0.805
52	0.324	0.398	0.128	0.150	0.819	0.802
53	0.324	0.398	0.128	0.150	0.816	0.799
54	0.324	0.398	0.128	0.150	0.814	0.797
55	0.303	0.377	0.141	0.179	0.812	0.794
56	0.303	0.377	0.141	0.179	0.811	0.792
57	0.303	0.377	0.141	0.179	0.809	0.791
58	0.303	0.377	0.141	0.179	0.808	0.790
59	0.303	0.377	0.141	0.179	0.808	0.790
60	0.266	0.353	0.164	0.217	0.807	0.787
61	0.266	0.353	0.164	0.217	0.807	0.787
62	0.266	0.353	0.164	0.217	0.806	0.786
63	0.266	0.353	0.164	0.217	0.806	0.786
64	0.266	0.353	0.164	0.217	0.806	0.786
65	0.239	0.343	0.174	0.244	0.806	0.784
66	0.239	0.343	0.174	0.244	0.805	0.784
67	0.239	0.343	0.174	0.244	0.805	0.784
68	0.239	0.343	0.174	0.244	0.805	0.783
69	0.239	0.343	0.174	0.244	0.804	0.783
70	0.187	0.313	0.193	0.307	0.803	0.760
71	0.187	0.313	0.193	0.307	0.802	0.759
72	0.187	0.313	0.193	0.307	0.801	0.758
73	0.187	0.313	0.193	0.307	0.800	0.756
74	0.187	0.313	0.193	0.307	0.798	0.755
75	0.161	0.293	0.195	0.351	0.796	0.749
76	0.161	0.293	0.195	0.351	0.793	0.746
77	0.161	0.293	0.195	0.351	0.790	0.743
78	0.161	0.293	0.195	0.351	0.786	0.740
79	0.161	0.293	0.195	0.351	0.782	0.736
80	0.127	0.235	0.192	0.445	0.778	0.712
81	0.127	0.235	0.192	0.445	0.773	0.707
82	0.127	0.235	0.192	0.445	0.767	0.702
83	0.127	0.235	0.192	0.445	0.760	0.696
84	0.127	0.235	0.192	0.445	0.753	0.689
85	0.124	0.184	0.164	0.528	0.746	0.676
86	0.124	0.184	0.164	0.528	0.737	0.668
87	0.124	0.184	0.164	0.528	0.727	0.660
88	0.124	0.184	0.164	0.528	0.717	0.651
89	0.124	0.184	0.164	0.528	0.706	0.640

Appendix Table A.8: Stage-specific utility values at 18 months from diagnosis

Stage	EQ-5D score	Relative decrement[a]
1	80.45	1
2	80.43	1
3	77.68	0.98
4	69.59	0.88

[a] Decrement relative to average background EQ-5D score from ages 50-89 (0.791) as shown in Appendix Table A.7.
Results are from the NHS England Cancer Quality of Life Survey, March 2024 [30].

Resource use

Assessment of suspected prostate cancers

Non-screened cohort

Based on previous work [12], we used an estimate of 1.88 mpMRI scans required to detect one cancer, using results from the PROMIS trial [31]. We assumed that there were 20% more PSA tests than MRI scans [7]. We estimated that two-thirds of those having an mpMRI would go on to have a biopsy (67%, 95% CI: 55%-77%) [5].

Screened cohorts

PSA-screened: Amongst the PSA-screened cohort, in keeping with the ERSPC, those with a PSA test result of $\geq$3ng/ml were deemed positive. We estimated that 16.8% (16.6%-17.0%) of screening PSA tests would be positive [4]. As PSA testing is the dominant method by which individuals are clinically suspected to have prostate cancer, we assumed that two-thirds (see non-screened above) of those receiving an mpMRI after a positive test would go on to have a biopsy.

MRI screened: In both IP1-PROSTAGRAM [6] and RE-IMAGINE [14], a non-significant but higher proportion of screening tests were positive than in the ERSPC study. In IP1-PROSTAGRAM, 17.6% (14.0%-21.3%) had a positive screening MRI (without concurrent use of PSA testing), whilst in the RE-IMAGINE study, 21.1% (95% CI: 16.5%-25.7%) tested positive with either MRI or PSA density.

Test positivity would be expected to reduce in subsequent rounds of screening as the number of screen-detected cancers reduces after the prevalence screen. However, in the absence of follow-on data from further screening rounds, we have used the prevalence scan estimates from IP1-PROSTAGRAM for further test rounds and vary this value in scenario analyses.

Costing descriptions

We included costs for screening, assessment, diagnosis, treatment, and palliation and death from prostate cancer. Pathways are based on NICE guidelines [32]. Individual resource costs are presented in Appendix Table A.2 and A.9. Given uncertainties in their estimation, we modelled costs using a Gamma distribution where the spread was the central estimate +/- 1/3 and subject them to probabilistic one-way sensitivity analyses. All costs use either 2025/2026 NHS Tariffs or have been inflated to prices as of August 2025.

Appendix Table A.9: Detailed costings

Resource	Description	Cost (£)	Source
PSA test	Cost of phlebotomy and biochemistry	16 (7–28)	[7, 8]
Multiparametric (mp)-MRI	NHS 2025/26 tariff cost (RD03Z)	198 (91–345)	[9]
Screening MRI	The cost of a non-contrast MRI scan on one area is £129 (code RD01A) including reading the scan. This tallies with the cost considered in the PRIME trial for a biparametric MRI [33].	129 (60–225)	[9]
Transrectal ultrasound guided biopsy	NHS 2025/26 tariff code LB76Z for a transrectal ultrasound guided biopsy of the prostate (£491) combined with one urological appointment (code 101 – WF01B first attendance, single professional in a Urology Service, £164). 1.3% (95% CI: 0.8%–2.1%) were estimated to be admitted after a biopsy with sepsis (ProtecT study [34]). The mean cost of a non-elective spell in hospital with sepsis (NHS Tariff Codes WJ06A-J: Sepsis with & without interventions) was rounded to £7,682. Total cost: £491 + £164 + (0.013 × £7682)	755 (350–1,317)	[9]
Staging costs	We considered the following costs for staging a prostate cancer: • Urological appointment £107 Source: NHS 2025/26 tariff, code: 101 • Isotope bone scan £249 including reporting source: NHS 2025/26 tariff, code: RN15A • Urology MDT £211 Source: NHS 2025/26 tariff, code: 101 multi-professional (WF02B) Not all patients will receive a bone scan, and some may have a CT pelvis. We account for this uncertainty probabilistically.	567 (262–987)	[9]

Continued on next page

Appendix Table A.9: Costings (August 2025), continued

Resource	Description	Cost (£)	Source
Radical prostatectomy	Urological appointment £107 Source: NHS 2025/26 tariff, code: 101 In 2019, the most recent (pre-COVID) year for which the National Prostate Cancer Audit has reported, 89% of prostatectomies were robotic, 6% laproscopic, and 5% open. The guide prices for these are £9,186, £8,277, and £8,804 (codes LB69Z, LB22Z and mean of £11,131 and £6,476 for LB21A/B). In addition, 14% were re-admitted as an emergency within 90-days of radical prostatectomy. We have not estimated the impact of complications such as incontinence directly.	11,258 (5,196–19,611)	[9]
Radical radiotherapy	Appointment with a clinical oncologist, preparation for IMRT, its delivery and adverse effects. From Callender et al. 2019 [7] with uplift for inflation.	7,749 (3,574–13,502)	[7, 8]
Chemotherapy	Assumptions follow NICE resource impact assessment: • First (£322) outpatient and one follow-up appointment (£150) with a clinical oncologist (code 800 of NHS tariff 2025/26). • Cost of delivery of simple parenteral chemotherapy at the first attendance (£182) (SB12Z), followed by the cost of subsequent rounds of chemotherapy (SB15Z) (£265). • Up to 10 cycles of docetaxel are recommended, however an average of 6 has been used based on the NICE guideline resource impact report. • Docetaxel costs £17.88 for 160mg/8ml solution, so average cost of 17.88 $\times$ 6 = £107.28	2,586 (1,194–4,512)	[9–11]
Brachytherapy	Sourced from Callender et al. 2019, inflated to 2025 costs.	2,197 (1,014–3,830)	[7, 8]

Continued on next page

Appendix Table A.9: Costings (August 2025), continued

Resource	Description	Cost (£)	Source
Androgen deprivation therapy	Sourced from Callender et al. 2019, inflated to 2025 costs.	804 (371–1,401)	[7, 8]
Active surveillance	Sourced from Callender et al. 2021, inflated to 2025 costs.	6,366 (2937–11,104)	[8, 12]
End of life costs	Sourced from Round and colleagues, inflated to 2025 values	11,074 (886–33,546)	[8, 13]

References

1. National Cancer Institute. *DevCan: Probability of Developing or Dying of Cancer Software* version 6.7.9. 2021. https://surveillance.cancer.gov/devcan/.
2. Roobol, M. J. *et al.* European Study of Prostate Cancer Screening — 23-Year Follow-up. *New England Journal of Medicine* **393,** 1669–1680. https://www.nejm.org/doi/full/10.1056/NEJMoa2503223 (2025).
3. Holmström, B. *et al.* Prostate Specific Antigen for Early Detection of Prostate Cancer: Longitudinal Study. *BMJ* **339,** b3537. http://dx.doi.org/10.1136/bmj.b3537 (2009).
4. Hugosson, J. *et al.* A 16-Yr Follow-up of the European Randomized Study of Screening for Prostate Cancer. *Eur. Urol.,* 1–9. http://dx.doi.org/10.1016/j.eururo.2019.02.009 (2019).
5. Elwenspoek, M. M. C. *et al.* Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy With Systematic Biopsy Alone for the Diagnosis of Prostate Cancer. *JAMA Network Open* **2,** e198427. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2747475 (2019).
6. Eldred-Evans, D. *et al.* Population-Based Prostate Cancer Screening With Magnetic Resonance Imaging or Ultrasonography: The IP1-PROSTAGRAM Study. *JAMA Oncol* **7,** 395–402. http://dx.doi.org/10.1001/jamaoncol.2020.7456 (2021).
7. Callender, T. *et al.* Polygenic Risk-Tailored Screening for Prostate Cancer: A Benefit–Harm and Cost-Effectiveness Modelling Study. *PLoS Med.* **16,** e1002998. https://dx.plos.org/10.1371/journal.pmed.1002998 (2019).
8. Office for National Statistics. *CPI Index 06.3: Hospital Services* https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7fc/mm23.
9. NHS England. *2025/26 NHS Payment Scheme* https://www.england.nhs.uk/publication/2025-26-nhs-payment-scheme/ (2025).
10. NICE. *Resource Impact Report: Prostate Cancer: Diagnosis and Management (Update) (NG131)* research rep. (2019). https://www.nice.org.uk/guidance/ng131/resources/resource-impact-report-pdf-6779259325.
11. *Drugs and Pharmaceutical Electronic Market Information Tool (eMIT)* {UK Department of Health and Social Care}. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (2024).
12. Callender, T., Emberton, M., Morris, S., Pharoah, P. D. P. & Pashayan, N. Benefit, Harm, and Cost-effectiveness Associated With Magnetic Resonance Imaging Before Biopsy in Age-based and Risk-stratified Screening for Prostate Cancer. *JAMA Netw Open* **4,** e2037657. http://dx.doi.org/10.1001/jamanetworkopen.2020.37657 (2021).
13. Round, J., Jones, L. & Morris, S. Estimating the Cost of Caring for People with Cancer at the End of Life: A Modelling Study. *Palliat. Med.* **29,** 899–907. http://dx.doi.org/10.1177/0269216315595203 (2015).

14. Moore, C. M. *et al.* Prevalence of MRI Lesions in Men Responding to a GP-led Invitation for a Prostate Health Check: A Prospective Cohort Study. *BMJ Oncology* **2.** https://bmjoncology.bmj.com/content/2/1/e000057 (2023).

15. Office for National Statistics. *Mortality Statistics - Underlying Cause, Sex, and Age 2017-2019* https://www.nomisweb.co.uk/ (2023).

16. Pashayan, N. *et al.* Mean Sojourn Time, Overdiagnosis, and Reduction in Advanced Stage Prostate Cancer Due to Screening with PSA: Implications of Sojourn Time on Screening. *Br. J. Cancer* **100,** 1198–1204. http://dx.doi.org/10.1038/sj.bjc.6604973 (2009).

17. Duffy, S. W., Hudson, S., Vulkan, D., Duffy, T. E. & Binysh, K. Recovery of the Breast Screening Programme Following Pandemic-Related Delays: Should We Focus on Round Length or Uptake? *J. Med. Screen.,* 9691413211066476. http://dx.doi.org/10.1177/09691413211066476 (2022).

18. Day, N. E. & Walter, S. D. Simplified Models of Screening for Chronic Disease: Estimation Procedures from Mass Screening Programmes. *Biometrics* **40,** 1. https://www.jstor.org/stable/2530739?origin=crossref (1984).

19. Pashayan, N. *et al.* Reducing Overdiagnosis by Polygenic Risk-Stratified Screening: Findings from the Finnish Section of the ERSPC. *Br. J. Cancer* **113,** 1086–1093. http://dx.doi.org/10.1038/bjc.2015.289 (2015).

20. Schröder, F. H. *et al.* Screening and Prostate-Cancer Mortality in a Randomized European Study. *N. Engl. J. Med.* **360,** 1320–1328. http://dx.doi.org/10.1056/NEJMoa0810084 (2009).

21. Drost, F.-J. H. *et al.* Prostate MRI, with or without MRI-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer. *Cochrane Database Syst. Rev.* **18,** e728–e729. http://doi.wiley.com/10.1002/14651858.CD012663.pub2 (2019).

22. Martin, R. M. *et al.* Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial. *JAMA* **331,** 1460–1470. https://jamanetwork.com/journals/jama/fullarticle/2817322 (2024) (2024).

23. McHugh, J. K. *et al.* Assessment of a Polygenic Risk Score in Screening for Prostate Cancer. *New England Journal of Medicine* **392,** 1406–1417. https://www.nejm.org/doi/full/10.1056/NEJMoa2407934 (2025) (2025).

24. Ripping, T. M., Ten Haaf, K., Verbeek, A. L. M., van Ravesteyn, N. T. & Broeders, M. J. M. Quantifying Overdiagnosis in Cancer Screening: A Systematic Review to Evaluate the Methodology. *J. Natl. Cancer Inst.* **109.** http://dx.doi.org/10.1093/jnci/djx060 (2017).

25. Paci, E., Warwick, J., Falini, P. & Duffy, S. W. Overdiagnosis in Screening: Is the Increase in Breast Cancer Incidence Rates a Cause for Concern? *J. Med. Screen.* **11,** 23–27. http://dx.doi.org/10.1177/096914130301100106 (2004).

26. McNamara, S., Schneider, P. P., Love-Koh, J., Doran, T. & Gutacker, N. Quality-Adjusted Life Expectancy Norms for the English Population. *Value Health* **26,** 163–169. https://pubmed.ncbi.nlm.nih.gov/35965226/ (2023).

27. *Cancer Registration Statistics, England 2020* NHS England Digital. https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2020 (2024).

28. Gnanapragasam, V. J. *et al.* Improving Clinical Risk Stratification at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. *PLoS Med.* **13,** e1002063. http://dx.doi.org/10.1371/journal.pmed.1002063 (2016).

29. Tan, E. H. *et al.* Incidence, Prevalence, and Survival of Prostate Cancer in the UK. *JAMA Netw. Open* **7,** e2434622. https://jamanetwork.com/journals/jamanetworkopen/articlepdf/2823751/tan_2024_oi_241026_1725981924.90632.pdf (2024) (2024).

30. NHS England. *Cancer Quality of Life Survey* https://www.cancerqol.england.nhs.uk/index.html (2024).

31. Ahmed, H. U. *et al.* Diagnostic Accuracy of Multi-Parametric MRI and TRUS Biopsy in Prostate Cancer (PROMIS): A Paired Validating Confirmatory Study. *Lancet* **389,** 815–822. http://dx.doi.org/10.1016/S0140-6736(16)32401-1 (2017).

32. NICE. *Prostate Cancer Diagnosis and Treatment. Clinical Guideline CG175* research rep. (National Institute of Health and Care Excellence, London, U.K., 2019).

33. Ng, A. B. *et al.* Biparametric vs Multiparametric MRI for Prostate Cancer Diagnosis: The PRIME Diagnostic Clinical Trial. *JAMA*. https://doi.org/10.1001/jama.2025.13722 (2025).

34. Rosario, D. J. *et al.* Short Term Outcomes of Prostate Biopsy in Men Tested for Cancer by Prostate Specific Antigen: Prospective Evaluation within ProtecT Study. *BMJ* **344,** d7894–d7894. http://www.bmj.com/cgi/doi/10.1136/bmj.d7894 (jan09 1 2012).