

Utility of polygenic risk scores in UK cancer screening: a modelling analysis



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Summary

Background It is proposed that, through restriction to individuals delineated as high risk, polygenic risk scores (PRSs) might enable more efficient targeting of existing cancer screening programmes and enable extension into new age ranges and disease types. To address this proposition, we present an overview of the performance of PRS tools (ie, models and sets of single nucleotide polymorphisms) alongside harms and benefits of PRS-stratified cancer screening for eight example cancers (breast, prostate, colorectal, pancreas, ovary, kidney, lung, and testicular cancer).

Methods For this modelling analysis, we used age-stratified cancer incidences for the UK population from the National Cancer Registration Dataset (2016–18) and published estimates of the area under the receiver operating characteristic curve for current, future, and optimised PRS for each of the eight cancer types. For each of five PRS-defined high-risk quintiles (ie, the top 50%, 20%, 10%, 5%, and 1%) and according to each of the three PRS tools (ie, current, future, and optimised) for the eight cancers, we calculated the relative proportion of cancers arising, the odds ratios of a cancer arising compared with the UK population average, and the lifetime cancer risk. We examined maximal attainable rates of cancer detection by age stratum from combining PRS-based stratification with cancer screening tools and modelled the maximal impact on cancer-specific survival of hypothetical new UK programmes of PRS-stratified screening.

Findings The PRS-defined high-risk quintile (20%) of the population was estimated to capture 37% of breast cancer cases, 46% of prostate cancer cases, 34% of colorectal cancer cases, 29% of pancreatic cancer cases, 26% of ovarian cancer cases, 22% of renal cancer cases, 26% of lung cancer cases, and 47% of testicular cancer cases. Extending UK screening programmes to a PRS-defined high-risk quintile including people aged 40–49 years for breast cancer, 50–59 years for colorectal cancer, and 60–69 years for prostate cancer has the potential to avert, respectively, a maximum of 102, 188, and 158 deaths annually. Unstratified screening of the full population aged 48–49 years for breast cancer, 58–59 years for colorectal cancer, and 68–69 years for prostate cancer would use equivalent resources and avert, respectively, an estimated maximum of 80, 155, and 95 deaths annually. These maximal modelled numbers will be substantially attenuated by incomplete population uptake of PRS profiling and cancer screening, interval cancers, non-European ancestry, and other factors.

Interpretation Under favourable assumptions, our modelling suggests modest potential efficiency gain in cancer case detection and deaths averted for hypothetical new PRS-stratified screening programmes for breast, prostate, and colorectal cancer. Restriction of screening to high-risk quintiles means many or most incident cancers will arise in those assigned as being low-risk. To quantify real-world clinical impact, costs, and harms, UK-specific cluster-randomised trials are required.

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Introduction

There is a renewed focus on improving cancer control through screening and early diagnosis, following recognition of the challenges of effective treatment of advanced cancers. The UK National Health Service (NHS) Long Term Plan has set a target that, by 2028, more than 75% of cancers in the UK should be diagnosed early (ie, during stage 1 or 2), a 21 percentage point improvement on the current state of 54%.¹ The efficacy of cancer screening is predicated on multiple factors, including disease incidence, natural history, and harms

from overdiagnosis.² Most high-income countries, including the UK, offer population screening for breast, cervical, and colorectal cancer, albeit with substantial variation in the age ranges to which screening is offered, the type of screening, and its frequency.

Genome-wide association studies (GWASs) have identified associations between common genetic variants (mainly single nucleotide polymorphisms [SNPs]) and the risk of developing different types of cancer. Panels of these SNPs have been developed to produce polygenic risk scores (PRSs) in the hope of applying them in

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Research in context

Evidence before this study

We searched PubMed from database inception to Oct 1, 2022, for articles published in English on the predictive performance of polygenic risk score (PRS) tools for cancer and their application in UK screening using the search terms (“PRS” OR “PGS” OR “polygenic score” OR “polygenic risk score”) AND (“cancer” OR “malignancy”) AND (“screening”) AND (“UK” OR “United Kingdom” OR “England”). There is an extensive literature presenting different PRS tools (models) constructed from sets of associated single nucleotide polymorphisms (SNPs) for various cancers using different mathematical approaches. The performance of these PRS tools is typically quantified by their predictive accuracy for 5-year or 10-year cancer incidence in research cohorts, usually combined with the predictive contribution of age, family history, and other physiological, lifestyle, and investigational data available for the cohort. Multiple proposed PRS-stratified screening scenarios have also been modelled, largely applying multimodal PRS tools derived from and validated on longitudinal epidemiological cohorts. Most analyses focus on a single type of cancer. The public health impact of PRS stratification is often presented as the proportion of individuals predicted to be shifted up and down between hypothetical risk categories, sometimes also quantifying the number of additional cancers detected. PRS modelling analyses often allude to but do not quantify the potential for future PRS performance improvement. No modelling analyses were identified that estimated the annual UK impact of PRS-stratified cancer screening as absolute numbers of cancer cases detected and deaths averted.

Added value of this study

In this study, we modelled the application of PRS stratification using UK metrics to quantify potential absolute annual numbers of additional cancers detected and deaths averted, systematically presenting relevant data across eight cancer types for a range of clinically relevant age strata. We also considered the UK-specific public health burden, presenting reference age-stratified population sizes, and modelled the annual volumes of screening and confirmatory tests, and overdiagnosed cancers,

for various scenarios. We first conducted our modelling analyses for PRS tools based on current SNP sets and also present analyses for projected (future) PRS tools achievable from hypothetical, larger genome-wide association studies (GWASs). We explored the specific clinical implementation scenarios for PRS stratification that we believe to be most logistically credible for the UK—namely, screening of new predefined age groups restricted to a PRS-defined subgroup. We modelled screening for breast cancer (in women aged 40–49 years), colorectal cancer (in people aged 50–59 years), and prostate cancer (in men aged 60–69 years). We applied a number of favourable assumptions, so as to provide credible maximal estimates for current and future impact of PRS-stratified UK cancer screening.

Implications of all the available evidence

PRS stratification enables the delineation of a PRS-defined high-risk population quantile modestly enriched for cancer incidence, presenting an opportunity to improve the efficiency of screening. For the plausible use cases of breast, prostate, and colorectal cancer, the potential absolute impact on annual deaths averted will be modestly improved compared with applying the equivalent screening resource on the basis of age alone. If the modelled benefits of PRS stratification are deemed to justify the logistical costs and other limitations of PRS stratification (ancestry bias in particular), then independent, individual-level randomised and cluster-randomised UK trials must be conducted, powered for all-cause mortality or legitimate surrogates. This will provide an opportunity to evaluate issues such as inequity of uptake, unintended behavioural consequences, and public comprehension of complex risk data. Larger GWASs than those already done will improve PRS predictions modestly; predictiveness is inherently constrained by the low heritability of most common late-onset cancers. For rare cancers, the absolute numbers of cancer in the PRS-defined high-risk quantiles remain too modest for screening to be plausible. PRS stratification does nothing to improve the performance of cancer-screening tools that are flawed in regard of overdiagnosis, lead-time bias, or impact on cancer survival.

individualised risk estimation. It is proposed that such risk estimation could enable the streamlining of existing population screening programmes, the extension of screening programmes to those at high polygenic risk in younger age groups, and increase the feasibility of previously rejected screening frameworks (eg, prostate-specific antigen [PSA] screening for prostate cancer).^{3,4}

To address this proposition, we present an overview of the performance of PRS tools (ie, models and SNP sets) for eight example cancers.

Methods

Study design

For this modelling analysis, we used published estimates of the area under the receiver operating characteristic

curve (AUC) to assess current, future, and optimised PRSs for each of eight cancer types: breast, prostate, colorectum, pancreas, ovary, kidney, lung, and testis. For each of five PRS-defined high-risk quantiles (ie, the top 50%, 20%, 10%, 5%, and 1%) and according to each of the three PRS tools (ie, current, future, and optimised) for eight cancers, we calculated the relative proportion of cancers arising, the odds ratios (ORs) of a cancer arising compared with the population average (middle 20%), and the lifetime cancer risk. We used UK age-stratified data for cancer incidence and integrated the sensitivity and specificity of real-world screening tools to model cancer detection rates for the five PRS-defined quantiles. We modelled the impact of three hypothetical new UK programmes of screening: introduction of prostate

cancer screening for men aged 60–69 years and extension of current national screening programmes for breast cancer to women aged 40–49 years and for colorectal cancer to people aged 50–59 years. In each case, we compared deaths averted by screening the PRS-defined high-risk quintile (20%) with deaths averted by screening the oldest quintile, a randomly selected 20% of the screening population and the full 10-year age group. We considered capacity requirements for screening every year and every 2 years. Additional explanatory details regarding PRS and measures of cancer screening are in the appendix (pp 3–5).

Data sources, assumptions, and the full methods are shown in figure 1 and the appendix (pp 6–12).

Data sources

For each of the eight cancer types, we used the PRS tools presented by Fritsche and colleagues,⁵ which are based on SNP sets assembled from the literature and GWAS databases, for which up to seven PRS methods had been compared using the UK Biobank to select the method producing the best AUC (referred to as current PRS). We used the estimates from Zhang and colleagues⁶ for each of the eight cancer types for AUCs from a hypothetical GWAS with a sample size four times larger than the largest meta-analysis to date (referred to as future PRS) and for AUCs for all common genetic variation underlying disease heritability (referred to as optimised PRS).

Cancer incidence (2016–18), cancer-specific and age-specific 10-year survival rates (2008–17), and routes to diagnosis by tumour type, age, and stage (2018) were provided by the National Cancer Registration and Analysis Service, using data from the National Cancer Registration dataset. Data on the age structure of the UK population

(2016–18) were obtained from the Office for National Statistics Analysis population estimates tool. Metrics for the sensitivity and specificity of currently used, real-world screening tools for each cancer were obtained from published data from national population screening programmes or trials and, where available, meta-analyses (appendix p 13).^{7–14}

Statistical analysis

We calculated the cancer ORs and proportion of cases arising per PRS-defined quantile using methods described by Wald and colleagues¹⁵ and Hingorani and colleagues.¹⁶ Lifetime risks for each cancer were estimated using the current probability method with a period approach to account for competing risks.¹⁷ To estimate deaths averted, we took the additional numbers predicted to be detected by screening for each hypothetical scenario, to which we proportionately reassigned cancers presenting by other routes. We then recalculated the relevant stage distributions and calculated age-specific, stage-specific 10-year net (cancer-specific) survival for the new revised stage distributions. Analyses were done using R version 3.6.1 and Excel statistical functions.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Analyses of PRS-based stratified screening are presented for eight cancers, examining current, future, and optimised PRS tools in each case. Analyses assumed full population uptake for both PRS profiling and subsequent cancer

See Online for appendix

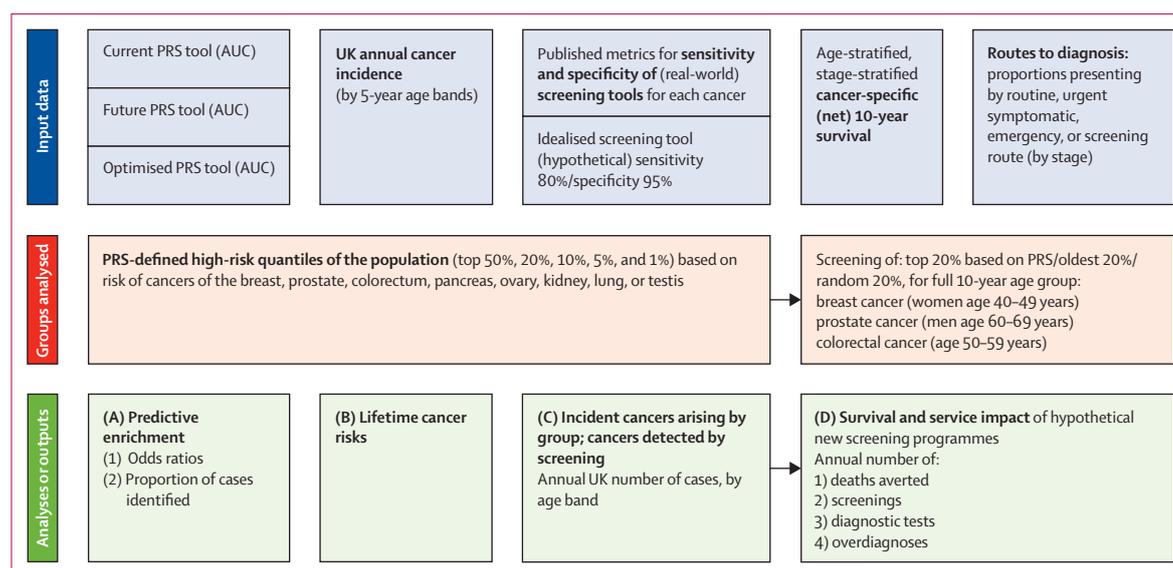


Figure 1: Overview of analyses, data sources, and screening scenarios

AUC=area under the receiver operating characteristic curve. PRS=polygenic risk score.

screening. Analyses are also simplified by the favourable assumption that all cancers that are expected to occur within the screening interval are present at the time of screening (ie, regardless of screening periodicity, there are no interval cancers).

Restriction to progressively smaller, high-risk quantiles (eg, top PRS-defined 20%, 10%, or 1%) increased the enrichment for cancer (ie, OR for cancer compared with the population average; table 1; appendix p 14). However, restriction to a smaller high-risk quantile also increased the absolute numbers of cancers missed within the corresponding PRS-defined low-risk group. This so-called enrichment trade-off is well illustrated for breast cancer: individuals in the PRS-defined high-risk quintile (20%) had an OR for breast cancer of 2.13 compared with the average woman, and this group is estimated to capture 37% of the breast cancers (thus excluding 63%). The PRS-defined high-risk half (50%), as a group, had an estimated OR for risk of breast cancer of 1.59 compared with the average woman. However, restriction of screening to this group would capture almost 70% of cancers, thus excluding 30%. The current PRS for breast cancer had an AUC of 0.64; for the future PRS (AUC=0.69), the PRS-defined high-risk 50% was estimated to capture 76% of breast cancers.

For women, the population lifetime risk of breast cancer was 14.3%; for the PRS-defined top risk quintile, the lifetime risk of breast cancer was estimated to be 25.3% (table 1; appendix p 15). For those in the PRS-defined top 1% of risk, which was estimated to capture 4% of cancers (appendix p 15), the lifetime risk was estimated to be 43.4%, a risk level at which risk-reducing mastectomy might be considered. For less common cancers, such as pancreatic, renal, and ovarian cancers, the absolute lifetime risk in the PRS-defined high-risk groups, although elevated, was still modest. Prophylactic salpingo-oophorectomy is offered to individuals at more than 5% lifetime risk of ovarian cancer—for example, women with germline mutations in *BRCA1* (lifetime ovarian cancer risk 41%).¹⁸ However, compared with a population lifetime risk of 2.1%, the estimated lifetime risk of ovarian cancer in the PRS-defined high-risk quintile of the female population was only 2.7% and in the top 1% was only 3.5% (table 1; appendix p 15).

Screening programmes are typically offered to a pre-specified age group, selected to balance cancer incidence and potential gain in life years. In table 2 and the appendix (pp 16–21), we present cancer incidence for the top 50%, 20%, 10%, 5%, and 1% of the population by PRS-defined risk for the eight cancers in relevant age

	PRS AUC	Odds ratio for cancer for PRS-defined high-risk quantile (vs population average)		Percentage of cancers captured within the PRS-defined high-risk quantile		Percentage lifetime cancer risk in PRS-defined high-risk quantile		
		Top 50%	Top 20%	Top 50%	Top 20%	Population average	Top 50%	Top 20%
Current PRS								
Breast (women)	0.64	1.59	2.13	70%	37%	14.3%	19.5%	25.3%
Prostate (men)	0.70	2.01	2.99	77%	46%	15.2%	22.6%	32.0%
Colorectum (all)	0.62	1.45	1.84	66%	34%	6.7%	8.9%	11.2%
Pancreas (all)	0.58	1.27	1.50	61%	29%	1.7%	2.1%	2.5%
Ovary (women)	0.56	1.19	1.34	58%	26%	2.1%	2.4%	2.7%
Kidney (all)	0.52	1.05	1.09	52%	22%	2.0%	2.1%	2.2%
Lung (all)	0.55	1.17	1.30	57%	26%	7.7%	8.9%	9.9%
Testis (men)	0.70	2.05	3.07	77%	47%	0.5%	0.8%	1.3%
Future PRS								
Breast (women)	0.69	1.91	2.79	76%	44%	14.3%	20.9%	29.3%
Prostate (men)	0.72	2.16	3.32	79%	48%	15.2%	23.1%	33.5%
Colorectum (all)	0.64	1.58	2.10	70%	37%	6.7%	9.3%	12.2%
Pancreas (all)	0.65	1.64	2.22	71%	38%	1.7%	2.4%	3.3%
Ovary (women)	0.61	1.43	1.81	66%	33%	2.1%	2.8%	3.5%
Kidney (all)	0.65	1.60	2.15	70%	38%	2.0%	2.8%	3.8%
Lung (all)	0.61	1.41	1.76	65%	33%	7.7%	10.1%	12.5%
Testis (men)	0.84	4.76	9.20	92%	71%	0.5%	1.0%	1.9%

AUC for current PRS is as estimated by Fritsche and colleagues⁵ (PRS as per amalgamation of published single nucleotide polymorphism associations). AUC for future PRS is as estimated by Zhang and colleagues⁶ (PRS projected for GWAS with sample size four times larger than the largest meta-analysis to date). Additional measures are shown in the appendix (pp 14–15). AUC=area under the receiver operator characteristic curve. GWAS=genome-wide association study. PRS=polygenic risk score.

Table 1: Characteristics of current and future PRS tools for eight cancers

bands, along with the numbers of cancers that would be detected for each group using currently used (ie, real-world) cancer-specific screening tools (albeit using thresholds or methods with performance superior to those routinely deployed in NHS screening programmes). For example, of the 55 545 annual cases of breast cancer in women, 26 320 (47%) arise in women aged 50–69 years, to whom national screening is currently offered in the UK. If screening were restricted to the PRS-defined high-risk quintile, 9823 (37%) of 26 320 breast cancers would be detected in the high-risk group. Thus, given a sensitivity of 70% for digital mammography, the overall detection rate for the age group would be 6876 (26%) of 26 320 cases. If screening were restricted to the PRS-defined top 50%, 12 858 (70%) of 18 368 cancers in this group would be detected on screening. 7952 (30%) of

26 320 cancers would occur in those excluded from screening due to being defined as low-risk. We also illustrate the impact of screening delivered via a hypothetical idealised cancer screening tool (providing a sensitivity of 80% for 95% specificity) in the appendix (pp 22–27).

To illustrate PRS-stratified screening in a lower-frequency cancer type, we considered PRS-stratified pancreatic screening initiated in individuals aged 60–74 years, among whom 4100 (39%) of 10 452 annual pancreatic cancer cases arise (table 3). Using a current PRS, 1180 (29%) of 4100 cancers are predicted to arise in the PRS-defined high-risk quintile, increasing to 1572 (38%) using a future PRS. Considering an idealised screening tool of 80% sensitivity, 944 (80%) of 1180 cases would be detected (increasing to 1257 [80%] of 1572 with

	Population size	Cancers arising per year	Top 20% of PRS					Top 50% of PRS				
			Number requiring screening in high-risk group	Cancers in high-risk group	Missed cancers in unscreened low-risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Number requiring screening in high-risk group	Cancers in high-risk group	Missed cancers in unscreened low-risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group
Breast cancer												
Total aged 40–49 years	4 369 703	7 533	873 941	2 811	4 722	843	1 968	2 184 851	5 257	2 276	1 577	3 680
Total aged 50–69 years*	8 126 689	26 320	1 625 338	9 823	16 497	2 947	6 876	4 063 345	18 368	7 952	5 510	12 858
Prostate cancer												
Total aged 50–59 years	4 355 391	5 897	871 078	2 704	3 193	1 839	865	2 177 696	4 538	1 359	3 086	1 452
Total aged 60–69 years	3 461 821	16 853	692 364	7 728	9 125	5 255	2 473	1 730 911	12 970	3 883	8 820	4 150
Colorectal cancer												
Total aged 50–59 years	8 839 717	5 052	1 767 943	1 702	3 350	511	1 192	4 419 858	3 350	1 702	1 005	2 345
Total aged 60–74 years*	10 175 760	16 621	2 035 152	5 601	11 020	1 680	3 921	5 087 880	11 021	5 600	3 306	7 715

Screening methods are digital mammography (sensitivity 70%) for breast cancer, prostate-specific antigen (3 ng/mL; sensitivity 32%) for prostate cancer, and faecal immunochemical test (20–50 µg/g; sensitivity 70%) for colorectal cancer. Numbers of cancers are annual for the UK (population around 66 million). PRS=polygenic risk scores. * Age ranges currently included for national screening in the UK; the rest are age groups for which we present hypothetical PRS-based risk-stratified screening projections.

Table 2: Modelling of PRS-based risk-stratified screening for breast, prostate, and colorectal cancer, applying current PRS to define a high-risk quantile (top 20% and top 50%)

	Population size	Cancers arising per year	Number in high-risk quintile of population	Current PRS				Future PRS			
				Missed cancers in unscreened low-risk group	Cancers in high-risk group	Cancers missed on screening in high-risk group*	Cancers detected on screening in high-risk group	Missed cancers in unscreened low-risk group	Cancers in high-risk group	Cancers missed on screening in high-risk group*	Cancers detected on screening in high-risk group
Total aged 50–59 years	8 839 717	1075	1 767 943	766	309	62	248	663	412	82	330
Total aged 60–74 years	10 175 760	4100	2 035 152	2 920	1 180	236	944	2 528	1 572	314	1 257
All ages	66 041 278	10 452

A high-risk quintile (20%) is defined for two age ranges using current and future PRS tools (the future PRS tool is based on a genome-wide association study with a sample around four times larger than that of the largest meta-analysis to date). An idealised screening tool is modelled, which has a sensitivity of 80%. Numbers of cancers are annual for the UK (population around 66 million). PRS=polygenic risk scores. *Assuming screening sensitivity of 80%.

Table 3: Modelling of PRS-based risk-stratified screening for pancreatic cancer (with idealised screening tool)

	Breast cancer	Prostate cancer	Colorectal cancer
Population metrics and parameter estimates			
Age range	40–49 years	60–69 years	50–59 years
Population size	4 369 703	3 461 821	8 839 717
Cancers arising annually	7533	16 853	5052
Annual cancer-specific deaths	694	1262	1715
Overdiagnosis rate (proportion of screen-detected cancers)	11%	42%	3·8%
Screening tool (sensitivity/specificity)	Digital mammography (70%/92%)	Prostate-specific antigen: cutoff 3 ng/mL (32%/85%)	Faecal immunochemical test: cutoff 20–50 µg/g (70%/95%)
Overdiagnosed cancers per one death averted	2·4	11·3	0·25
PRS-defined high-risk quintile (20%)			
Size of screened group	873 941	692 364	1 767 943
Cancers arising outside of screened group	4722	9125	3350
Cancers arising in screened group	2811	7728	1702
Cancers detected in screened group	1968	2473	1192
Cancers missed in screened group	843	5255	511
Screening tests required per year			
Screening once a year	873 941	692 364	1 767 943
Screening once every 2 years	436 970	346 182	883 971
Confirmatory (diagnostic) tests required per year			
Screening once a year	71 658	105 168	89 504
Screening once every 2 years	35 829	52 584	44 752
Additional cancers (overdiagnoses)	243	1791	47
Deaths averted	102	158	188
Overall reduction in deaths	14·7%	12·5%	11·0%
Overall improvement in survival	1·4%	0·9%	3·7%
Individuals screened for 10 years per one death averted	854	439	940
Oldest quintile (20%)			
Size of screened group	937 850	702 786	1 596 060
Cancers arising outside of screened group	5335	12 185	3649
Cancers arising in screened group	2198	4668	1403
Cancers detected in screened group	1538	1494	982
Cancers missed in screened group	659	3174	421
Screening tests required per year			
Screening once a year	937 850	702 786	1 596 060
Screening once every 2 years	468 925	351 393	798 030
Confirmatory (diagnostic) tests required per year			
Screening once a year	76 390	106 212	80 716
Screening once every 2 years	38 195	53 106	40 358
Additional cancers (overdiagnoses)	190	1082	39
Deaths averted	80	95	155
Overall reduction in deaths	11·6%	7·5%	9·0%
Overall improvement in survival	1·1%	0·6%	3·1%
Individuals screened for 10 years per one death averted	1166	738	1030
Presented are modelled outcomes for screening of PRS-defined high-risk quintile (20%) and the oldest quintile (20%) of the population. Data presented are modelled for the UK population (around 66 million people) for annual cancers arising, deaths averted, and overdiagnoses. These are inflated estimates based on several favourable assumptions, which include that all cancers arising in the screening interval are present at time of screening (ie, no interval cancers) and full population uptake for PRS and screening. Cancer survival is based on UK diagnoses for 2008–17. We include the number of screenings and confirmatory (diagnostic) tests required based on screening once a year or once every 2 years. PRS=polygenic risk score.			
Table 4: Impact of approaches to screening for a specified 10-year age group for cancers of the breast (40–49 years), prostate (60–69 years), and colorectum (40–49 years)			

a future PRS). With a UK population of 10 175 760 individuals aged 60–74 years, 2 035 152 people (the PRS-defined high-risk quintile) would require screening to detect these 944 cancers each year. This hypothetical scenario presupposes the emergence of a screening tool of this sensitivity and specificity that might meaningfully affect pancreatic cancer survival.

We modelled a hypothetical new UK screening programme for prostate cancer in men aged 60–69 years, an age window selected to balance disease incidence and life expectancy. Of the 3 461 821 men aged 60–69 years, 692 364 would be assigned to the high-risk quintile on the basis of their PRS. Of the 16 853 prostate cancers arising annually in this age group, 7728 (46%) would be predicted to arise in the PRS-defined high-risk quintile and 9125 (54%) in the low-risk unscreened population (table 4). PSA screening at a 3 ng/mL cutoff has a sensitivity of 32% for a specificity of 85%: thus, only 2473 (32%) of 7728 prostate cancers arising in the PRS-defined high-risk quintile would be detected. Of 16 853 men aged 60–69 years diagnosed with prostate cancer annually, 1262 (7%) are expected to die of their disease within 10 years. Under favourable assumptions, it is predicted that PSA screening of the PRS-defined

high-risk quintile would avert up to 158 (13%) of 1262 deaths, compared with 95 (8%) from screening the oldest quintile (20%; table 4). Multi-parametric MRI offers a sensitivity of 89% for a specificity of 73%, meaning that screening of the PRS-defined high-risk quintile would be predicted to increase detected cancers to 6878 (41%) of 16 853 and deaths averted annually to 438 (35%) of 1262 (appendix p 28). For prostate cancer, if screening were offered once a year (or once every 2 years) to men aged 60–69 years, 692 364 (or 346 182) screening tests would be required annually (table 4). Given that about 3.6 million MRIs are performed every year in England across all indications, first-line multi-parametric MRI screening for just the PRS-defined high-risk quintile of men aged 60–69 years would require an immediate 19.2% (or 9.6% for screening once every 2 years) national increase in MRI capacity. This extra capacity is predicted to cost approximately £208 (or £104) million per year (estimated from a cost of £301 per multi-parametric MRI).^{19,20} Due to the 73% specificity of multi-parametric MRI, an additional 191 730 (or 95 865) follow-up or confirmatory tests (typically biopsies) would be required annually compared with 105 168 (or 52 584) follow-up or confirmatory tests for PSA-based screening.

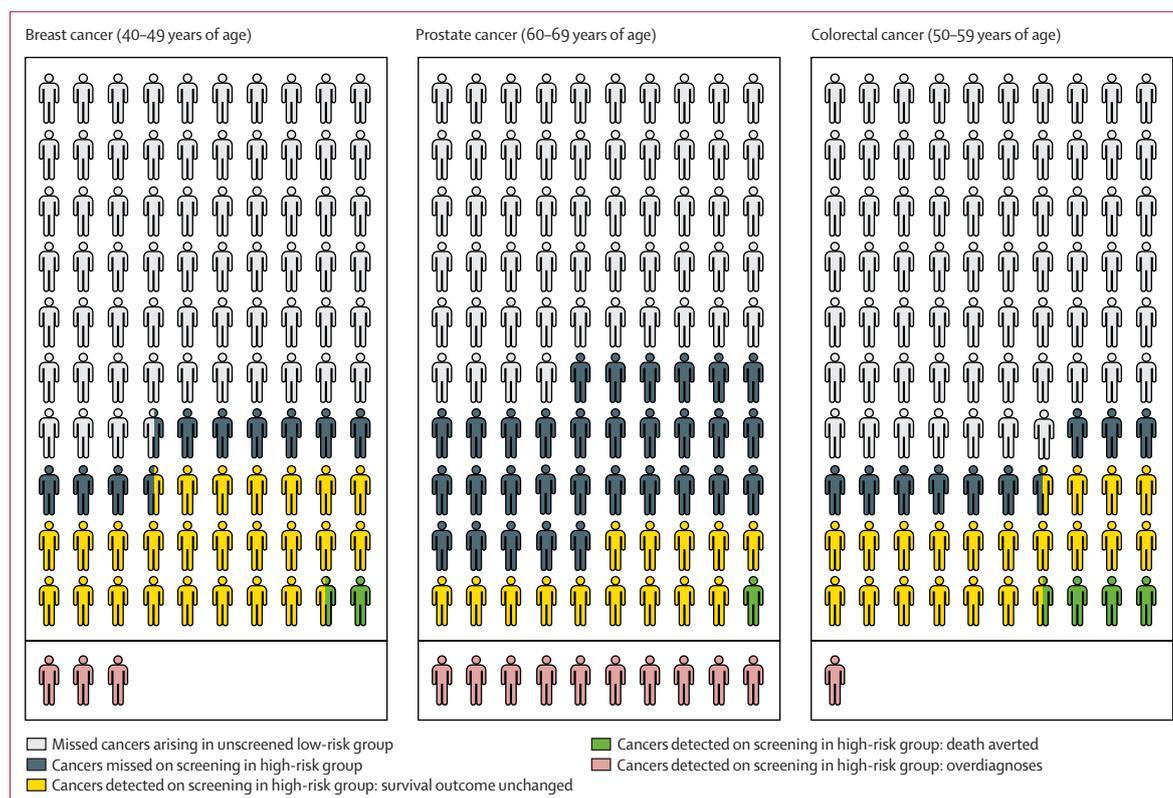


Figure 2: Modelled outcomes for new screening for 100 individuals who would currently present with incident symptomatic cancers

Presented are outcomes if a new screening programme were offered to the PRS-defined high-risk quintile (20%) of the population for breast cancer aged 40–49 years (screened using digital mammography), prostate cancer aged 60–69 years (screened using prostate-specific antigen [3 ng/mL]), and colorectal cancer aged 50–59 years (screened using faecal immunochemical test [20–50 µg/g threshold]). Assumptions include full uptake for PRS profiling and screening and that all cancers in the screened population are present at the time of screening (rather than arising as interval cancers). Cancer survival is based on UK diagnoses for 2008–17.

Furthermore, it is estimated from PSA screening studies that 42% of prostate cancers detected are overdiagnoses.²¹ On the basis of this estimation, for 1.4 men with prostate cancer detected by screening who would have otherwise presented symptomatically, one man has a cancer detected by screening which would have never manifested disease in his lifetime. For each death averted via screening, we predicted that 11.3 men will be overdiagnosed with prostate cancer. There is no theoretical reason to expect differences in the rate of overdiagnoses by PRS stratum; thus, in this PRS-stratified PSA-based screening scenario, we predicted that there would be an additional 1791 overdiagnosed prostate cancer cases per year (appendix p 4). Data for prostate cancer screening for men aged 50–59 years are also shown in the appendix (p 28).

In a hypothetical extension of UK breast cancer screening to women aged 40–49 years, 2811 (37%) of 7533 breast cancers occurring annually in women aged 40–49 years would arise in the PRS-defined high-risk quintile (table 4). Of these 2811, 1968 (70%) might be detected on digital mammography. Of the 7533 UK women diagnosed with breast cancer annually in this age range, 694 (9%) would be expected to die from their disease within 10 years. Compared with no screening in this age group, screening of the PRS-defined high-risk quintile could avert up to 102 (15%) of these 694 deaths, compared with 80 (12%) deaths from screening of the oldest quintile (ie, those aged 48–49 years), 55 (8%) from screening a randomly selected 20% of women, and 274 (39%) from screening all women in this age group (table 4; appendix p 28). If screening were offered once a year (or once every 2 years) to a quintile of women aged 40–49 years, an estimated 873 941 (or 436 970) mammograms and 71 658 (or 35 829) follow-up biopsies would be required annually (table 4).

Hypothetical extension of colorectal cancer faecal immunochemical test (FIT) screening to individuals aged 50–59 years, would avert up to an estimated 188 (11%) of 1715 annual colorectal cancer-specific deaths in the PRS-defined high-risk quintile (1767943 of 8839717 in this age group in the population; table 4). By comparison, we estimated that 155 (9%) of 1715 deaths could be averted from screening of the oldest quintile (ie, those aged 58–59 years), 112 (7%) from screening a randomly selected 20%, and 558 (33%) deaths from screening everyone in this age group (appendix p 28).

Modelled outcomes for new hypothetical screening for breast cancer, prostate cancer, and colorectal cancer per 100 individuals who currently would present with incident symptomatic cancers are shown in figure 2.

Discussion

We have shown how PRS-defined high-risk groups are enriched for cancers, but that the inherently modest predictiveness of PRSs means that, even with optimistic forecasts for larger GWASs, a substantial proportion

of incident cases will always be excluded from PRS-stratified screening programmes because they are deemed to be low risk. We present breast, colorectal, and prostate cancer as being the most plausible use cases for PRS stratification on account of the combination of stronger PRS predictiveness and higher disease frequency than other cancers, along with the availability of established cancer screening tools. We illustrate that modest absolute numbers of deaths from these cancers could potentially be averted in the UK by introduction of new PRS-stratified screening activities, as opposed to screening of an equivalently sized group from the upper end of the respective age range. Their lower incidence or modest heritability (or both), in addition to a scarcity of cancer screening tools with proven efficacy, render other cancers less plausible as use cases.

Some limitations of our study include applying multiple assumptions anticipated to overestimate the impact of screening; accordingly, estimates for the benefit of PRS stratification will be inflated. All estimates were based on an assumption of complete uptake of cancer screening. Thus, the difference between the estimated 102 deaths that might be averted annually by restricting breast cancer screening to the top quintile of women aged 40–49 years according to PRS-defined risk versus the 80 deaths if screening were restricted to the oldest quintile (ie, those aged 48–49 years) would be attenuated from 22 to 15 if breast cancer screening uptake were 70% (appendix p 5). We assumed that all cancers arising during the screening window are present at screening; in practice, a proportion will present as interval cancers, especially if deploying a longer screening periodicity than that assumed in this analysis. We used cancer survival data for 2008–17. Disregarding treatment-related improvements in stage-specific survival since 2008 could result in overestimation of the survival gain from any screening-related stage shift. We also model real-world screening tools that are superior to those currently implemented in the UK (eg, FIT at a threshold of 20–50 µg/g compared with the current threshold of 120 µg/g). We assumed cancer screening performed with equivalent sensitivity in younger age groups as in older populations (eg, disregarding any reduction in sensitivity from higher breast density in younger women). We also assumed complete uptake of PRS profiling and applied PRS enrichment as per a population with wholly western European ancestry; adjusting for these assumptions would attenuate survival impacts in the PRS-stratified screening scenarios.

In our models, screening sensitivity, overdiagnosis, biology, and lead time do not differ across PRS quantiles. This assumption is consistent with PRSs constructed from SNP associations from GWASs of disease cases unselected with regard to outcome or lethality, meaning that the cancers would not be anticipated to differ systematically between PRS-defined quantiles in their biology, clinical characteristics, or clinical behaviour.

In any analyses of PRS-stratified screening, there will always be contention regarding the PRS tools applied and accordant AUCs of performance. Although the PRS tools we used were selected because they had the best performance among multiple PRS methods, marginal improvements in AUC might be gained from alternative mathematical approaches or from addition of newly reported SNPs. Conversely, we might be criticised for these AUCs being potentially inflated on account of having been validated through the UK Biobank, as some constituent SNPs would have also been identified in the UK Biobank.²² There will also potentially be contention regarding the proposed system of clinical implementation for which PRS stratification is modelled. Many PRS projections model clinical implementation in which participating individuals would have risk analysis integrating a multitude of detailed physiological, clinical, pedigree, and sometimes investigational risk factors, after which the individual would be entered into screening at an individualised age and potentially have an individualised periodicity of screening.

We recognise that in validation analyses of PRS tools against cancer incidence in longitudinal cohort data, age is a powerful predictor of the likelihood of developing nearly all types of cancer during the following 5 or 10 years (appendix p 29). However, in the context of prospective design of a screening programme, it would be inappropriate for the following reasons to simply port across an AUC that was based on retrospective model fitting including age at cancer incidence (strongly driven by predictions of older-onset cancers). First, a screening programme is intended to provide survival benefit for the individual and the population. Thus, screening is typically discontinued as participants approach older age (ie, 70–75 years) because potential survival benefits decrease precipitously on approaching population median life expectancy (approximately age 81 years). Second, so-called personalised screening delivery at perfectly individualised initiation age and periodicity is logistically infeasible. The gains in impact would be modest compared with more logistically feasible precision screening based on allocation (according to risk) to one of three or four prestructured screening packages. Third, it is likely to be politically unpopular to remove or reduce screening from existing programmes. Therefore, we modelled roll out of screening activity for new prespecified age ranges, which would potentially be restricted to a PRS-defined high-risk population subgroup. For example, for breast cancer, we used PRS stratification to identify a new subgroup of women who might be offered the existing UK so-called middle-tier breast cancer screening package (initiation from the age of 40 years). For the UK's existing packages of breast cancer screening defined by the National Institute for Health and Care Excellence, which vary by age of initiation (age 25, 40, or 50 years), screening periodicity (annually or once every 3 years), and screening method

(mammography or MRI), only a few women are in the middle or highest tiers for screening, with allocation currently just based on reactive ascertainment of family history and gene mutational status (eg *BRCA1* and *BRCA2*).

Various other lifestyle and epidemiological factors have also been incorporated into models to predict cancer incidence in the population, including family history, smoking status, body-mass index (BMI), alcohol use, and hormonal risk factors (eg, contraceptive use, age of menopause, and parity). For example, on validation of the widely used, multimodal PRS tool BOADICEA against a well annotated Swedish breast cancer research dataset, an AUC of 0.69 was attained for the full multimodal model (incorporating age, PRS, mammographic breast density, BMI, family history, and endocrine and lifestyle factors) compared with an AUC of 0.67 for a model based on PRS plus age.²³ The AUC was further boosted from 0.69 to 0.70 when data on pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *CHECK2*, *ATM*, *RAD51C*, *RAD51D*, and *BARD1* were included in the model. As well as having modest impact on AUC, although well captured in highly annotated research cohorts, availability is poor for these types of additional, detailed risk-factor data within routine health-care records.²⁴ Thus, on the basis of logistical complexity, and the modest additional value of collections of individualised, multimodal risk-factor data, we modelled screening delivery to a predefined age range and applied AUCs in our analyses that reflect the performance of PRS-only tools.

For breast cancer, for example, the total heritability is estimated to be 31%, meaning that 69% of factors influencing development of breast cancer are non-genetic. Furthermore, less than 50% of that breast cancer heritability is estimated to reside in common genetic variants identifiable by GWAS. Overall total heritability is estimated to be 15% for colorectal cancer and 57% for prostate cancer.²⁵ Thus, because most of the causes of common cancers are non-genetic, the predictiveness of PRS tools will ultimately be limited by the modest heritability. This limitation is well illustrated by the optimised PRS tools we present, in which the totality of associated common variants is captured. Moreover, it is unclear whether for even the future PRS tools we present, the requisite four-times increase in total case samples will ever be achieved. Thus, we would propose the future PRS tools presented should be viewed as indicative of PRS tool performance attainable in the foreseeable future, reasonably reflecting predictive gains probably attainable from new studies, improved mathematical methods, multimodal risk data, or more individualised screening windows.

PRS tools to date have been derived from GWASs conducted predominantly in participants of western European ancestry, which means that non-European populations will not be equivalently served by proposed PRS-based screening programmes. Thus, existing

inequalities in screening participation could potentially be exacerbated.²⁶ There might be differential uptake of PRS profiling across different societal groups relating to concerns about future potential for genomic discrimination, by insurers and beyond. The cancers arising in the unscreened (PRS-defined low-risk) group are of equivalent natural history and lethality to those arising in the screened high-risk group. Being assigned as low-risk—or even just as not belonging to the high-risk group—might offer false reassurance and even result in individuals disregarding general lifestyle advice or ignoring relevant symptoms. Conversely, there might be considerable anxiety associated with assignment as high-risk, with people not appreciating that the absolute risks of cancer are still low.²⁷ Genetics are often portrayed in discourse as predictive and clear-cut, and this framing poses several challenges in the communication around PRS, given that the majority of the risk for most cancers will lie in factors that are not genetic and cannot be measured by PRS.

Research into new screening programmes typically involves very skewed participation, and the acceptability and uptake of polygenic risk profiling remains unexplored for the majority of the UK population. If the modelled benefits of PRS stratification are deemed to justify the logistical costs and other limitations of PRS stratification (in particular, ancestry bias), then as well as individual-level randomised studies, independent cluster-randomised UK trials must be conducted in pre-registered, fully transparent, controlled circumstances, evaluating the endpoint of all-cause mortality (or a legitimate surrogate). If these trials show favourable impact, whole-system considerations and capacity analyses are still required, comparing PRS-stratified screening to wider public health interventions, their comparative merits and hazards, opportunity costs, and impact on services used by people with symptomatic or more advanced cancers. It was announced in October, 2022, that up to 5 million non-randomised adult NHS patients are to be offered PRS profiling through the UK Our Future Health research programme with an option to receive their results; it has yet to be clarified how or if this programme will address or evaluate these crucial questions.

PRS stratification does not redress the many major challenges that often thwart cancer screening endeavours—namely, overdiagnosis of indolent cancers, poor sensitivity and specificity trade-off for screening tools, the paradox of age benefit, lead-time bias, and little impactful reduction in mortality. Given that PRS solely provides a modest level of risk stratification, it is improbable that a screening framework significantly compromised by these shortcomings would suddenly become a convincing value proposition just because it was restricted to or withheld from specified PRS-defined risk quantiles of the population. Only small improvements in PRS tool performance will be attainable from larger

GWASs, novel methods, and incorporation of other individualised risk factors. For established screening frameworks, such as those for breast or colorectal cancer, restriction of screening to a PRS-defined group would be compelling if such stratification enabled delineation of, for instance, 20% of the population in which 90% of the cancers were concentrated. PRS tools do not achieve such delineation; they are inherently much weaker. Most individuals in the high-risk groups never develop the cancer in question. There is an enrichment trade-off (akin to Rose's paradox): when restricting screening to a smaller PRS-defined high-risk quantile (ie, the top 20% or 10%), enrichment is stronger, but the majority of cancers will arise in the low-risk group. If a larger quantile is screened (eg, the PRS-defined high-risk 50%), fewer cancers are excluded but enrichment is weaker and there is lesser overall impact on screening volumes.

Our modelling suggests that PRS stratification might afford some very modest improvement in screening efficiency and survival. Robust quantitation of benefits versus harms requires rigorous, randomised, national-level investigation also exploring ancestral inequity, societal acceptability, potential diminution of existing screening uptake, and logistical costs and complexities. It is important to remember: "All screening programs do harm; some do good as well, and, of these, some do more good than harm at reasonable cost".²⁸

Contributors

CT, AS, MEJ, and RSH designed the analyses. JB generated and quality-assured the National Cancer Registration and Analysis Service datasets. MEJ provided models for lifetime cancer risk and age quantile risk. ADH provided models for PRS tool discrimination. CH undertook literature review for parameterisation of the models. CH and BT did statistical analyses and generated tables for presentation. BT assembled figures for presentation. CFR assembled data for presentation. AL, MM, CS, HH, and KS provided clinical interpretations of the data. RW provided project administration. CT drafted the manuscript. All authors contributed to the final manuscript. CT, CH, BT, and MEJ have accessed and verified the raw data. CT, RSH, MEJ, AL, ADH, AS, and CH were responsible for the decision to submit the manuscript for publication.

Declaration of interests

ADH acknowledges funding from the British Heart Foundation (AA/18/6/34223) and UKRI-NIHR (MR/V033867/1), is a member of the Advisory Group for the Industrial Strategy Challenge Fund Accelerating Detection of Disease Challenge, and a co-opted member of the National Institute for Health and Care Excellence Guideline update group for Cardiovascular disease: risk assessment and reduction, including lipid modification, CG181. CS acknowledges grants from AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, Roche-Ventana, Invitae (previously Archer Dx—collaboration in minimal residual disease sequencing technologies), Ono Pharmaceutical, and Personalis; is chief investigator for the AZ MeRmaid 1 and 2 clinical trials and is the Steering Committee chair; is co-chief investigator of the NHS Galleri trial funded by GRAIL and a paid member of GRAIL's Scientific Advisory Board; receives consultant fees from Achilles Therapeutics (and is also a Scientific Advisory Board member), Bicycle Therapeutics (and is also a Scientific Advisory Board member), Genentech, Medixi, China Innovation Centre of Roche (formerly Roche Innovation Centre—Shanghai), Metabomed (until July, 2022), and the Sarah Cannon Research Institute; has received honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Illumina, MSD, Novartis, Pfizer, and Roche-Ventana; has previously held stock options in Apogen Biotechnologies and GRAIL, and currently has stock options in Epic

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Bioscience and Bicycle Therapeutics, and has stock options and is co-founder of Achilles Therapeutics; has a patents issued for an immune checkpoint intervention in cancer (PCT/EP2016/071471), in treating cancer based on identification of clonal neo-antigens (PCT/EP2016/059401), in lung cancer detection (PCT/US2017/028013), in detecting tumour recurrence (PCT/GB2017/053289), in treating cancer (PCT/EP2016/059401), in treating cancer by targeting insertion-deletion mutations (PCT/GB2018/051893), in identifying insertion-deletion mutation targets (PCT/GB2018/051892), in determining whether an HLA allele is lost in a tumour (PCT/GB2018/052004), in identifying responders to cancer treatment (PCT/GB2018/051912), and in predicting survival rates for cancer patients (PCT/GB2020/050221). CT has received personal fees from AstraZeneca and Roche. HH has received personal fees from AstraZeneca. KS has received personal fees from BUPA, AstraZeneca, Pfizer, Merck, and AXA. MM receives royalties from authorship of books and book chapters, in addition to freelance journalism; consulting fees from her work as an NHS general practitioner; and fees for acting as an expert witness to the Infected Blood Inquiry and for lectures at Oxford and Glasgow Universities. All other authors declare no competing interests.

Data sharing

The data used in these analyses are available either publicly or on request from the National Disease Registration Service. The source data and analytical code presented in this manuscript are available at <https://github.com/BTORR-icr/Modelling-the-utility-of-polygenic-risk-scores-in-UK-cancer-screening>.

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References

- NHS England. The NHS Long Term Plan. Jan 7, 2019. <https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/> (accessed Dec 3, 2022).
- Wilson JMG, Jugner G. Principles and practice of screening for disease. Geneva: World Health Organization, 1968.
- Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. *Hum Mol Genet* 2019; **28**: R133–42.
- Davies SC. Annual report of the Chief Medical Officer 2016: generation genome. July, 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/631043/CMO_annual_report_generation_genome.pdf (accessed Dec 3, 2022).
- Fritsche LG, Patil S, Beesley LJ, et al. Cancer PRSweb: an online repository with polygenic risk scores for major cancer traits and their evaluation in two independent biobanks. *Am J Hum Genet* 2020; **107**: 815–36.
- Zhang YD, Hurson AN, Zhang H, et al. Assessment of polygenic architecture and risk prediction based on common variants across fourteen cancers. *Nat Commun* 2020; **11**: 3353.
- Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005; **353**: 1773–83.
- Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010; **60**: 70–98.
- Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014; **160**: 171–81.
- Zhang Y, Yang J, Li H, Wu Y, Zhang H, Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. *Int J Clin Exp Med* 2015; **8**: 11683–91.
- Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016; **387**: 945–56.
- Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. *World J Urol* 2018; **36**: 1341–53.
- Horeweg N, Scholten ET, de Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol* 2014; **15**: 1342–50.
- Almstrup K, Lippert M, Mogensen HO, et al. Screening of subfertile men for testicular carcinoma in situ by an automated image analysis-based cytological test of the ejaculate. *Int J Androl* 2011; **34**: e21–30.
- Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999; **319**: 1562–65.
- Hingorani A, Gratton J, Finan C, et al. Performance of polygenic risk scores in screening, prediction, and risk stratification. *medRxiv* 2022; published online Dec 19. <https://doi.org/10.1101/2022.02.18.22271049> (preprint).
- Esteve J, Benhamou E, Raymond L. Statistical methods in cancer research, volume IV: descriptive epidemiology. *IARC Sci Publ* 1994; **128**: 1–302.
- Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *JAMA* 2017; **317**: 2402–16.
- NHS England, NHS Improvements. Diagnostic imaging dataset statistical release. Jan 23, 2020. <https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2020/01/Provisional-Monthly-Diagnostic-Imaging-Dataset-Statistics-2020-01-23.pdf> (accessed Dec 3, 2022).
- NHS England. 2020/21 National Cost Collection data publication. July 27, 2022. <https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/> (accessed Dec 3, 2022).
- Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009; **101**: 374–83.
- Kachuri L, Graff RE, Smith-Byrne K, et al. Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction. *Nat Commun* 2020; **11**: 6084.
- Yang X, Eriksson M, Czene K, et al. Prospective validation of the BOADICEA multifactorial breast cancer risk prediction model in a large prospective cohort study. *J Med Genet* 2022; **59**: 1196–205.
- Briggs SEW, Law P, East JE, et al. Integrating genome-wide polygenic risk scores and non-genetic risk to predict colorectal cancer diagnosis using UK Biobank data: population based cohort study. *BMJ* 2022; **379**: e071707.
- Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA* 2016; **315**: 68–76.
- Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 2019; **51**: 584–91.
- Ballard LM, Horton RH, Fenwick A, Lucassen AM. Genome sequencing in healthcare: understanding the UK general public's views and implications for clinical practice. *Eur J Hum Genet* 2019; **28**: 155–64.
- Gray JAM, Patnick J, Blanks RG. Maximising benefit and minimising harm of screening. *BMJ* 2008; **336**: 480–83.