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Supplementary appendix

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Modelling the utility of polygenic risk scores in UK cancer screening

Appendix

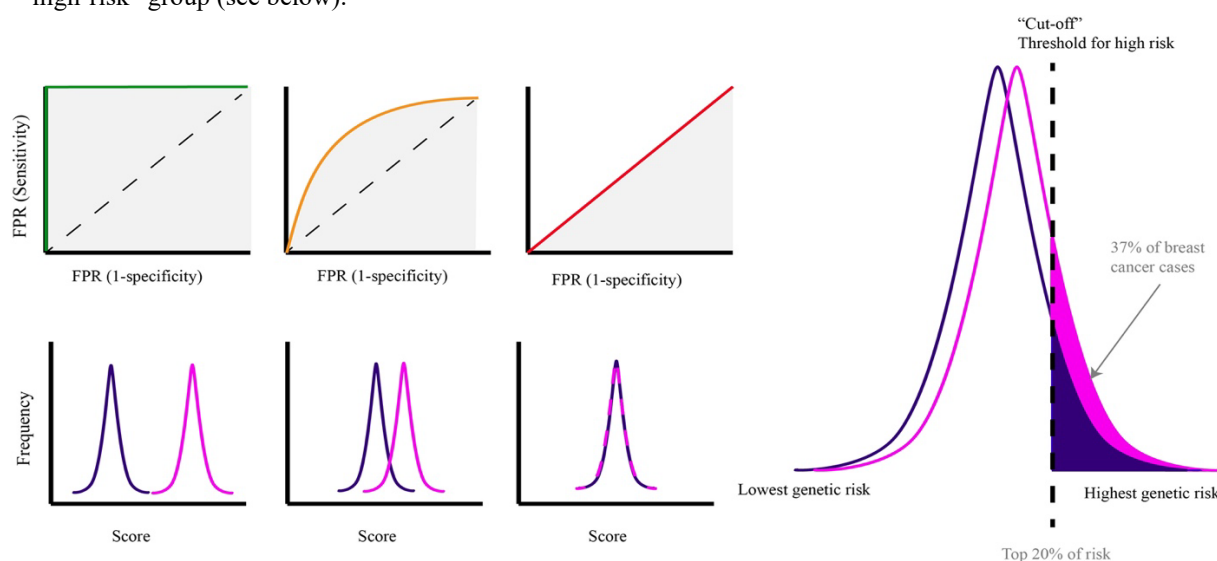
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SUPPLEMENTARY INFORMATION BOXES

BOX 1: Polygenic Risk Scores: factors to consider in relation to cancer screening

- 1) **Predictive value:** The performance of a PRS-tool (model, SNP-set) in distinguishing between those who will develop cancer (cases) from those who will remain unaffected can be quantified by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) to generate an AUC (area under the curve). More simply, the AUC equates to the likelihood of correctly ascribing an individual as a (future) case versus remaining unaffected, within a population comprising equal proportions of the two. AUC=0.5: no predictive discrimination, AUC=1.0: perfect prediction. Current PRS-tools for common cancers have AUCs of up to 0.70. For an AUC of 0.64, for a threshold that includes 20% of the population, 37% of those who will develop cancer (cases) are included in this “high-risk” group (see below).



Other metrics frequently presented to represent predictive performance of PRS include:

- OR for disease occurrence in PRS-defined top 1%/10% compared to population average
 - OR for disease occurrence in PRS-defined top 1%/10% compared to bottom 1%/10%
 - the OR for disease per one standard deviation of population PRS distribution
- 2) **Genetic ancestry:** SNP-sets for current PRS-tools are largely derived from GWAS of European populations. Individuals from non-European populations would be disproportionately misclassified by PRS derived from European populations. To properly redress the ancestral inequity of PRS-tools would require (i) for each different ancestral group a sufficiently large case-control GWAS to generate a PRS which captures a proportionally equivalent heritable cancer risk when compared to that of European populations and (ii) each participant undergoing PRS estimation to undergo an individualised weighting of the different ancestry-specific SNP-sets to reflect their individual ancestry admixture.
- 3) **Multimodal PRS-tools:** Some PRS-tools incorporate additional ‘individual-level’ risk factors (family history, breast density, body mass index, lifestyle/physiological factors). (1) In analyses by which PRS-tool predictions are validated against 5 or 10-year cancer incidence in longitudinal cohort data, the AUC presented may also reflect the predictive contribution of age of cancer incidence. Age is a ‘population-level’ rather than ‘individual-level’ risk factor, reflected in screening/interventions being offered to pre-specified age-groups.
- 4) **Future improvements in PRS:** The predictive performance of a PRS-tool is (i) ultimately constrained by the heritability of the disease, which is often comparatively low for many common complex diseases of late onset, (ii) determined by how much of the total heritable risk is captured by the SNPs contributing to the PRS-tool.

BOX 2: Cancer screening: factors to consider regarding PRS-based stratification

Polygenic risk scores are constructed from SNPs exhibiting association with disease in GWAS of disease cases unselected in regard of outcome/lethality (i.e. the PRS will predict cancer incidence but not disease outcome). Risk stratification would potentially differentiate aggressive/lethal cancers only if the underlying GWAS had been restricted to aggressive/lethal cases of disease.(2) It is thus anticipated that stratification using the GWAS-derived PRS will only impact the numeric distribution of cancers across the quantiles; the cancers will not differ systematically between PRS-defined quantiles in their biology, clinical characteristics or clinical behaviour.

- 1) **Overdiagnosis (overdetection):** Screening detects cancers that otherwise would never have come to medical attention during the person's lifetime (cancers the patient would have “died with” rather than “died from”).(3) For example, it is estimated that 11% of breast cancers detected on breast mammography and 42% of prostate cancers detected on PSA screening are “overdiagnoses”.(4,5) Aside from substantial costs, if there is concomitant “overtreatment”, this can cause harms such as incontinence and impotence. Furthermore, increased rates of suicide and cardiovascular death have been reported immediately after a diagnosis of prostate cancer.(6) As per above, although some studies have reported small differences in overdiagnosis rates, the *proportion* of detected cancers that are overdiagnoses would be predicted to be consistent across PRS-defined strata, i.e. at a rate the same as in unstratified population-based screening.(7,8)
- 2) **The impact of cancer screening on survival:** Survival benefit from screening is a function of (i) improving stage at diagnosis compared to symptomatic presentation, (ii) this “downstaging” translating into improvement in long-term survival (iii) lead-time bias, where true outcomes are unchanged but appear improved purely on account of earlier detection. For breast cancer, symptomatic presentation is typically at early stage and long-term survival rates are high for stages 1-3 (in part due to improvements in adjuvant therapies) and increasingly stage 4. There is thus limited ‘headroom’ by which screening might improve survival for such a “good prognosis” cancer. Conversely, over 80% of those diagnosed with stage 1 pancreatic cancer die from their disease within 10 years. For poor-outcome cancers the headroom for improving survival may also be narrow if (i) cancer-specific mortality is high across all disease stages (like pancreatic cancer) and/or (ii) screening only leads to minimal downstaging-related survival improvement (as recently demonstrated in trials of ovarian cancer screening).(9) There is no rationale to suggest PRS-based risk stratification would influence the impact of a given cancer-screening tool on cancer survival or impact on lead-time bias. Cancer-specific mortality will only account for deaths directly due to the cancer. All-cause mortality is more meaningful evaluation metric, factoring in the deaths consequent from screening, treatment and concurrent morbidities, but requires very substantial power and thus duration of follow-up.
- 3) **Sensitivity and specificity:** Tools screening for presence *today* of a particular cancer must be low-cost, low-harm, convenient, and scalable. Sensitivity is the proportion of all people with cancer that have a positive screening test (true positive rate). Specificity is the proportion of all people without cancer who have a negative result (1- false positive rate). The threshold for defining a cancer screening result as ‘positive’ will be selected to provide most acceptable balance between sensitivity and specificity. Sensitivity and specificity are essentially innate to the screening tool (when applied to cancers in a specified patient group). Whilst it has been proposed that sensitivity/specificity of some types of tests may differ for contexts in which where disease prevalence varies widely, performance of cancer screening tools is unlikely to differ in meaningful fashion between PRS-defined quantiles. (10)
- 4) **Diagnostic tests:** Individuals with a positive screening result require a follow-up diagnostic (confirmatory) test, typically involving imaging, endoscopy, and/or biopsy. These diagnostic tests are usually more expensive, invasive, and/or inconvenient than the initial screening test. Limited capacity for these modalities is a key factor in design of screening programs. Some screening protocols involve more complex algorithms of multistage or tiered follow-up. For example, free-to-total prostate-specific antigen (PSA) ratio may be used for follow-up of moderately elevated PSA before proceeding to biopsy.(11)
- 5) **Interval cancers:** Some cancers will present symptomatically between screens. The periodicity of a screening program (e.g. one-yearly versus two-yearly versus three-yearly) will influence the proportion of cancers diagnosed as interval cancers versus as screen-detected. In the current NHS breast-screening program of 3-yearly mammography aged 50-69, for every 10 breast cancers picked-up on screening, 3 genuine interval breast cancers

arise in screened women.(12) Distinction between imperfect screening sensitivity and interval cancers can be complex.

- 6) **Age-specific cancer incidence:** For each cancer type the total lifetime likelihood of developing that cancer (e.g. ~1.7% for pancreatic cancer) is unequally distributed across the decades of life. The age window for which screening is offered requires balancing of age-specific cancer incidence versus the life-years gained from a death averted (with UK median life expectancy being ~81 years currently).(13) Most common cancers are diseases predominantly of older age, when life years gained are fewest (>47% of pancreatic and >43% colorectal cancers arise after the age of 75). Risk stratification does nothing to solve this “age paradox”.
- 7) **Uptake:** For current national screening programs, uptake in the UK is typically 65-70%, with variation by region, socio-economic status, and other parameters.(5) Uptake of PRS-profiling when offered as part of a study within the UK NHSBSP (NHS Breast Screening Program) was <20%, but will likely be highly context- and population-specific.(14)

SUPPLEMENTARY METHODS

Cancer Types

Eight solid tumours were selected for inclusion in this analysis based on (i) availability from data generated by Fritsche et al. (2020) of AUC (area under the curve) for validation against UKBiobank of a “PRS-only” risk prediction tool (i.e. AUC without inclusion of age in the prediction) (ii) availability of data generated by Zhang et al. (2020) for projected AUC of “PRS-only” tools based on larger GWAS and totality of common variation (iii) availability of screening tools for which published data on sensitivity/specificity could be identified.

Polygenic Risk Scores

Fritsche et al. (2020) identified from literature and databases, sets of SNPs associated with specified cancers, for which they undertook up to seven approaches to construction of PRS comprising fixed p-value thresholding, LD pruning and thresholding and lassosum. The AUC of the best performing approach on validation against UKBiobank was taken forward for the subsequent analyses and ascribed as the “current” PRS. Zhang et al. used summary-level data from GWAS of European ancestry across multiple cancer sites to estimate the total underlying number of common susceptibility variants (polygenicity) and effect-size distribution. From these they calculate the AUC if the totality of variance due to common variants were captured: this we ascribe as our “optimised” PRS-tool. They also present estimation of AUC for a hypothetical GWAS comprising 4-fold the sample number of the largest GWAS meta-analysis reported to date: this we ascribe as our “future” PRS-tool.

We use the AUC values for the “current, “future” and “optimised” PRS-tools for each cancer type to then derive the related performance metrics inherent to the AUC, which comprise odds ratios (comparing the odds of cancer in the top 50%, 20%, 10%, 5%, and 1% of the PRS to the middle quintile), and the percent of cancers in the population captured by the top 50%, 20%, 10%, 5%, and 1% of the PRS. These metrics are estimated using the assumptions and methods described in detail by Wald and Hingorani *et al.*, and summarised briefly in Supplementary Table 1.(15,16) In brief, these methods rely on the conceptualization of Polygenic Risk Score distributions across a population as two normal distribution curves: one representing those with (or who will develop) cancer (affected), and one representing those without (unaffected).(15) The areas under these curves, represented by the cumulative distribution function (CDF), were used to estimate relative proportions of cases captured at different PRS thresholds, allowing calculation of Odds Ratios (ORs). Calculation of the CDFs for these curves required three parameters: μ_A (the mean of the distribution of the PRS among those affected by cancer), μ_U (the mean of the distribution of the PRS among those unaffected by cancer, and $SD(\sigma)$ (the standard deviation of each curve). $SD(\sigma)$ was assumed to be 1 for both curves, μ_U was assumed to be 0, and μ_A was determined from the AUC of the PRS as per methods and equations further detailed in the supplementary methods of Hingorani et al.(15)

Lifetime Risks

We then estimated lifetime risk of cancer using a ‘current probability’ method and period approach.(17,18) This approach accounts for deaths from cancer *and* all other causes and utilises the methods of Cancer Research UK used in their lifetime risk calculations.(18) In brief, for each cancer, we constructed a life table dividing the population into 5-year age bands. To estimate lifetime risks, we started by dividing the population into two groups: the top $n\%$ (as represented by the top 50%/20%/10%/5%/1% of the PRS) and the remainder. We estimated the cancer incidence rate in the top $n\%$ of the population by splitting the average incidence into two parts (scaled by the relative population size and the OR of the top $n\%$ compared to the remainder). We estimated the death rate in

top $n\%$ by up scaling the average death rate in the total population according to a ratio of death to incidence rate. Finally, we exposed a ‘hypothetical cohort’ to the cancer incidence rate in the top $n\%$ of the PRS. From each age band to the next, we reduced the cohort size in accordance with competing and cancer risks. We estimated an overall lifetime risk by summing the number of events expected in each age group of the cohort.

Cancers detected by screening

We estimated the number of cancers occurring in the top $n\%$ (50%, 20%, 10%, 5%, and 1%) of the PRS, based on our “current”, “future”, and “optimised” PRS-tools, by application of the percentage of cancers captured within the PRS-defined high risk quantile (Table 1) to CRUK/NDRS data on the number of cancers arising in 5-year age bands. From this, we estimated the number of cancers that would be detected by a hypothetical stratified screening programme using published sensitivity metrics for the cancer-specific “real world” screening tool (Supplementary Table 3, Supplementary Tables 6A-C). To account for potential emergence of improved cancer screening tools, especially for “underserved” cancers, we then repeated the analysis using hypothetical “idealised” screening tool, which we arbitrarily assigned as having a sensitivity of 80% for specificity of 95% (Supplementary Tables 7A-C).

Survival

We modelled the change in 10-year survival that would result from offering various screening programmes to age groups currently falling outside of population screening programmes: women aged 40-49 for breast cancer, men aged 60-69 for prostate cancer, and men and women aged 50 to 59 for colorectal cancer. The approaches evaluated comprised screening within these age-bands i) without restriction (ii) of the PRS-defined high risk 20% (quintile), (iii) of the oldest 20% (iv) of a random 20%.

In brief, these analyses involved re-allocation of cancers across from the routine, urgent (2 week wait) and emergency “routes-to-diagnosis” over to screening. The accordant stage-specific distributions were then re-applied for the updated numbers in each route. The accordant 10-year age-specific, stage-specific net cancer survival figures were then applied.

Within the routes-to-diagnosis datasets utilised, for breast and colorectal cancers small numbers of individuals in these age groups have received screening via age-extension studies. To model ‘baseline’ survival to there being no screening, we re-allocated these cancers proportionally between the three remaining routes to diagnosis (two week wait, routine and emergency), adjusting baseline figures for survival accordingly. For prostate cancer, where no screening is offered, we used the routes-to-diagnosis data with no changes.

We estimated the proportion of cancers that would be detected by screening by applying published sensitivity and specificity metrics to the expected number of cancers in each pre-specified section of the population (total age band, random quantile of age band, top $n\%$ of the PRS, top two years of age band).

- For the total age band, the expected number of cancers was that shown in the CRUK data (Supplementary table 1)
- For the random quintile, it was a scaled version of this total (i.e., we would expect 20% of cancers in 20% of the population).
- For the PRS-defined high-risk 20%, we applied the percentage of cancers captured within the PRS-defined high risk quintile (as per Supplementary Table 4) to CRUK data on the number of cancers arising in respective 5-year age bands (Supplementary Table 1).
- To estimate the number of expected cancers in the top two years of each relevant age band (48-49 for breast, 58-59 for colorectal, and both 58-59 and 60-69 for prostate), we used linear

interpolation across adjacent 5-year age bands to estimate the age-specific incidence rates for each individual year. We then used the age-specific incidence rates for these new ‘one-year age bands’ in conjunction with population size estimates derived from ONS data to calculate the number of cancers expected across the two years (Supplementary Table 1).

Any remaining cancers (expected to occur in the age band, but not detected by screening) were allocated between three routes of detection (routine, urgent and emergency presentation) in proportion to the distribution shown in the baseline NCRAS routes-to-diagnosis data.

We then estimated the stage distribution of cancers in each age band in proportion to the stage distribution of tumours detected by each route to diagnosis in the NCRAS data. Finally, we estimated the proportion surviving 10-years using 10-year age-specific, stage-specific net survival, using the stage distributions amended on account of addition of screening. We then calculated the annual difference in the number of people surviving 10-years with no screening (baseline) and our modelled screening programmes.

The code and raw data underling these models can be downloaded from GitLab [here](https://git.icr.ac.uk/chuntley/modelling-the-utility-of-polygenic-risk-scores-in-uk-cancer-screening).
<https://git.icr.ac.uk/chuntley/modelling-the-utility-of-polygenic-risk-scores-in-uk-cancer-screening>

SUPPLEMENTARY TABLES

Supplementary Table 1: Data Sources utilised in analyses

Data Item	Details	Reference/Source
Analysis: Polygenic Risk Scores (Table 1, Sup Table 4)		
Area under the Curve (AUC) for 'current' polygenic risk scores (PRS) for 8 cancers	PRS constructed using SNPs and GWAS summary statistics from multiple sources via up to seven approaches; AUCs from validation in UKBiobank (best AUC retained)	Fritsche et al., American Journal of Human Genetics(19)
AUC for 'future' PRS for 8 cancers	Projected AUC for a PRS constructed from underlying GWAS with a 4x increased sample size compared to largest published metaanalysis	Zhang et al., Nature Communications(20)
AUC for 'perfect' PRS for 8 cancers	Estimate of maximum AUC achievable for PRS capturing variance attributable to all common genetic variants	Zhang et al., Nature Communications(20)
Analysis: Lifetime Cancer Risks, overall and PRS-defined strata (Table 2, Sup Table 5)		
Age-specific all-cause mortality rates	Estimates for England and Wales, 2018	Office for National Statistics(21)
Age- and sex- specific incidence rates	Estimates for the UK, 2016-2018. Derived by Cancer Research UK (CRUK) from data provided by the National Cancer Registration and Analysis Service (NCRAS), ISD Scotland, the Welsh Cancer Intelligence and Surveillance Unit, Health Intelligence Division, Public Health Wales, and the Northern Ireland Cancer Registry. *Invasive breast cancers (C50) only	Cancer Research UK(22)
Age- and sex- cancer-specific mortality rates for 8 cancers	Estimates for the UK, 2017-2019. Derived by Cancer Research UK (CRUK) from data provided by Nomis mortality statistics, ISD Scotland, the Northern Ireland Cancer Registry, and the Office for National Statistics. *Invasive breast cancers (C50) only	Cancer Research UK(22)
Odds Ratios comparing risk of cancer in top n% of PRS vs. remainder	Derived from the AUCs for current, future, and optimised PRS for 8 cancers (as described in Polygenic Risk Score section of this table, above)	Fritsche et al., American Journal of Human Genetics(19), Zhang et al., Nature Communications(20)
Analysis: Cancers Detected by Screening PRS-defined strata or age band overall using current or idealised screening tools (Table 3, Supplementary Tables 6A-D, 7A-D)		
Cancers arising in 5-year age bands	Number of cancers recorded in the UK for each 5-year age band in 2016-2018. Derived by Cancer Research UK (CRUK) from data provided by the National Cancer Registration and Analysis Service (NCRAS), ISD Scotland, the Welsh Cancer Intelligence and Surveillance Unit, Health Intelligence Division, Public Health Wales, and the Northern Ireland Cancer Registry. *Invasive breast cancers (C50) only	Cancer Research UK(22)
Age-specific annual incidence rates per 100,000 for 8 cancers	Estimates for the UK in 2016-2018. Derived by Cancer Research UK (CRUK) from data provided by the National Cancer Registration and Analysis Service (NCRAS), ISD Scotland, the Welsh Cancer Intelligence and Surveillance Unit, Health Intelligence Division, Public Health Wales, and the Northern Ireland Cancer Registry. *Invasive breast cancers (C50) only	Cancer Research UK(22)
Reference size population for each 5-year age band	Average of estimates for the UK for the years 2016-2018. Analysis of population estimates tool, the Office for National Statistics.	Office for National Statistics(23)
Sensitivity estimates for 'real-world' screening tools	Breast cancer (digital mammography),(24) prostate cancer (PSA, 4ng/mL threshold(25) and mpMRI(26)), colorectal cancer (FIT, 20-50 µg/g threshold),(27) pancreatic cancer (CA19-9 20 U/mL threshold),(28) ovarian cancer (MMS (CA-125 + TVU),(9) kidney cancer (USS),(29) lung cancer (low dose CT),(30) and testicular cancer (semen assay).(31)	Published estimates from clinical trials(9,24,25,30,31) and meta-analyses.(26-29)
Sensitivity/sensitivity estimates for hypothetical 'idealised' screening tool	Standard estimate applied across all cancers of sensitivity 80% (for sensitivity 95%).	Hypothetical estimate
Survival analysis (Table 4, Supplementary Tables 8A-E)		
Route-to-diagnosis for breast, prostate, and colorectal cancers in England.	Proportions of cancer diagnoses from (i) screening*, (ii) routine detection**, (iii) urgent symptomatic (two-week wait) and (iv) emergency presentation. Data for England from 2018. Derived by the National Cancer Registration and Analysis Service on request, from the National Cancer Registration Dataset.	National Cancer Registration and Analysis Service (NHSD)(32)

	<p>*National screening programs included small numbers of younger subjects from age-extension trials (e.g. AgeX)</p> <p>**Includes some routine follow-up of high-risk individuals (e.g., those with family history and/or pathogenic variants)</p>	
Stage distribution of breast, prostate, and colorectal cancers according to route of diagnosis in England.	Proportion of cancers of each stage as determined by route to diagnosis. Prostate cancer estimates include routine, urgent symptomatic and emergency routes to diagnosis only. Data for England from 2018. Derived by the National Cancer Registration and Analysis Service on request, from the National Cancer Registration Dataset.	National Cancer Registration and Analysis Service (NHSD)(32)
Stage distribution of prostate cancers diagnosed via screening.	Stage distribution of cancers identified in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), conducted across multiple European countries during the 1990s and early 2000s.(33) T and M staging data from the ERSPC trial were mapped onto the '1-4' staging described by CRUK and used by NCRAS.(34)	ERSPC trial(33)
Net 10-year age-specific, stage-specific survival rates for breast, colorectal, and prostate cancers in England.	<p>Estimates for England, 2008-2017 (net 10-year age-specific, all-stage mortality) and 2013-2017 (net 5-year age-specific, stage-specific mortality).</p> <p>Net 10-year age-specific, stage-specific survival was derived from age, site, and stage-specific net 5-year cancer survival, provided by the National Cancer Registration and Analysis Service on request, from the National Cancer Registration Dataset.</p> <p>Overall survival has been adjusted for background age-specific death rates to reflect net cancer-specific mortality.</p>	National Cancer Registration and Analysis Service (NCRAS)(32)
Overdiagnosis rates	<p>Proportion of total cancers detected on screening that would not have been detected without screening on long-term follow-up.</p> <p>Breast cancer: 11%,(5)</p> <p>Colorectal cancer 3.8% (midpoint of reported estimate range),(35)</p> <p>Prostate cancer (PSA screening) 42%.(4,36,37)</p>	Publishes estimates from follow up of national screening programme trials(5).(4,35-37)

Supplementary Table 2: Assumptions utilised in analyses

Assumption	Justification, source, and implications
Polygenic Risk Scores	
Polygenic risk scores show a Gaussian distribution in populations	Support from central limit theorem(15,38)
Polygenic risk score distributions have the same standard deviation in affected and unaffected individuals	Empirical support from previously published scores and mathematical relationships(15,39)
Polygenic risk scores select for disease incidence, not biology or outcome	Polygenic risk scores are constructed from SNP-associations for GWAS of disease cases unselected in regard of outcome/lethality (i.e. the PRS predict cancer incidence). There is minimal evidence to suggest that SNPs associated with cancer incidence will, on case-only GWAS, be associated with disease outcome. Hence, we assume that disease mortality and overdiagnosis rates will not vary by PRS-defined risk quantile.
Lifetime Risks	
A period approach can be applied for the calculation of lifetime risks.	Lifetime risks are calculated through the application of a cross-section of the age-specific incidence and mortality rates in the UK for 2018. These risks represent the risk that would be incurred to a theoretical population living through the cross-section of rates from 2018. This approach is limited by the fact that it does not account for changes in incidence and mortality over time.
Cancer-specific mortality in the top $n\%$ of the PRS is increased in proportion to the change in incidence between the top $n\%$ of the PRS and the remainder.	Cancer-specific mortality in the top $n\%$ of the PRS is expected to increase in comparison to the average mortality, due to the presence of a higher number of cancers in this group. The OR for death in the top $n\%$ of the PRS is unknown, so the average mortality rate can be scaled in proportion to the increase in incidence that occurs in the top $n\%$ of the PRS.
Cancers Arising	
The proportion of cancers expected in the n th percentile of the PRS is equal to the cumulative distribution function at point n of the Gaussian curve describing the distribution of polygenic risk scores in cancer cases.	This is inherent from assumptions and justifications described in Polygenic Risk Scores section above.
Cancers Detected by Screening	
All cancers that are expected to occur within the screening period are present at the time of screening	We model screening programs using a modality of given sensitivity. We assume that all cancers that will develop in that period have already developed at the time of the screen, regardless of screening periodicity. Thus, we over-estimate the impact of the screening, as we discount occurrence of 'interval' cancers (which would not exhibit the shifted stage distribution). We do not explicitly specify screening periodicity; we indicate the capacity requirements of screening two-yearly in regard of screening and diagnostic tests. The assumption is progressively more favourable for longer periodicity of screening.
The sensitivity and specificity of screening tools is constant across PRS-defined risk quantiles.	The sensitivity and specificity of a test is innate to the combination of test, disease, and patient population. It is assumed cancers will not differ systematically in their biology, clinical characteristics or clinical behaviour between the different risk quantiles on account of the underlying GWAS having identified SNP associations from comparison to controls of broad cancer case series, which have been ascertained agnostic to biology and clinical outcome.(10,40)
The sensitivity and specificity of screening tools is constant across age groups	The sensitivity and specificity calculated from screening data in older populations has been applied in our hypothetical analyses of screening in younger populations. In practice it is likely that test performance may be poorer, for example digital mammography in younger women may have poorer sensitivity and specificity on account of higher breast density. In this event, our analyses will overestimate the detection rate and survival benefit for these younger populations.
The cancers detected when screening is introduced are displaced proportionately from the other 3 routes to diagnosis	When modelling introduction of screening, we modelled proportionate shift into screening from across the current routes to diagnosis. In practice, those attending screening are possibly more likely to otherwise present as routine or urgent symptomatic (GP referral routes) than emergency. Accordingly, the predicted survival gain from introduction of screening may be over-emphasised.
The proportion of cancers that are overdiagnoses is constant across PRS-defined risk quantiles.	It is assumed cancers will not differ systematically in their biology, clinical characteristics or clinical behaviour between the different risk quantiles on account of the underlying GWAS having identified SNP associations from comparison to controls of broad cancer case series, which have been

	ascertained agnostic to biology or clinical outcome.(10,40). Accordingly, if trials demonstrate that 42% of cancers detected on unselected population screening are overdiagnoses, we have assumed that 42% of cancers diagnosed in any risk quartile will be overdiagnoses.
Uptake	
There is 100% uptake for SNP-genotyping and screening	This is a deliberate simplification to illustrate maximal theoretical impact for PRS-risk-based screening. In practice, uptake of national screening programs is typically $\leq 70\%$ with bias away from population groups at highest cancer risk (relating to their socio-economic and lifestyle factors). Uptake of PRS-SNP genotyping will likely be context- and population-specific; reported uptake of PRS-based stratification when offered as part of a study within the UK NHSBSP (NHS Breast Screening Program) was $<20\%$.(14)
Survival	
Cancer-specific survival has remained static since 2008.	Application of survival data for 2008-2017 for future predictions around screening assumes no change in stage-specific survival. Improvements in stage-specific survival since 2008 will likely mean that survival gains from stage-shift are over-estimated (but would depend on any stage-specific patterns)
The age-stage-specific 10-year survival can be approximated from the age-specific 10-year survival adjusted for the ratio of 5-year stage-specific survival.	For most solid tumours, survival at 10 years post diagnosis typically equates to long-term survival. NCRAS only routinely generated stage-specific survival from 2013. Hence, to obtain stage-specific 10-year survival, we applied established methods of applying the ratio of stage-specific to all stage survival at 5 years (2013-17) to all-stage survival at 10-years (2008-2017).
One-year age specific incidence rates can be estimated from adjacent 5-year age-specific incidence rates using linear interpolation	5-year age-specific incidence rates rise with age across all cancers, but do so in a variable format. Simple linear interpolation allows estimation of one-year age-specific incidence rates within age-bands.
Cancers currently detected by screening in the target age groups would be proportionally detected by other routes to diagnosis in the absence of screening	<p>For breast cancers aged 40-49 and colorectal cancers aged 40-59, a small proportion are currently diagnosed by screening. This is predominantly due to inclusion via an age extension trial (e.g., Age X)*. We model these groups of individuals who are currently having breast screening age 40-49 or colorectal screening age 40-59 as being redistributed into other routes of diagnosis in proportion to the rest of the population. Screening uptake may be higher in individuals of higher socio-economic status, and these individuals may also be less likely to be diagnosed via an emergency presentation. Thus, when redistributing screen-diagnosed individuals proportionally into other routes of diagnosis, we may over-estimate the number of individuals presenting by the emergency route as the baseline.</p> <p>Thus, we are establishing a favourable baseline for comparison in regard of there being absolutely no screening to start, and may even be further lowering the survival rates for this baseline group.</p> <p>*Annual mammography 40-49 for women who carry a high penetrance germline gene mutation (e.g., BRCA1) or early-life mantle radiotherapy have only been migrated to NHSBSP in 2018, and thus will not distort these figures. Women who are eligible for annual mammography aged 40-49 via the NICE moderate-risk pathway are included in the 'Routine' diagnosis route as these mammograms are not conducted via NHSBSP</p>
Proportion of cancers of each stage in each route to diagnosis remains constant despite reduction for cancers detected by screening.	It is assumed that subtraction of a group of cancers for detection by screening does not alter the distribution of stage of detection for each of the other three other routes to diagnosis.

Supplementary Table 3. Screening tool characteristics. Description of currently available “real world” screening tools for cancer and their characteristics including sensitivity and specificity.

Cancer Site	Screening Tool	Sensitivity	Specificity	Detail	Trial/Source	Reference
Colorectal	FIT 20 µg/g threshold (CRC)	89	91	20 µg/g threshold (CRC)	Systematic review and meta-analysis	Lee J.K. et al. <i>Ann. Intern. Med.</i> (2014).
	FIT 20-50 µg/g threshold (CRC)	70	95	20-50 µg/g threshold (CRC)	Systematic review and meta-analysis	
	FIT >50 µg/g threshold (CRC)	67	96	>50 µg/g threshold (CRC)	Systematic review and meta-analysis	
Pancreas	CA19-9_20U/mL cut-off	67·8	83	20 U/mL cut-off	Meta-analysis	Zhang Y. et al. <i>Int. J. Clin. Exp. Med.</i> (2015).
	CA19-9_37U/mL cut-off	76·4	72·9	37 U/mL cut-off	Meta-analysis	
Lung	Low dose CT	84·6	98·6	Three rounds of low-dose CT	NELSON Trial	Herwig N. et al. <i>Lancet Oncol.</i> (2014).
Breast	Film mammography	66	92	All women, with use of BIRADS Score	DMIST Trial	Pisano E.D. et al. <i>N. Engl. J. Med.</i> (2005).
	Digital mammography	70	92	All women, with use of BIRADS Score	DMIST Trial	
Ovary	MMS (CA-125 + TVU)	84	99	First line screening with CA-125 interpreted via ROCA and second-line screening via TVU	UKCTOCS Trial	Jacobs I.J. et al. <i>Lancet</i> (2015).
	USS	72·9	96·8	First and second line screening via TVU	UKCTOCS Trial	
Prostate	PSA_4ng/mL cut-off	21	91	4ng/mL cut-off	Prostate Cancer Prevention Trial (USA)	Wolf A.M.D. et al. <i>Cancer J Clin.</i> (2010).
	PSA_3ng/mL cut-off	32	85	3ng/mL cut-off	Prostate Cancer Prevention Trial (USA)	
	mpMRI	89	73	Mend suspected or diagnosed with prostate cancer, with use of PI-RADSv2 score	Meta-analysis	Woo S. et al. <i>Eur. Urol.</i> (2017).
Testis	Semen assay	67	98	automated immunocytochemical staining, scanning microscopy and in silico image analysis	Single Study	Amstrad K. et al. <i>Int. J. Andros.</i> (2011).
Kidney	USS	82	98	Renal ultrasound scan	Literature Review	Rossi S.H. et al. <i>World J. Urol.</i> (2018).

Supplementary Table 4. Summary of PRS Characteristics

PRS Characteristics			Odds Ratios of quartile versus average (middle quintile)					Percentage of cancers captured within the PRS-defined high risk quintile					
Cancer Site	Number of Variants	AUC	Top 50%	Top 20%	Top 10%	Top 5%	Top 1%	Top 50%	Top 20%	Top 10%	Top 5%	Top 1%	
Current PRS	Breast	286,144	0.64	1.59	2.13	2.54	2.96	4.03	70%	37%	22%	13%	4%
	Prostate	178,259	0.70	2.01	2.99	3.83	4.75	7.32	77%	46%	29%	18%	6%
	Colorectal	87	0.62	1.45	1.84	2.12	2.41	3.09	66%	34%	19%	11%	3%
	Pancreas	10	0.58	1.27	1.50	1.65	1.80	2.13	61%	29%	16%	9%	2%
	Ovary	12	0.56	1.19	1.34	1.44	1.53	1.74	58%	26%	14%	8%	2%
	Kidney	12	0.52	1.05	1.09	1.11	1.13	1.17	52%	22%	11%	6%	1%
	Lung	19	0.55	1.17	1.30	1.39	1.47	1.64	57%	26%	14%	7%	2%
	Testis	44	0.70	2.05	3.07	3.95	4.93	7.65	77%	47%	30%	19%	6%
Future PRS	Breast	..	0.69	1.91	2.79	3.52	4.32	6.48	76%	44%	28%	17%	5%
	Prostate	..	0.72	2.16	3.32	4.34	5.49	8.76	79%	48%	32%	20%	6%
	Colorectal	..	0.64	1.58	2.10	2.50	2.92	3.94	70%	37%	22%	13%	3%
	Pancreas	..	0.65	1.64	2.22	2.67	3.14	4.33	71%	38%	23%	14%	4%
	Ovary	..	0.61	1.43	1.81	2.08	2.35	3.00	66%	33%	19%	11%	3%
	Kidney	..	0.65	1.60	2.15	2.58	3.01	4.11	70%	38%	22%	13%	4%
	Lung	..	0.61	1.41	1.76	2.01	2.26	2.86	65%	33%	19%	11%	3%
	Testis	..	0.84	4.76	9.20	14.13	20.80	45.55	92%	71%	55%	40%	18%
Optimised PRS	Breast	7,599	0.71	2.11	3.22	4.17	5.24	8.28	78%	48%	31%	19%	6%
	Prostate	4,530	0.73	2.33	3.68	4.90	6.30	10.43	81%	51%	34%	22%	7%
	Colorectal	1,484	0.68	1.85	2.65	3.31	4.03	5.94	75%	43%	27%	16%	5%
	Pancreas	1,757	0.71	2.11	3.22	4.17	5.24	8.28	78%	48%	31%	19%	6%
	Ovary	1,015	0.64	1.57	2.09	2.49	2.89	3.90	69%	37%	22%	13%	3%
	Kidney	2,220	0.70	2.02	3.01	3.86	4.80	7.40	77%	46%	29%	18%	6%
	Lung	6,096	0.67	1.77	2.50	3.08	3.70	5.34	73%	41%	25%	15%	4%
	Testis	2,598	0.88	7.35	15.33	25.04	39.15	97.79	95%	79%	65%	51%	25%

Supplementary Table 5. Lifetime risk of eight cancers for the general population, and for the top 50%, 20%, 10%, 5%, and 1% of current, future, and optimised PRS.
 Lifetime risk is calculated using the current probability method and a period approach, which takes into account competing risks.

PRS	Cancer Site	PRS AUC	Absolute lifetime risk (%)											
			Population average		top 50% of PRS		top 20% of PRS		top 10% of PRS		top 5% of PRS		top 1% of PRS	
			Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Current PRS	Breast	0.64	-	14.3	-	19.5	-	25.3	-	29.5	-	33.7	-	43.4
	Prostate	0.70	15.2	-	22.6	-	31.9	-	39.1	-	46.4	-	63.2	-
	Colorectal	0.62	7.6	5.9	10.0	7.7	12.6	9.8	14.4	11.2	16.2	12.7	20.5	16.0
	Pancreas	0.58	1.8	1.6	2.2	2.0	2.6	2.3	2.8	2.6	3.1	2.8	3.7	3.3
	Ovary	0.56	-	2.1	-	2.4	-	2.7	-	3.0	-	3.1	-	3.5
	Kidney	0.52	2.6	1.5	2.7	1.5	2.8	1.6	2.8	1.6	2.9	1.7	3.0	1.7
	Lung	0.55	8.4	7.1	9.6	8.2	10.7	9.1	11.4	9.7	12.0	10.2	13.4	11.4
	Testis	0.70	0.5	-	0.8	-	1.3	-	1.6	-	2.0	-	3.1	-
Future PRS	Breast	0.69	-	14.3	-	20.9	-	29.3	-	35.7	-	42.2	-	57.6
	Prostate	0.72	15.2	-	23.1	-	33.5	-	41.6	-	49.8	-	66.8	-
	Colorectal	0.64	7.6	5.9	10.5	8.1	13.7	10.7	16.2	12.6	18.7	14.6	24.7	19.4
	Pancreas	0.65	1.8	1.6	2.5	2.3	3.4	3.1	4.1	3.8	4.9	4.4	6.7	6.1
	Ovary	0.61	-	2.1	-	2.8	-	3.5	-	4.0	-	4.5	-	5.7
	Kidney	0.65	2.6	1.5	3.6	2.1	4.8	2.8	5.7	3.3	6.6	3.8	8.9	5.2
	Lung	0.61	8.4	7.1	10.9	9.3	13.5	11.5	15.4	13.2	17.3	14.8	21.7	18.5
	Testis	0.84	0.5	-	1.0	-	1.9	-	2.9	-	4.3	-	9.2	-
Optimised PRS	Breast	0.71	-	14.3	-	21.6	-	31.3	-	39.0	-	46.8	-	65.3
	Prostate	0.73	15.2	-	23.6	-	34.9	-	43.9	-	53.1	-	74.0	-
	Colorectal	0.68	7.6	5.9	11.2	8.7	15.8	12.3	19.4	15.2	23.3	18.3	32.9	26.1
	Pancreas	0.71	1.8	1.6	2.8	2.6	4.3	3.9	5.5	5.0	6.9	6.3	10.9	9.9
	Ovary	0.64	-	2.1	-	2.9	-	3.8	-	4.6	-	5.3	-	7.1
	Kidney	0.70	2.6	1.5	3.9	2.3	5.8	3.4	7.4	4.3	9.1	5.3	13.8	8.1
	Lung	0.67	8.4	7.1	12.2	10.4	17.0	14.5	20.9	17.8	24.8	21.3	35.4	30.2
	Testis	0.88	0.5	-	1.0	-	2.1	-	3.5	-	5.4	-	13.0	-

Supplementary Table 6c(i). Cancers detected by offering risk stratified screening according to optimised PRS using sensitivity of currently available “real world” screening tools (Cancers of the Breast, Prostate, Colorectum and Pancreas)

Cancer Type	Screening modality	Age Group	Annual Incidence (per 100,000 for ageband)		Population		Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS											
			Male	Female	Population Size	Cancers arising per year	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unselected low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unselected low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unselected low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unselected low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified						
Breast	Digital mammography	40 to 44	0.0	124.6	2,054,223	2,559	1,077,112	2,004	595	601	1,409	55	410,845	1,219	1,940	966	859	99	305,422	750	1,769	257	559	22	102,711	497	2,062	149	948	14	30,542	157	2,402	47	110	4
Breast	Digital mammography	45 to 49	0.0	214.8	2,515,479	4,994	1,152,740	3,895	1,099	1,168	2,736	55	463,096	2,370	2,604	711	1,659	99	231,548	1,597	3,457	461	1,076	22	115,774	966	4,008	230	676	14	23,155	905	4,669	92	214	4
Breast	Digital mammography	50 to 54	0.0	279.8	2,964,638	6,616	1,182,919	5,181	1,495	1,954	3,677	55	472,908	3,152	3,464	946	2,207	99	236,464	2,074	4,182	613	1,431	22	118,232	1,285	5,391	386	900	14	23,646	406	6,210	122	284	4
Breast	Digital mammography	55 to 59	0.0	285.5	2,119,687	6,052	1,059,844	4,799	1,313	1,422	3,317	55	423,937	2,884	3,168	865	2,019	99	211,969	1,870	4,182	561	1,309	22	105,984	1,176	4,876	393	823	14	21,197	371	5,681	111	260	4
Breast	Digital mammography	60 to 64	0.0	338.0	1,877,174	6,709	918,587	4,862	1,947	1,499	4,000	55	367,495	2,958	3,261	888	2,071	99	181,717	1,918	4,291	575	1,349	22	91,859	1,306	5,093	362	844	14	18,572	381	5,828	114	267	4
Breast	Digital mammography	65 to 69	0.0	412.3	1,845,180	7,949	918,458	5,828	1,615	1,749	4,080	55	366,038	3,226	3,587	1,064	2,569	22	180,519	2,299	5,144	650	1,650	22	90,180	1,456	5,997	434	1,012	14	18,062	456	6,987	155	320	4
Breast	Digital mammography	70 to 74	0.0	372.7	1,629,610	8,977	801,875	4,680	1,977	1,494	3,716	55	399,722	3,218	3,529	854	1,998	99	160,969	1,846	4,381	247	1,147	22	80,180	1,161	4,916	364	814	14	16,095	367	6,010	110	287	4
Breast	Digital mammography	75 to 79	0.0	403.0	1,181,645	4,762	590,223	3,729	1,023	1,119	2,610	55	286,329	2,369	2,493	681	1,588	99	118,165	1,471	3,291	441	1,090	22	59,082	925	3,837	278	648	14	11,816	292	4,470	88	204	4
Breast	Digital mammography	Total 40-69	0.0	270.9	12,966,392	33,853	6,248,136	26,509	7,344	7,993	18,596	55	2,699,778	16,190	17,723	4,839	11,291	99	1,349,639	10,457	23,396	3,137	7,320	22	630,830	6,577	27,276	1,973	4,604	14	134,964	2,076	31,777	623	1,453	4
Breast	Digital mammography	Total 40-69	0.0	172.4	4,369,703	7,533	2,184,851	5,809	1,634	1,770	4,129	55	873,941	5,389	5,944	1,077	2,512	22	436,970	2,327	5,206	698	1,629	22	218,485	1,463	6,070	439	1,024	14	43,697	462	7,071	139	323	4
Breast	Digital mammography	Total 50-59	0.0	282.5	4,484,123	12,668	2,242,163	9,920	2,748	2,976	6,944	55	896,865	6,016	6,612	1,811	4,225	99	448,493	3,913	8,795	1,174	2,739	22	234,216	2,461	10,207	738	1,725	14	44,843	777	11,891	293	544	4
Breast	Digital mammography	Total 50-59	0.0	323.9	8,126,689	26,520	4,063,345	20,610	5,710	6,189	14,437	55	1,625,338	12,541	13,779	3,462	8,778	99	812,669	6,190	18,190	2,439	5,691	22	406,334	5,113	23,207	1,534	3,579	14	81,267	1,614	24,706	484	1,140	4
Breast	Digital mammography	Total 60-74	0.0	374.2	5,395,394	19,629	7,622,987	15,371	4,258	4,611	10,760	55	1,091,195	9,393	10,266	2,806	6,547	99	574,997	6,064	15,565	1,819	4,344	22	302,399	3,818	15,816	1,144	2,669	14	52,483	1,203	18,425	361	883	4
Breast	Digital mammography	Total 40-79	0.0	291.8	15,281,647	44,592	7,640,834	34,919	9,673	10,476	24,443	55	3,056,329	21,347	23,345	6,374	14,873	99	1,528,165	13,775	30,817	4,132	9,642	22	764,082	8,663	35,929	2,599	6,064	14	152,816	2,735	41,857	820	1,914	4
Breast	Digital mammography	Total (all ages)	0.0	166.0	39,438,052	95,545																														
Prostate	PSA 3ng/mL cut-off	40 to 44	4.3	0.0	2,021,385	88	1,010,692	71	17	48	29	26	404,277	45	49	91	14	16	302,138	30	58	30	10	11	101,069	19	69	19	6	7	20,214	6	82	4	2	2
Prostate	PSA 3ng/mL cut-off	45 to 49	20.5	0.0	2,251,680	461	1,125,840	572	89	293	119	26	450,936	235	226	160	75	16	225,168	156	305	106	50	11	112,584	101	960	68	92	7	22,517	9	428	23	11	2
Prostate	PSA 3ng/mL cut-off	50 to 54	75.7	0.0	2,293,473	1,737	1,146,736	1,402	335	393	449	26	458,695	886	851	602	283	16	229,947	589	1,148	401	188	11	114,674	579	1,358	258	121	7	22,995	125	1,612	85	40	4
Prostate	PSA 3ng/mL cut-off	55 to 59	201.8	0.0	2,061,919	4,160	1,030,959	5,977	803	2,381	1,074	26	412,384	2,122	2,008	1,449	679	16	206,192	2,131	2,749	999	451	11	103,096	908	3,252	617	290	7	20,619	900	3,860	304	96	2
Prostate	PSA 3ng/mL cut-off	60 to 64	356.1	0.0	1,864,828	6,205	882,414	5,072	1,233	3,489	1,625	26	392,366	3,205	3,000	2,180	1,036	16	176,483	2,431	4,154	1,449	647	11	88,241	1,372	4,913	939	499	7	17,648	454	5,891	309	145	2
Prostate	PSA 3ng/mL cut-off	65 to 69	622.7	0.0	1,606,993	10,638	848,497	8,528	2,060	5,399	2,739	26	399,399	5,900	5,598	3,665	1,739	26	169,699	3,984	6,384	2,457	1,147	11	81,893	2,306	8,262	1,568	718	7	16,959	763	9,895	519	284	3
Prostate	PSA 3ng/mL cut-off	70 to 74	759.8	0.0	1,467,965	11,159	739,983	9,000	2,193	6,100	2,880	26	399,599	5,688	5,465	3,868	1,820	26	146,957	3,782	7,371	2,572	1,210	11	73,998	2,494	8,719	1,655	779	7	14,680	825	10,548	547	258	2
Prostate	PSA 3ng/mL cut-off	75 to 79	867.2	0.0	1,007,965	8,796	501,683	7,044	1,687	4,794	2,260	26	301,473	4,455	4,381	3,000	1,426	16	100,797	2,622	5,774	2,014	910	11	50,968	1,906	6,830	1,296	610	7	10,074	631	8,105	429	202	2
Prostate	PSA 3ng/mL cut-off	Total 40-69	192.7	0.0	12,020,727	23,299	6,045,139	18,801	4,408	12,784	6,016	26	2,418,055	11,882	11,417	8,000	3,802	16	1,209,028	10,001	19,398	5,373	2,528	22	604,514	5,084	18,215	3,457	1,627	7	130,029	1,682	21,617	1,144	538	2
Prostate	PSA 3ng/mL cut-off	Total 40-69	12.8	0.0	4,273,065	549	2,136,512	443	105	301	142	26	854,615	280	269	190	102	16	427,906	186	363	137	60	11	213,693	120	429	81	38	7	42,791	40	509	27	19	2
Prostate	PSA 3ng/mL cut-off	Total 50-59	135.4	0.0	4,955,991	5,897	2,177,696	4,758	1,139	3,236	1,529	26	871,078	3,077	2,880	2,095	962	16	495,599	2,000	3,887	1,360	640	11	217,770	1,287	4,610	875	412	7	49,554	426	5,471	289	136	2
Prostate	PSA 3ng/mL cut-off	Total 50-59	486.8	0.0	3,461,821	16,839	7,922,911	15,971	4,254	9,367	4,352	26	692,364	4,995	4,258	3,894	2,350	16	346,182	5,715	11,138	3,886	1,829	22	171,091	3,678	13,175	2,501	1,177	7	34,618	1,217	15,636	827	389	2
Prostate	PSA 3ng/mL cut-off	Total 60-74	291.0	0.0	7,817,213	22,790	3,908,606	18,358	4,902	12,483	5,874	26	1,563,445	11,602	11,148	7,889	3,713	16	781,721	7,015	15,095	2,646	2,469	11	390,861	4,965	17,785	3,376	1,589	7	78,172	1,682	21,108	1,117	526	2
Prostate	PSA 3ng/mL cut-off	Total 60-74	568.1	0.0	4,929,786	28,006	2,464,893	22,599	5,407	15,367	7,232	26	985,957	14,283	13,723	9,712	4,570	16	492,979	9,497	18,509	6,458	3,039	11	246,489	6,112	21,894	4,156	1,956	7	49,298	2,022	29,984	1,575	647	2
Prostate	PSA 3ng/mL cut-off	Total 40-79	296.5	0.0	14,565,608	43,188	7,282,804	34,850	8,338	23,698	11,152	26	2,913,122	22,025	21,163	14,977	7,048	16	1,456,561	14,645	28,583	9,959														

Supplementary Table 6c(ii). Cancers detected by offering risk stratified screening according to optimised PRS using sensitivity of currently available “real world” screening tools (Cancers of the Ovary, Kidney, Lung, Testis)

Cancer Type	Screening modality	Age Group	Annual Incidence (per 100,000 for ageband)		Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS															
			Male	Female	Population Size	Cancers arising per year	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unscreened low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unscreened low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unscreened low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in unscreened low risk group	Cancers missed on screening in high-risk group	Cancers detected on screening in high-risk group	Percent of cancers identified								
Ovary																																						
Ovary	MBS (CA-125 + TVU)	40 to 44	0.0	13.2	2,054,223	270	1,027,112	187	83	30	157	58	410,845	100	170	16	84	91	305,422	59	211	9	50	18	102,711	94	236	6	29	11	20,542	9	261	1	8	9		
Ovary	MBS (CA-125 + TVU)	45 to 49	0.0	19.4	2,515,479	448	1,152,740	911	157	50	261	58	463,096	165	283	26	139	91	231,548	98	350	16	83	18	115,774	57	391	9	48	11	23,155	15	433	2	13	9		
Ovary	MBS (CA-125 + TVU)	50 to 54	0.0	27.1	2,964,638	640	1,182,919	444	196	71	373	58	472,928	236	404	38	198	91	236,464	140	500	22	118	18	115,732	82	558	19	69	11	23,646	22	618	4	19	9		
Ovary	MBS (CA-125 + TVU)	55 to 59	0.0	34.8	2,119,687	738	1,059,844	512	236	82	430	58	423,937	272	466	44	229	91	21,969	162	576	26	136	18	105,984	94	644	15	79	11	21,197	25	713	4	21	9		
Ovary	MBS (CA-125 + TVU)	60 to 64	0.0	41.6	1,877,174	764	918,587	530	234	85	445	58	367,495	282	482	45	237	91	183,717	168	596	27	141	18	91,859	97	667	16	82	11	18,727	26	738	4	22	9		
Ovary	MBS (CA-125 + TVU)	65 to 69	0.0	52.3	1,805,180	994	1,805,180	595	289	105	508	58	36,038	348	596	56	259	91	180,519	207	757	39	174	18	30,130	130	824	19	101	11	18,052	32	912	5	27	9		
Ovary	MBS (CA-125 + TVU)	70 to 74	0.0	69.8	1,629,610	975	801,878	677	238	108	508	58	300,472	360	615	58	302	91	160,961	214	761	30	104	11	16,036	134	851	30	104	11	16,036	94	941	5	28	9		
Ovary	MBS (CA-125 + TVU)	75 to 79	0.0	73.8	1,181,645	872	502,823	605	267	97	508	58	236,329	322	520	51	270	91	118,165	191	681	31	161	18	59,082	111	768	11	93	11	11,816	30	842	5	25	9		
Ovary	MBS (CA-125 + TVU)	Total 40-69	0.0	30.4	12,496,392	3,804	6,248,196	2,640	1,164	422	2,117	58	2,499,738	1,403	2,401	225	1,179	91	1,349,639	834	2,970	133	701	18	634,830	485	3,319	78	408	11	134,964	131	3,673	21	110	9		
Ovary	MBS (CA-125 + TVU)	Total 40-69	0.0	16.4	4,369,703	718	2,184,851	2,640	230	80	419	58	873,941	265	453	42	223	91	436,970	157	561	25	132	18	218,485	92	626	15	77	11	43,697	25	693	4	21	9		
Ovary	MBS (CA-125 + TVU)	Total 50-59	0.0	30.7	4,484,123	1,378	2,242,163	956	422	153	803	58	896,865	508	870	81	427	91	448,493	302	1,076	48	254	18	234,216	176	1,202	28	148	11	44,863	47	1,931	8	40	9		
Ovary	MBS (CA-125 + TVU)	Total 50-59	0.0	38.0	8,126,689	3,086	4,063,345	2,141	995	343	1,599	58	1,625,338	1,159	1,987	182	956	91	812,669	677	2,409	108	508	18	406,334	394	2,602	63	931	11	81,267	106	2,580	17	89	9		
Ovary	MBS (CA-125 + TVU)	Total 60-74	0.0	51.1	5,395,374	2,683	2,622,987	1,862	821	308	1,564	58	1,091,195	920	1,659	158	831	91	574,977	588	2,095	94	494	18	362,399	342	2,341	56	238	11	52,463	92	2,591	15	78	9		
Ovary	MBS (CA-125 + TVU)	Total 40-79	0.0	37.0	15,281,647	5,651	7,640,834	5,921	1,700	627	3,294	58	3,056,329	2,085	3,566	334	1,751	91	1,528,165	1,239	4,412	138	1,041	18	764,082	721	4,930	115	606	11	152,816	195	5,456	31	163	9		
Ovary	MBS (CA-125 + TVU)	Total (all ages)	0.0	22.8	37,428,052	7,695																																
Kidney																																						
Kidney	USS	40 to 44	10.1	5.0	4,075,608	507	2,057,804	237	70	64	179	56	815,122	141	166	38	103	94	407,561	90	217	25	66	21	303,780	56	251	15	41	13	40,756	17	250	5	13	4		
Kidney	URS	45 to 49	17.7	7.8	4,567,159	580	2,283,580	447	193	121	326	56	913,432	267	313	72	195	94	456,716	171	409	46	125	21	228,338	106	474	29	77	13	45,672	33	547	9	24	4		
Kidney	URS	50 to 54	26.8	12.7	4,608,111	915	2,329,055	705	210	191	514	56	911,622	421	494	114	307	94	465,811	270	645	73	197	21	232,906	168	747	45	122	13	46,381	92	863	14	38	4		
Kidney	URS	55 to 59	37.1	18.6	4,181,606	1,160	2,090,803	804	266	262	652	56	836,321	514	626	145	489	94	418,161	342	818	99	249	21	209,000	213	947	58	155	13	41,816	66	1,094	18	48	4		
Kidney	URS	60 to 64	53.7	26.2	3,602,022	1,429	1,801,001	1,024	327	289	803	56	720,400	658	771	178	479	94	360,200	421	1,008	114	307	21	180,100	262	1,167	71	199	13	36,020	81	1,548	22	59	4		
Kidney	URS	65 to 69	79.9	36.4	3,502,181	1,919	1,751,092	1,473	438	399	1,074	56	700,477	879	1,032	238	641	94	370,911	564	1,361	193	410	21	191,000	320	1,561	95	255	15	35,027	308	1,803	29	78	4		
Kidney	URS	70 to 74	91.2	45.1	3,071,575	2,063	1,535,787	1,590	479	431	1,159	56	614,915	949	1,114	257	692	94	307,157	608	1,455	165	443	21	159,579	378	1,685	102	276	13	30,716	117	1,946	32	85	4		
Kidney	URS	75 to 79	110.1	57.2	2,189,011	1,785	1,094,505	1,376	409	379	1,001	56	497,802	821	964	253	599	94	218,901	536	1,259	143	383	21	109,451	327	1,438	80	218	13	21,800	101	1,684	27	74	4		
Kidney	URS	Total 40-69	34.6	16.9	24,586,669	6,302	12,293,335	4,858	1,444	1,316	3,541	56	4,917,334	2,900	3,402	786	2,114	94	2,458,667	1,857	4,445	503	1,154	21	1,229,339	1,155	5,147	313	842	13	245,267	356	5,946	97	260	4		
Kidney	URS	Total 40-69	14.1	6.5	8,642,767	887	4,321,384	684	203	185	498	56	1,728,593	408	479	111	298	94	864,777	361	626	71	191	21	492,138	162	725	44	118	13	86,428	50	837	14	37	4		
Kidney	URS	Total 50-59	31.7	15.5	8,839,717	2,075	4,419,828	1,599	476	439	1,166	56	1,767,943	955	1,120	259	696	94	883,972	611	1,464	166	446	21	441,396	380	1,695	109	277	13	88,397	117	1,958	32	85	4		
Kidney	URS	Total 50-59	46.8	22.6	15,993,902	5,415	7,971,951	4,174	1,261	1,191	3,001	56	3,188,780	2,492	2,923	675	1,817	94	1,594,900	1,195	3,820	432	1,161	21	797,195	932	4,423	269	729	13	159,499	308	5,103	83	229	4		
Kidney	URS	Total 60-74	71.8	35.5	10,175,760	5,403	5,087,880	4,165	1,238	1,129	3,036	56	2,085,152	2,486	2,917	674	1,813	94	1,017,576	1,592	3,811	431	1,160	21	508,788	930	4,413	268	722	13	101,758	905	5,028	83	223	4		
Kidney	URS	Total 40-79	45.5	23.0	29,847,255	10,150	14,923,627	7,824	2,326	2,120	5,704	56	5,969,451	4,671	5,479	1,266	3,405	94	2,984,725	2,990	7,160	810	2,180	21	1,492,363	1,859	8,291	504	1,956	13	298,473	574	9,576	155	418	4		
Kidney	URS	Total (all ages)	29.2	14.8	66,041,278	13,923																																
Lung																																						
Lung	Low dose CT	40 to 44	6.0	5.8	4,075,608	240	2,057,804	176	64	77	149	62	815,122	99	141	1																						

Supplementary Table 7a(i). Cancers detected by offering risk stratified screening according to current PRS using an idealised screening tool with a sensitivity of 0.8 (Cancers of the Breast, Prostate, Colorectum and Pancreas)

Cancer Type	Age Group	Annual Incidence (per 100,000) for age-band		Population		Screening offered to top 50% of PRS						Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS						
		Male	Female	Population Size	Cancers arising	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in uncensored 'low risk' group	Cancers missed on screening in 'high-risk' group	Cancers detected on screening in 'high-risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in uncensored 'low risk' group	Cancers missed on screening in 'high-risk' group	Cancers detected on screening in 'high-risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in uncensored 'low risk' group	Cancers missed on screening in 'high-risk' group	Cancers detected on screening in 'high-risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in uncensored 'low risk' group	Cancers missed on screening in 'high-risk' group	Cancers detected on screening in 'high-risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in uncensored 'low risk' group	Cancers missed on screening in 'high-risk' group	Cancers detected on screening in 'high-risk' group	Percent of cancers identified	
Breast																																				
Breast	40 to 44	0.0	124.6	2,054,225	2,559	1,027,112	1,786	773	357	1,429	56	410,845	955	1,604	191	764	30	205,422	570	1,989	114	456	18	102,711	393	2,226	67	266	10	20,542	90	2,469	18	72	9	
Breast	45 to 49	0.0	214.8	2,315,479	4,974	1,157,940	4,771	1,505	694	2,777	56	463,096	1,836	3,118	371	1,485	56	231,548	1,107	3,867	221	886	18	115,774	646	4,528	129	517	10	23,155	176	4,798	35	140	9	
Breast	50 to 54	0.0	279.8	2,364,898	6,616	1,182,319	4,617	1,999	923	3,694	56	472,928	2,469	4,147	494	1,975	56	236,464	1,479	5,143	295	1,178	18	118,232	850	5,756	172	688	10	23,646	294	6,582	47	187	9	
Breast	55 to 59	0.0	285.5	2,119,687	6,052	1,059,844	4,274	1,828	845	3,739	56	423,917	2,259	3,793	452	1,807	56	211,969	1,948	4,704	270	1,078	18	105,984	787	5,265	157	629	10	21,197	214	5,818	43	171	9	
Breast	60 to 64	0.0	338.0	1,877,174	6,209	918,587	4,393	1,876	867	3,466	56	367,435	2,317	3,892	463	1,854	56	183,717	1,882	4,827	276	1,105	18	91,859	807	5,402	161	646	10	18,372	219	5,900	44	175	9	
Breast	65 to 69	0.0	412.3	1,802,190	7,443	902,595	5,194	2,249	1,029	4,155	56	361,038	2,778	4,665	556	2,222	56	180,519	1,657	5,786	391	1,326	18	90,260	967	6,476	193	774	10	18,052	263	7,180	53	210	9	
Breast	70 to 74	0.0	372.7	1,603,610	5,977	801,805	4,171	1,806	834	3,397	56	320,722	2,231	3,746	446	1,785	56	160,361	1,931	4,646	266	1,065	18	80,180	777	5,200	155	621	10	16,036	211	5,566	42	169	9	
Breast	75 to 79	0.0	403.0	1,181,645	4,762	590,823	3,323	1,439	665	2,659	56	273,941	1,777	2,985	355	1,422	56	118,165	1,060	3,702	212	848	18	59,082	619	4,143	124	495	10	11,816	168	4,594	34	134	9	
Breast	Total 40-69	0.0	270.9	12,496,992	39,853	6,248,196	26,625	10,228	4,725	18,900	56	2,499,278	12,635	21,218	2,527	10,108	56	1,249,619	7,538	26,315	1,508	6,030	18	624,820	4,400	29,453	880	3,520	10	124,964	1,195	32,658	299	956	9	
Breast	Total 40-69	0.0	172.4	4,369,703	7,593	2,184,851	5,257	2,276	1,051	4,206	56	873,941	2,811	4,722	562	2,349	56	436,970	1,677	5,856	395	1,342	18	218,485	979	6,554	196	783	10	43,697	266	7,267	53	213	9	
Breast	Total 50-59	0.0	282.5	4,494,325	12,668	2,242,163	8,811	3,827	1,768	7,073	56	806,865	4,728	7,940	946	3,782	56	448,433	2,821	9,847	564	2,256	18	224,216	1,646	11,022	329	1,317	10	44,843	447	12,221	89	958	9	
Breast	Total 50-59	0.0	323.9	8,126,689	26,520	4,063,345	18,368	7,952	3,674	14,694	56	1,625,338	8,829	16,497	1,965	7,859	56	812,669	5,860	20,440	1,172	4,288	18	406,334	5,421	22,899	684	2,737	10	81,267	929	25,391	186	743	9	
Breast	Total 60-74	0.0	374.2	5,245,974	19,639	2,622,987	13,499	5,930	2,740	10,959	56	1,019,195	7,336	12,303	1,465	5,861	56	534,937	4,370	15,259	874	3,496	18	262,339	2,951	17,078	510	2,041	10	52,640	699	18,936	199	554	9	
Breast	Total 40-79	0.0	291.8	15,281,647	44,592	7,640,834	31,120	13,472	6,224	24,896	56	3,056,329	16,649	27,949	3,329	13,514	56	1,528,165	9,929	34,663	1,986	7,943	18	764,082	5,795	38,797	1,159	4,636	10	152,816	1,574	40,018	515	1,259	9	
Breast	Total (All ages)	0.0	166.0	33,438,052	55,545																															
Prostate																																				
Prostate	40 to 44	4.3	0.0	2,021,385	88	1,010,692	68	20	14	54	62	404,277	40	48	8	32	97	202,138	26	62	5	21	25	101,069	16	72	3	19	15	20,214	5	83	1	4	4	
Prostate	45 to 49	20.5	0.0	2,251,680	461	1,125,840	355	106	71	284	62	450,336	211	250	42	169	97	225,168	135	326	27	108	25	112,584	84	577	17	67	15	22,517	26	435	5	21	4	
Prostate	50 to 54	75.7	0.0	2,293,479	1,797	1,146,736	1,017	400	267	1,069	62	458,695	797	940	159	637	97	229,347	509	1,228	102	407	23	114,674	316	1,421	63	253	15	22,995	97	1,640	19	78	4	
Prostate	55 to 59	201.8	0.0	2,061,919	4,160	1,050,939	3,322	958	640	2,561	62	412,884	1,908	2,252	382	1,526	97	205,192	1,220	2,940	244	976	29	109,296	758	3,402	152	606	15	20,619	93	5,927	47	187	4	
Prostate	60 to 64	356.1	0.0	1,764,828	6,285	882,414	4,817	1,448	967	3,870	62	352,866	2,882	3,403	576	2,306	97	176,483	1,843	4,442	369	1,474	23	88,241	1,145	5,140	229	916	15	17,648	352	5,993	70	282	4	
Prostate	65 to 69	622.7	0.0	1,696,993	10,568	848,497	8,133	2,435	1,627	6,507	62	399,399	4,846	5,722	969	3,877	97	169,699	3,099	7,689	630	2,479	23	84,850	1,925	8,643	985	1,540	15	16,970	592	9,976	118	474	4	
Prostate	70 to 74	759.8	0.0	1,467,965	11,153	733,983	8,383	2,570	1,717	6,867	62	293,599	5,114	6,039	1,023	4,091	97	146,697	3,270	7,883	654	2,616	23	73,998	2,021	9,122	406	1,625	15	14,680	625	10,528	125	500	4	
Prostate	75 to 79	867.2	0.0	1,007,365	8,796	503,683	6,723	2,013	1,345	5,379	62	201,473	4,006	4,790	801	3,205	97	100,737	2,562	6,174	512	2,049	23	50,568	1,591	7,145	118	1,273	15	10,074	490	8,246	98	392	4	
Prostate	Total 40-69	192.7	0.0	12,090,277	23,299	6,045,139	17,991	5,368	3,386	14,345	62	2,418,055	10,684	12,615	2,137	8,547	97	1,209,028	6,832	16,467	1,366	5,465	23	604,514	4,343	19,056	819	3,395	15	120,903	1,306	21,999	261	1,045	4	
Prostate	Total 40-69	12.8	0.0	4,275,065	549	2,136,532	423	126	85	398	62	854,613	252	297	50	201	97	427,306	161	388	32	129	23	219,653	100	449	20	80	15	42,731	1	518	6	25	4	
Prostate	Total 50-59	135.4	0.0	4,355,391	5,897	2,177,696	4,398	1,559	908	3,818	62	873,941	2,704	3,193	541	2,163	97	435,999	1,729	4,168	346	1,289	23	217,770	1,074	4,823	215	859	15	43,554	391	5,566	66	264	4	
Prostate	Total 60-69	486.8	0.0	3,461,821	16,833	1,730,911	12,970	3,883	2,594	10,376	62	692,364	7,728	9,125	1,546	6,182	97	346,182	4,942	11,911	988	3,993	23	173,091	3,069	13,784	614	2,455	15	34,618	945	15,908	189	756	4	
Prostate	Total 50-69	291.0	0.0	7,817,215	22,750	3,908,606	17,509	5,241	3,502	14,007	62	1,563,443	10,432	12,318	2,086	8,346	97	781,721	6,671	16,079	1,934	5,937	23	390,861	4,149	18,607	829	3,315	15	78,172	1,275	21,475	255	1,020	4	
Prostate	Total 60-74	366.1	0.0	4,925,786	28,006	2,464,899	21,554	6,452	4,311	17,243	62	985,957	12,842	15,164	2,568	10,274	97	492,979	8,212	19,794	1,642	6,570	23	246,449	5,101	22,905	1,020	4,080	15	49,298	1,570	26,436	314	1,256	4	
Prostate	Total 40-79	296.5	0.0	14,565,608	43,188	7,382,804	39,238	9,950	6,648																											

Supplementary Table 7b(i). Cancers detected by offering risk stratified screening according to future PRS using an idealised screening tool with a sensitivity of 0.8 (Cancers of the Breast, Prostate, Colorectum and Pancreas)

Cancer Type	Age Group	Annual incidence (per 100,000) for age-band		Population		Screening offered to top 50% of PRS						Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS							
		Male	Female	Population Size	Cancers arising	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in uncensored low risk group	Cancers missed on screening in high risk group	Cancers detected on screening in high risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in uncensored low risk group	Cancers missed on screening in high risk group	Cancers detected on screening in high risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in uncensored low risk group	Cancers missed on screening in high risk group	Cancers detected on screening in high risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in uncensored low risk group	Cancers missed on screening in high risk group	Cancers detected on screening in high risk group	Percent of cancers identified	Number requiring screening in high risk group	Cancers arising in high risk group	Missed cancers arising in uncensored low risk group	Cancers missed on screening in high risk group	Cancers detected on screening in high risk group	Percent of cancers identified		
Breast																																					
Breast	40 to 44	0	125	2,054,223	2,559	1,027,112	1,914	625	387	1,548	60	410,845	1,129	1,490	226	905	35	205,422	712	1,847	142	569	22	102,711	437	2,122	87	349	14	20,542	131	2,428	26	105	4		
Breast	45 to 49	0	215	2,315,479	4,974	1,157,740	3,760	1,214	752	3,008	60	463,096	2,194	2,780	439	1,755	35	231,548	1,384	3,590	277	1,107	22	115,774	849	4,125	170	679	14	23,155	255	4,719	51	204	4		
Breast	50 to 54	0	280	2,364,638	6,616	1,182,919	5,001	1,615	1,000	4,001	60	473,922	2,918	3,698	584	2,334	35	236,464	1,800	4,776	368	1,472	22	118,232	1,129	5,487	226	905	14	23,646	339	6,277	68	271	4		
Breast	55 to 59	0	286	2,119,687	6,052	1,059,844	4,575	1,477	915	3,660	60	423,937	2,669	3,383	534	2,135	35	211,969	1,683	4,369	337	1,347	22	105,984	1,033	5,019	207	826	14	21,197	310	5,742	62	248	4		
Breast	60 to 64	0	338	1,837,174	6,209	918,387	4,693	1,516	999	3,755	60	367,495	2,738	3,471	548	2,191	35	183,717	1,727	4,432	345	1,382	22	91,859	1,060	5,149	212	848	14	18,372	318	5,891	64	254	4		
Breast	65 to 69	0	412	1,803,190	7,443	902,995	5,626	1,817	1,125	4,501	60	361,038	3,282	4,161	686	2,626	35	180,519	2,070	5,373	414	1,656	22	90,260	1,770	6,179	254	1,016	14	18,052	381	6,062	76	305	4		
Breast	70 to 74	0	578	1,603,919	5,377	620,825	4,538	1,459	904	3,634	60	320,722	2,656	3,341	527	2,109	35	160,363	1,663	4,314	333	1,390	22	80,180	1,020	4,957	204	816	14	16,286	306	5,691	61	245	4		
Breast	75 to 79	0	403	1,181,645	4,762	590,823	3,600	1,162	720	2,880	60	236,329	2,100	2,662	430	1,680	35	118,165	1,325	3,437	265	1,050	22	59,082	813	3,949	163	650	14	11,816	244	4,518	49	195	4		
Breast	Total 40-69	0	271	12,496,922	33,853	6,348,196	25,950	8,263	5,118	20,472	60	2,499,278	14,900	18,923	2,986	11,944	35	1,249,639	9,417	24,456	1,883	7,533	22	624,830	5,777	28,076	1,155	4,621	14	124,964	1,734	32,119	347	1,387	4		
Breast	Total 70-79	0	172	4,369,703	7,533	2,184,851	5,694	1,839	1,139	4,555	60	873,941	3,322	4,211	664	2,668	35	436,970	2,025	5,438	419	1,676	22	218,485	1,285	6,248	252	1,028	14	43,697	386	7,147	77	309	4		
Breast	Total 50-59	0	282	4,484,325	12,668	2,342,163	9,576	3,092	1,915	7,661	60	896,865	5,587	7,081	1,117	4,669	35	444,433	3,524	9,144	705	2,819	22	224,216	2,162	10,506	437	1,739	14	44,843	649	12,019	130	519	4		
Breast	Total 50-69	0	324	8,126,889	26,320	4,063,345	19,806	6,424	3,979	15,917	60	1,625,338	11,608	14,712	2,322	9,286	35	812,669	7,321	18,999	1,464	5,857	22	406,334	4,491	21,829	838	3,593	14	81,267	1,348	24,972	270	1,079	4		
Breast	Total 60-74	0	374	5,245,974	19,629	2,622,987	14,838	4,921	2,968	11,870	60	1,049,195	8,657	10,972	1,731	6,925	35	524,597	5,460	14,169	1,092	4,368	22	262,299	3,950	16,279	630	2,680	14	52,460	1,005	18,624	201	804	4		
Breast	Total 40-79	0	292	15,281,647	44,592	7,640,824	33,708	10,884	6,742	26,966	60	3,066,329	19,666	24,926	3,993	15,793	35	1,528,165	12,404	32,188	2,481	9,925	22	764,082	7,609	36,983	1,522	6,088	14	152,816	2,284	42,308	457	1,827	4		
Breast	Total (all ages)	0	166	33,458,052	55,545																																
Prostate																																					
Prostate	40 to 44	4	0	2,021,385	88	1,010,692	69	19	14	56	63	404,277	43	45	9	34	39	202,138	28	60	6	22	25	101,069	18	70	4	14	16	20,214	6	82	1	4	5		
Prostate	45 to 49	21	0	2,251,680	461	1,125,840	364	73	79	291	63	450,356	223	238	45	173	39	225,108	146	315	29	117	25	112,584	92	369	18	34	16	22,517	29	492	6	24	5		
Prostate	50 to 54	76	0	2,203,479	1,237	1,146,736	1,371	365	274	1,097	63	458,695	852	825	168	674	39	229,847	549	1,188	110	439	25	118,674	347	1,389	69	278	16	22,395	111	1,626	22	89	5		
Prostate	55 to 59	22	0	2,061,919	4,160	1,050,959	3,283	877	687	2,626	63	412,384	2,016	2,144	401	1,613	39	206,192	1,316	2,844	263	1,052	25	101,096	832	3,328	166	666	16	20,619	266	1,894	53	213	5		
Prostate	60 to 64	956	0	1,764,828	6,285	882,414	4,960	1,325	992	3,968	63	352,366	3,047	3,238	609	2,437	39	176,483	1,988	4,297	398	1,590	25	88,261	1,257	5,028	251	1,005	16	17,648	401	5,884	80	321	5		
Prostate	65 to 69	623	0	1,696,993	10,568	884,497	8,339	2,229	1,668	6,671	63	339,399	5,123	5,445	1,025	4,028	39	169,639	3,412	7,226	668	2,674	25	84,850	2,114	8,454	423	1,691	16	16,970	675	9,893	135	540	5		
Prostate	70 to 74	760	0	1,467,965	11,135	733,983	8,801	2,352	1,760	7,041	63	293,959	5,406	5,747	1,081	4,325	39	146,797	3,527	7,626	705	2,822	25	73,968	2,231	9,222	446	1,785	16	14,880	712	10,441	142	570	5		
Prostate	75 to 79	867	0	1,007,365	8,736	503,683	6,894	1,842	1,379	5,515	63	201,473	4,235	4,501	847	3,388	39	100,737	2,363	5,973	553	2,210	25	50,368	1,747	6,989	349	1,938	16	10,074	538	8,178	112	446	5		
Prostate	Total 40-49	193	0	12,090,277	23,299	6,095,139	18,386	4,913	3,677	14,708	63	2,418,055	11,294	12,005	2,259	9,035	39	1,209,023	7,368	15,931	1,474	5,895	25	604,514	4,661	18,638	932	3,728	16	120,903	1,488	21,811	298	1,191	5		
Prostate	Total 50-59	13	0	4,273,065	549	2,165,532	493	116	87	347	63	854,613	266	283	53	213	39	427,305	178	375	35	139	25	213,653	110	499	22	88	16	42,731	35	514	7	28	5		
Prostate	Total 60-69	135	0	4,955,991	5,897	2,177,696	4,653	1,344	991	3,723	63	871,078	2,838	3,039	572	2,287	39	435,599	1,865	4,032	373	1,492	25	217,770	1,180	4,717	236	944	16	43,954	977	5,520	75	301	5		
Prostate	Total 70-79	487	0	3,461,821	16,859	1,730,911	13,289	3,554	2,660	10,639	63	363,364	8,169	8,584	1,639	6,535	39	346,182	5,390	11,523	1,066	4,364	25	179,091	5,371	15,482	616	2,697	16	34,618	1,077	15,776	215	861	5		
Prostate	Total 80-79	291	0	2,817,118	22,790	1,398,606	17,822	4,798	3,990	14,862	63	1,853,443	11,028	11,722	2,206	8,822	39	781,721	7,195	15,555	1,439	5,786	25	390,861	4,851	18,199	910	3,641	16	78,172	1,453	21,257	291	1,161	5		
Prostate	Total 40-74	568	0	4,929,786	28,005	2,464,893	22,100	5,906	4,430	17,680	63	985,957	13,575	14,431	2,715	10,860	39	492,979	8,867	19,149	1,771	7,086	25	246,489	5,602	22,404	1,120	4,482	16	49,298	1,789	26,217	358	1,431	5		
Prostate	Total 40-79	297	0	14,565,008	43,188	7,282,804	34,800	9,108	6,816	27,264	63	2,913,122	20,935	22,253	4,187	16,748	39	1,456,561	13,638	29,530	2,732	10,927	25	728,280	8,639	34,549	1,728	6,911	16	145,656	2,759	40,429	552	2,207	5		
Prostate	Total (all ages)	184	0	32,583,226	52,254																																
Colorectal																																					
Colorectal	40 to 44	15	14	4,075,608	570	2,037,804	396	174	79	317	56																										

Supplementary Table 7b(ii). Cancers detected by offering risk stratified screening according to future PRS using an idealised screening tool with a sensitivity of 0.8 (Cancers of the Ovary, Kidney, Lung, Testis)

Cancer Type	Age Groups	Annual Incidence (per 100,000) for age-band		Population		Screening offered to top 50% of PRS						Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS					
		Male	Female	Population Size	Cancers arising	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in 'unscreened' 'low risk' group	Cancers missed on screening in 'high risk' group	Cancers detected on screening in 'high risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in 'unscreened' 'low risk' group	Cancers missed on screening in 'high risk' group	Cancers detected on screening in 'high risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in 'unscreened' 'low risk' group	Cancers missed on screening in 'high risk' group	Cancers detected on screening in 'high risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in 'unscreened' 'low risk' group	Cancers missed on screening in 'high risk' group	Cancers detected on screening in 'high risk' group	Percent of cancers identified	Number requiring screening in 'high risk' group	Cancers arising in 'high risk' group	Missed cancers arising in 'unscreened' 'low risk' group	Cancers missed on screening in 'high risk' group	Cancers detected on screening in 'high risk' group	Percent of cancers identified
Ovary	40 to 44	0.0	13.2	2,094,223	270	1,027,112	178	92	36	142	53	410,845	90	180	18	72	27	205,422	52	218	10	41	15	102,711	29	241	6	23	9	20,542	7	263	1	6	2
Ovary	45 to 49	0.0	19.4	2,515,479	448	1,177,740	295	153	99	236	53	463,096	149	299	30	119	27	231,548	86	362	17	69	15	115,774	49	399	10	39	9	23,155	12	436	2	10	2
Ovary	50 to 54	0.0	27.1	2,564,638	640	1,182,319	422	218	84	337	53	472,298	213	427	43	170	27	236,464	123	517	25	98	15	118,232	69	571	14	56	9	23,646	18	622	4	14	2
Ovary	55 to 59	0.0	34.8	2,119,687	738	1,059,844	486	252	97	389	53	423,927	246	402	49	197	27	211,949	141	507	28	113	15	105,984	82	658	16	64	9	21,197	20	718	4	16	2
Ovary	60 to 64	0.0	41.6	1,837,174	764	918,587	503	261	101	403	53	367,435	254	510	51	203	27	183,717	146	618	29	117	15	91,859	82	681	17	66	9	18,372	21	743	4	17	2
Ovary	65 to 69	0.0	52.3	1,805,190	944	902,595	622	322	124	498	53	361,038	314	610	63	291	27	180,191	181	763	36	145	15	90,360	102	842	20	82	9	18,052	26	918	5	21	2
Ovary	70 to 74	0.0	60.8	1,603,610	975	801,805	643	332	129	514	53	300,722	325	690	65	260	27	160,361	187	788	37	150	15	80,180	106	869	21	85	9	16,056	27	948	5	22	2
Ovary	75 to 79	0.0	73.8	1,181,645	872	590,823	575	297	115	460	53	236,329	290	582	58	232	27	118,165	167	705	33	134	15	59,082	95	777	19	76	9	11,816	24	848	5	19	2
Ovary	Total 40-69	0.0	30.4	12,046,392	3,804	6,248,196	2,507	1,297	501	2,006	53	2,499,778	1,266	2,538	253	1,013	27	1,249,639	739	3,075	146	583	15	624,820	412	3,392	82	330	9	124,964	105	3,699	21	84	2
Ovary	Total 40-49	0.0	16.4	4,369,703	718	2,184,851	473	245	95	379	53	873,941	359	479	48	193	27	436,970	138	580	28	110	15	218,485	78	640	16	62	9	43,697	20	698	4	16	2
Ovary	Total 50-59	0.0	30.7	4,484,325	1,378	2,242,163	908	470	182	727	53	896,865	459	919	92	367	27	448,433	264	1,114	53	211	15	224,216	149	1,229	30	20	9	44,843	38	1,340	8	30	2
Ovary	Total 60-69	0.0	38.0	8,126,689	3,086	4,063,345	2,034	1,052	407	1,627	53	1,625,338	1,027	2,099	205	822	27	812,669	591	2,495	118	473	15	406,334	335	2,751	67	268	9	81,267	85	3,001	17	68	2
Ovary	Total 70-79	0.0	51.1	5,245,974	2,682	2,622,987	1,768	915	354	1,415	53	1,049,195	893	1,790	179	715	27	524,397	514	2,169	103	411	15	262,299	291	2,392	58	233	9	52,460	74	2,609	15	59	2
Ovary	Total (all ages)	0.0	22.8	33,458,052	7,495	17,640,824	3,724	1,927	734	2,979	53	5,056,329	1,881	3,770	376	1,505	27	1,528,165	1,083	4,508	217	866	15	764,082	613	5,038	123	490	9	152,816	156	5,495	31	125	2
Kidney	40 to 44	10.1	5.0	4,075,608	307	2,037,804	215	92	43	172	56	815,122	115	192	23	92	30	407,561	69	238	14	55	18	203,780	40	267	8	32	11	40,756	11	296	2	9	3
Kidney	45 to 49	17.7	7.8	4,567,159	580	2,283,580	406	174	81	325	56	913,432	218	362	44	175	30	456,716	130	346	26	104	18	228,358	76	504	15	61	11	45,672	21	559	4	17	3
Kidney	50 to 54	26.8	12.7	4,658,111	915	2,329,055	641	274	128	513	56	931,622	344	571	69	275	30	465,811	206	709	41	165	18	232,906	120	795	24	96	11	46,581	33	882	7	26	3
Kidney	55 to 59	37.1	18.6	4,181,606	1,160	2,090,803	813	347	163	690	56	836,321	466	724	87	349	30	418,161	261	859	52	209	18	209,080	153	1,007	31	122	11	41,816	42	1,118	8	33	3
Kidney	60 to 64	53.7	26.2	3,602,002	1,429	1,801,001	1,001	428	200	801	56	720,400	517	882	107	430	30	360,200	321	1,141	64	257	18	180,100	188	1,241	38	190	11	36,000	51	1,378	10	41	3
Kidney	65 to 69	73.9	36.4	3,502,183	1,911	1,751,092	1,359	572	288	1,071	56	700,437	719	1,192	144	579	30	350,218	420	1,408	86	344	18	175,109	251	1,660	50	201	11	35,022	69	1,842	14	55	3
Kidney	70 to 74	91.2	43.1	3,071,575	2,063	1,535,287	1,445	618	289	1,186	56	614,318	316	1,282	155	621	30	307,157	464	1,599	93	371	18	182,579	321	1,292	54	213	11	30,716	74	1,289	15	59	2
Kidney	75 to 79	110.1	57.2	2,189,011	1,785	1,094,505	1,250	535	250	1,000	56	437,802	401	1,114	134	537	30	218,901	401	1,384	80	321	18	109,451	255	1,590	47	188	11	21,890	64	1,721	13	51	3
Kidney	Total 40-69	34.6	16.9	24,586,669	6,302	12,293,335	4,415	1,887	883	3,532	56	4,917,334	2,770	3,992	474	1,896	30	2,458,667	1,417	4,885	283	1,134	18	1,229,333	829	5,473	166	663	11	245,867	226	6,076	45	181	3
Kidney	Total 40-49	14.1	6.5	8,642,767	887	4,321,384	621	266	124	497	56	1,728,593	334	563	67	267	30	864,277	200	687	40	160	18	432,138	117	770	23	93	11	86,428	32	855	6	25	3
Kidney	Total 50-59	31.7	15.5	8,839,717	2,075	4,419,858	1,454	621	291	1,163	56	1,467,943	780	1,295	156	634	30	883,972	467	1,608	93	373	18	441,986	273	1,802	55	218	11	88,397	74	2,001	15	60	3
Kidney	Total 60-69	45.8	22.6	15,943,902	5,415	7,971,951	3,793	1,622	799	3,035	56	3,188,780	2,037	3,578	407	1,629	30	1,594,390	1,218	4,197	244	974	18	797,195	712	4,703	142	570	11	159,439	194	5,229	39	155	3
Kidney	Total 70-79	71.8	35.3	10,175,780	5,403	5,087,880	3,785	1,618	757	3,028	56	2,035,152	2,037	3,371	406	1,626	30	1,017,576	1,215	4,188	243	972	18	508,788	711	4,692	142	569	11	101,758	194	5,209	39	155	3
Kidney	Total (all ages)	29.2	14.8	66,041,278	13,323	34,923,627	23,212	12,377	4,642	18,570	56	5,969,451	11,611	23,978	2,322	9,289	30	2,984,725	2,283	7,867	457	1,826	18	1,492,363	1,336	8,814	267	1,068	11	298,473	364	9,786	73	291	3
Lung	40 to 44	6.0	5.8	4,075,608	240	2,037,804	157	83	31	125	52	815,122	78	162	16	63	26	407,561	45	195	9	36	15	203,780	25	215	5	20	8	40,756	6	234	1	5	2
Lung	45 to 49	16.3	14.7	4,567,159	706	2,283,580	460	246	92	368	52	913,432	280	476	46	184	26	456,716	132	574	26	105	15	228,358	74	632	15	59	8	45,672	19	687	4	15	2
Lung	50 to 54	33.4	31.5	4,658,111	1,512	2,329,055	986	526	197	789	52	931,622	493	1,019	99	395	26	465,811	282	1,230	56	226	15	232,906	159	1,333	32	127	8	46,581	40	1,472	8	32	2
Lung	55 to 59	57.4	27.1	4,181,606	2,896	2,090,803	1,889	1,007	378	1,511	52	836,321	545	1,991	189	760	26	418,161	541	2,355	108	432	15	209,080	304	2,592	61	243	6	41,816	77	2,819			

Supplementary Table 7c(i). Cancers detected by offering risk stratified screening according to optimised PRS using an idealised screening tool with a sensitivity of 0.8 (Cancers of the Breast, Prostate, Colorectum and Pancreas)

Cancer Type	Age Group	Annual Incidence (per 100,000) for age-band		Screening offered to top 50% of PRS						Screening offered to top 20% of PRS						Screening offered to top 10% of PRS						Screening offered to top 5% of PRS						Screening offered to top 1% of PRS											
		Male	Female	Population		Number in 'high risk' screening group	Cancers arising in 'high risk' group	PRS false negative (missed cancers arising in 'low' risk)	screening false negatives	Total detected by screening	Percent of cancers detected	Number in 'high risk' screening group	Cancers arising in 'high risk' group	PRS false negative (missed cancers arising in 'low' risk)	screening false negatives	Total detected by screening	Percent of cancers detected	Number in 'high risk' screening group	Cancers arising in 'high risk' group	PRS false negative (missed cancers arising in 'low' risk)	screening false negatives	Total detected by screening	Percent of cancers detected	Number in 'high risk' screening group	Cancers arising in 'high risk' group	PRS false negative (missed cancers arising in 'low' risk)	screening false negatives	Total detected by screening	Percent of cancers detected	Number in 'high risk' screening group	Cancers arising in 'high risk' group	PRS false negative (missed cancers arising in 'low' risk)	screening false negatives	Total detected by screening	Percent of cancers detected				
		Population Size	Cancers arising																																				
Breast																																							
Breast	40 to 44	0.0	124.6	2,054,223	2,559	1,027,112	2,004	955	401	1,603	63	410,845	1,219	1,340	244	975	38	205,422	790	1,769	158	632	25	102,711	497	2,062	99	398	16	20,542	157	2,402	31	126	5				
Breast	45 to 49	0.0	214.8	2,315,479	4,974	1,157,740	3,895	1,079	779	3,116	63	463,096	2,370	2,604	474	1,896	38	231,548	1,537	3,437	307	1,229	25	115,774	966	4,008	193	773	16	23,155	305	4,669	61	244	5				
Breast	50 to 54	0.0	279.8	2,364,638	6,616	1,182,319	5,181	1,435	1,036	4,145	63	472,928	3,152	3,464	630	2,522	38	236,464	2,044	4,572	409	1,635	25	118,232	1,285	5,331	257	1,028	16	23,646	406	6,210	81	325	5				
Breast	55 to 59	0.0	285.5	2,119,887	6,052	1,059,844	4,739	1,313	948	3,791	63	423,937	2,884	3,168	577	2,307	38	211,969	1,870	4,182	374	1,496	25	105,984	1,176	4,876	235	941	16	21,197	371	5,681	74	297	5				
Breast	60 to 64	0.0	338.0	1,837,174	6,209	918,587	4,862	1,347	972	3,890	63	367,435	2,958	3,251	592	2,367	38	183,717	1,918	4,291	384	1,534	25	91,859	1,206	5,003	241	965	16	18,372	381	5,828	76	305	5				
Breast	65 to 69	0.0	412.3	1,805,190	7,443	902,595	5,828	1,615	1,166	4,663	63	361,038	3,546	3,897	709	2,837	38	180,519	2,299	5,144	460	1,839	25	90,260	1,446	5,997	289	1,157	16	18,052	456	6,987	91	365	5				
Breast	70 to 74	0.0	372.7	1,603,610	5,977	801,805	4,680	1,297	936	3,744	63	330,722	2,848	3,129	570	2,278	38	160,361	1,846	4,131	369	1,477	25	80,180	1,161	4,816	232	929	16	16,036	367	5,610	73	293	5				
Breast	75 to 79	0.0	403.0	1,181,645	4,762	590,823	3,729	1,033	746	2,983	63	236,329	2,269	2,493	454	1,815	38	118,165	1,471	3,291	294	1,177	25	59,082	925	3,837	185	740	16	11,816	292	4,470	58	234	5				
Breast	Total 40-69	0.0	270.9	12,496,392	33,853	6,248,196	26,509	7,344	5,302	21,207	63	2,499,278	16,130	17,723	3,226	12,904	38	1,249,639	10,457	23,396	2,091	8,366	25	624,820	6,577	27,276	1,315	5,261	16	124,964	2,076	31,777	415	1,661	5				
Breast	Total 40-49	0.0	172.4	4,369,703	7,533	2,184,851	5,899	1,654	1,180	4,719	63	873,941	3,589	3,944	718	2,871	38	436,970	2,327	5,206	465	1,862	25	218,485	1,463	6,070	293	1,171	16	43,697	462	7,071	92	370	5				
Breast	Total 50-59	0.0	282.5	4,484,325	12,668	2,242,163	9,920	2,748	1,984	7,936	63	896,865	6,036	6,632	1,207	4,829	38	448,433	3,913	8,755	783	3,131	25	224,216	2,461	10,207	492	1,969	16	44,843	777	11,891	155	621	5				
Breast	Total 50-69	0.0	323.9	8,126,689	26,320	4,063,345	20,610	5,710	4,122	16,488	63	1,625,338	12,541	13,779	2,508	10,033	38	812,669	8,130	18,190	1,626	6,504	25	406,334	5,113	21,207	1,023	4,091	16	81,267	1,614	24,706	323	1,291	5				
Breast	Total 60-74	0.0	374.2	5,245,974	19,629	2,622,987	15,371	4,258	3,074	12,297	63	1,049,195	9,353	10,276	1,871	7,482	38	524,997	6,064	13,565	1,213	4,851	25	262,299	3,813	15,816	763	3,051	16	52,460	1,204	18,425	241	963	5				
Breast	Total 40-79	0.0	291.8	15,281,647	44,592	7,640,824	34,919	9,673	6,984	27,935	63	3,056,329	21,247	23,345	4,249	16,997	38	1,528,165	13,775	30,817	2,755	11,020	25	764,082	8,663	35,929	1,733	6,930	16	152,816	2,735	41,857	547	2,188	5				
Breast	Total (all ages)	0.0	166.0	33,458,052	55,545																																		
Prostate																																							
Prostate	40 to 44	4.3	0.0	2,021,385	88	1,010,692	71	17	14	57	65	404,277	45	43	9	36	41	202,138	30	58	6	24	27	101,669	19	69	4	15	17	20,214	6	82	1	5	6				
Prostate	45 to 49	20.5	0.0	2,251,880	461	1,125,840	372	89	74	298	65	490,336	235	226	47	188	41	225,168	156	305	31	125	27	112,984	101	360	20	80	17	22,517	33	428	7	27	6				
Prostate	50 to 54	75.7	0.0	2,295,473	1,787	1,146,736	1,402	335	280	1,121	65	458,695	886	851	177	709	41	229,347	589	1,148	118	471	27	114,674	379	1,358	76	303	17	22,935	125	1,612	25	100	6				
Prostate	55 to 59	201.8	0.0	2,061,919	4,160	1,030,959	3,357	803	671	2,685	65	412,384	2,122	2,038	424	1,697	41	206,192	1,411	2,749	282	1,129	27	103,096	908	3,252	182	726	17	20,619	300	3,860	60	240	6				
Prostate	60 to 64	356.1	0.0	1,764,828	6,285	882,414	5,072	1,213	1,014	4,057	65	352,966	3,205	3,080	641	2,364	41	176,483	2,131	4,154	426	1,705	27	88,241	1,372	4,913	274	1,097	17	17,648	454	5,831	91	363	6				
Prostate	65 to 69	622.7	0.0	1,686,993	10,568	848,497	6,508	2,040	1,706	6,822	65	339,399	5,390	5,178	1,078	4,312	41	169,699	3,984	6,984	717	2,867	27	84,850	2,364	8,719	461	1,845	17	16,970	763	9,805	159	610	6				
Prostate	70 to 74	759.8	0.0	1,467,993	11,333	733,983	9,000	2,153	1,800	7,200	65	293,353	5,688	5,465	1,138	4,350	41	146,397	3,782	7,371	786	3,026	27	73,308	2,454	8,719	487	1,947	17	14,680	839	10,348	161	644	6				
Prostate	75 to 79	867.6	0.0	1,007,365	8,736	505,683	7,049	1,687	1,410	5,639	65	201,473	4,445	4,281	891	3,364	41	100,737	2,962	5,774	592	2,370	27	50,268	1,936	6,830	381	1,525	17	10,074	631	8,105	126	504	6				
Prostate	Total 40-69	192.7	0.0	12,090,277	25,259	6,045,139	18,801	4,498	3,760	15,041	65	2,418,055	11,882	11,417	2,376	9,506	41	1,209,028	7,901	15,398	1,580	6,321	27	604,514	5,084	18,215	1,017	4,068	17	120,903	1,882	21,617	336	1,345	6				
Prostate	Total 40-49	12.8	0.0	4,375,931	549	2,136,532	443	106	89	354	65	854,613	280	269	56	224	41	427,306	186	363	37	149	27	213,653	120	420	34	96	17	42,751	40	509	8	32	6				
Prostate	Total 50-59	135.4	0.0	4,455,917	5,897	2,177,696	4,738	1,139	952	3,807	65	871,078	3,007	2,830	601	2,406	41	355,399	2,000	3,897	400	1,600	27	217,770	1,287	4,610	267	1,029	17	43,954	426	5,471	85	341	6				
Prostate	Total 50-69	486.8	0.0	3,461,821	16,837	1,730,611	13,599	3,254	2,720	10,879	65	692,364	8,595	8,258	1,719	6,876	41	346,182	5,715	11,138	1,143	4,572	27	173,091	3,678	13,175	736	2,942	17	34,618	1,217	15,636	243	973	6				
Prostate	Total 60-74	291.0	0.0	7,817,213	22,790	3,930,606	18,338	4,392	3,672	14,686	65	1,563,443	11,602	11,148	2,320	9,282	41	781,721	7,715	15,035	1,543	6,172	27	390,861	4,965	17,785	993	3,972	17	78,172	1,642	21,108	328	1,314	6				
Prostate	Total 40-79	568.1	0.0	4,925,786	28,006	2,464,893	22,599	5,407	4,530	18,079	65	985,957	14,283	13,723	2,857	11,426	41	492,979	9,497	18,509	1,899	7,598	27	246,489	6,112	21,894	1,222	4,889	17	49,298	2,022	25,984	404	1,617	6				
Prostate	Total (all ages)	183.8	0.0	14,965,608	45,188	7,282,804	34,850	8,338	6,970	27,880	65	2,913,122	22,025	21,163	4,405	17,620	41	1,456,361	14,645	28,343	2,929	11,716	27	728,280	9,425	33,763	1,883	7,540	17	145,656	3,118	40,070	624	2,494	6				
Colorectal																																							
Colorectal	40 to 44	14.5	13.5	4,075,608	570	2,037,804	425	145	85	34																													

Supplementary Table 8. Outcomes including 10-year survival from screening offered to PRS-defined high risk 20% (current and future), oldest 20% and random 20%.

Impact of screening for cancers of the breast (40-49 years), colorectum (50-59 years) and prostate (50-59, 60-69 years). Presented are modelled outcomes for screening of the full population, a PRS-defined high-risk quintile (20%), the oldest quintile (20%), a randomly-selected fifth of the population and the full population. Metrics presented are modelled for the UK population (~66 million) for annual cancers arising and deaths averted. These are maximal estimates based on several favourable assumptions, which include (i) that all cancers arising in the screening interval are present at time of screen (i.e. no interval cancers) (ii) full population uptake for PRS and for screening (see methods).

	Cancer Type	Screening modality	Age-band	Population			10 year survival		Ten year survival (%)	Survival Improvement (%)	Reduction in deaths (%)	Individuals screened for 10 years per one death averted
				Population size	Cancers arising annually	Size of screened Group	Total	Deaths averted				
No screening (baseline)	Breast		40 to 49	4,369,703	7,533		6,839		90.8%			
	Prostate		50 to 59	4,355,391	5,897		5,385		91.3%			
	Prostate		60 to 69	3,461,821	16,853		15,591		92.5%			
	Colorectal		50 to 59	8,839,717	5,052		3,337		66.1%			
Screening Top 20% (current PRS)	Breast	Digital mammography	40 to 49	4,369,703	7,533	873,941	6,941	102	92.1%	1.4%	14.7%	854
	Prostate	PSA 3ng/mL cut-off	50 to 59	4,355,391	5,897	871,078	5,443	58	92.3%	1.0%	11.4%	1,495
	Prostate	PSA 3ng/mL cut-off	60 to 69	3,461,821	16,853	692,364	15,748	158	93.4%	0.9%	12.5%	439
	Prostate	mpMRI	50 to 59	4,355,391	5,897	871,078	5,547	162	94.1%	2.7%	31.7%	537
	Prostate	mpMRI	60 to 69	3,461,821	16,853	692,364	16,029	438	95.1%	2.6%	34.7%	158
	Colorectal	FIT 20-50 µg/g threshold (CRC)	50 to 59	8,839,717	5,052	1,767,943	3,525	188	69.8%	3.7%	11.0%	940
Screening Top 20% (future PRS)	Breast	Digital mammography	40 to 49	4,369,703	7,533	873,941	6,959	121	92.4%	1.6%	17.4%	723
	Prostate	PSA 3ng/mL cut-off	50 to 59	4,355,391	5,897	871,078	5,447	62	92.4%	1.0%	12.0%	1,414
	Prostate	PSA 3ng/mL cut-off	60 to 69	3,461,821	16,853	692,364	15,757	167	93.5%	1.0%	13.2%	416
	Prostate	mpMRI	50 to 59	4,355,391	5,897	871,078	5,556	171	94.2%	2.9%	33.5%	508
	Prostate	mpMRI	60 to 69	3,461,821	16,853	692,364	16,054	463	95.3%	2.7%	36.7%	149
	Colorectal	FIT 20-50 µg/g threshold (CRC)	50 to 59	8,839,717	5,052	1,767,943	3,544	207	70.1%	4.1%	12.0%	856
Screening oldest 20% in age group	Breast	Digital mammography	40 to 49	4,369,703	7,533	937,850	6,919	80	91.8%	1.1%	11.6%	1,166
	Prostate	PSA 3ng/mL cut-off	50 to 59	4,355,391	5,897	786,032	5,427	42	92.0%	0.7%	8.2%	1,872
	Prostate	PSA 3ng/mL cut-off	60 to 69	3,461,821	16,853	702,786	15,686	95	93.1%	0.6%	7.5%	738
	Prostate	mpMRI	50 to 59	4,355,391	5,897	786,032	5,502	117	93.3%	2.0%	22.8%	673
	Prostate	mpMRI	60 to 69	3,461,821	16,853	702,786	15,855	265	94.1%	1.6%	21.0%	265
	Colorectal	FIT 20-50 µg/g threshold (CRC)	50 to 59	8,839,717	5,052	1,596,060	3,492	155	69.1%	3.1%	9.0%	1,030
Screen randomly-selected 20%	Breast	Digital mammography	40 to 49	4,369,703	7,533	873,941	6,893	55	91.5%	0.7%	7.9%	1,594
	Prostate	PSA 3ng/mL cut-off	50 to 59	4,355,391	5,897	871,078	5,410	25	91.7%	0.4%	5.0%	3,427
	Prostate	PSA 3ng/mL cut-off	60 to 69	3,461,821	16,853	692,364	15,659	69	92.9%	0.4%	5.4%	1,007
	Prostate	mpMRI	50 to 59	4,355,391	5,897	871,078	5,456	71	92.5%	1.2%	13.8%	1,232
	Prostate	mpMRI	60 to 69	3,461,821	16,853	692,364	15,782	191	93.6%	1.1%	15.1%	362
	Colorectal	FIT 20-50 µg/g threshold (CRC)	50 to 59	8,839,717	5,052	1,767,943	3,449	112	68.3%	2.2%	6.5%	1,584
Full population	Breast	Digital mammography	40 to 49	4,369,703	7,533	4,369,703	7,113	274	94.4%	3.6%	39.5%	1,594
	Prostate	PSA 3ng/mL cut-off	50 to 59	4,355,391	5,897	4,355,391	5,512	127	93.5%	2.2%	24.8%	3,427
	Prostate	PSA 3ng/mL cut-off	60 to 69	3,461,821	16,853	3,461,821	15,934	344	94.5%	2.0%	27.2%	1,007
	Prostate	mpMRI	50 to 59	4,355,391	5,897	4,355,391	5,738	353	97.3%	6.0%	69.0%	1,232
	Prostate	mpMRI	60 to 69	3,461,821	16,853	3,461,821	16,546	956	98.2%	5.7%	75.7%	362
	Colorectal	FIT 20-50 µg/g threshold (CRC)	50 to 59	8,839,717	5,052	8,839,717	3,895	558	77.1%	11.0%	32.5%	1,584

Supplementary Table 9: Impact on AUC of incorporation of multimodal parameters into risk prediction model.

Adapted from Kachuri et al, Nature Communications 2020 Nov 27;11(1):6084. PRS_{IV} are calculated from inverse variance (IV) weights. AUC values were estimated at 5 years of follow-up using UKBiobank. Sex is only included in the predictive model for cancers of the colon/rectum, lung, kidney, and pancreas. Family history and other predictors are included where on univariate analysis they have been demonstrated to improve the model for prediction of cancer incidence.

Cancer site	Cases in UK-Biobank	Variants in PRS	AUC for predictive model including							
			(A) Age [+ sex]	(B) Age [+ sex] + family history	(C) Age [+ sex] + PRS _{IV} (instead of family history)	(D) Age [+ sex] + other predictors	(E) Age [+ sex] + family history + other predictors	(F) Age [+ sex] + family history + PRS _{IV}	(G) Age [+ sex] + other predictors + PRS _{IV}	(H) Age [+ sex] + family history + other predictors + PRS _{IV}
Prostate	4740	161	0.713	0.720	0.766			0.769		
Testis	52	52	0.658		0.787					
Breast	4760	162	0.548	0.562	0.626		0.573			0.637
Ovary	445	36	0.620	0.622			0.643			0.660
Colon/rectum	2725	103	0.680	0.681	0.708		0.688			0.716
Lung	1541	109	0.704	0.714	0.710		0.843			0.846
Kidney	612	19	0.687			0.713			0.722	
Pancreas	493	22	0.695				0.715	0.745		

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